Environmental Chemistry for a Sustainable World

Nandita Dasgupta · Shivendu Ranjan
Eric Lichtfouse *Editors*

Environmental Nanotechnology

Volume 1

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Environmental Nanotechnology

Volume 1

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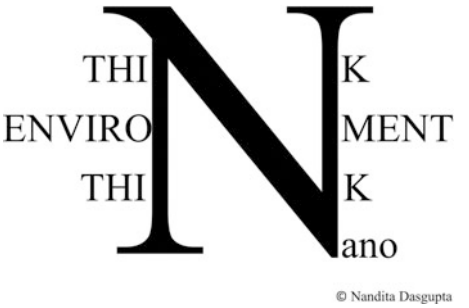
We dedicate this book to those who are affected by environmental hazards. We hope that this book may be a small contribution to improving their quality of life.



Think Environment – Think Nanomaterials
–Dr. Nandita Dasgupta

Preface

Nanotechnology will modify the environment both in a positive and negative way. On the one hand, new nanomaterials are promising for reducing greenhouse gases, cleaning toxic wastes and building alternative energy sources. On the other hand, some toxic nanoparticles enter and disrupt ecosystems. Therefore, research should focus on the sustainable use of nanomaterials to avoid environmental contamination. This book presents the environmental benefits of nanomaterials in agriculture, water purification and nanomedicine. This book is the first of several volumes on Environmental Nanotechnology, which will be published in series *Environmental Chemistry for a Sustainable World*.

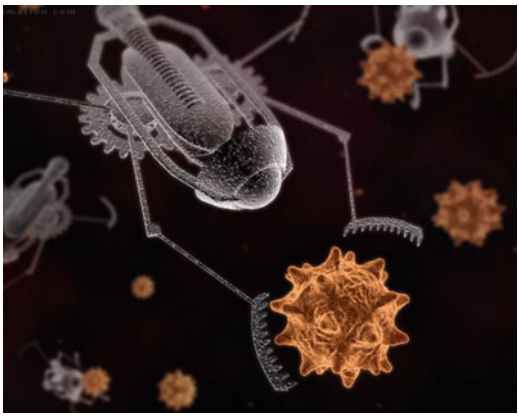
Food, Agriculture and Water

Hadef introduces the classification, structure and properties of nanomaterials in Chap. 1. This chapter also highlights the diverse applications of nanomaterials, including energy, environment, nanomedicine, sensors, nanoelectronics, textile, food and agriculture. Chapters 2 and 5 discuss the applications of nanomaterials in food and agriculture. Mousa and El-Hady review nanomaterials in food processing, packaging and safety in Chap. 2. They discuss, in particular, nanodelivery systems of bioactive food components. In Chap 5, Chandrika et al. present nanomaterials in agriculture, with applications such as nanopesticides, nanofertilizers, controlled-delivery devices, water and soil management and precision agriculture.

Source: International Food Information Council Foundation. http://www.foodinsight.org/articles/questions-and-answers-about-food-biotechnology

Medicine, Energy and Pollutants

Simeonidis explains the potential application of nanoparticles for water treatment in Chap. 3, with a special emphasis on the removal of heavy metals. In Chap. 4, Kuswandi reviews the nanomaterials used as biosensors for the detection of micropollutants. Chapter 6 by Rahman et al. discusses clay-polymer nanocomposites and its applications in various fields, ranging from automobile to biomedical. Dasari et al. review nanostructured photovoltaics as a medium of alternative energy in Chap. 7. Lateef et al. explain emerging applications of metallic nanoparticles for the management of blood coagulation disorders in Chap. 8. Osmani et al. in Chap. 9 describe cyclodextrin-based nanosponges in drug delivery and nanotherapeutics. In Chap. 10, Borzenkov et al. give an update on the application of gold nanoparticles in tissue engineering.



Source: Slaw.me http://slaw.me/naotechnology-size-does-matter-article-by-elizabeth-fiend/

Thanks for reading

Vellore, Tamil Nadu, India — Nandita Dasgupta
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Dr. Nandita Dasgupta has vast working experience in Micro/Nanoscience and is currently working at LV Prasad Eye Institute, Bhubaneswar, India. She has exposure of working at university, research institutes, and industries including VIT University, Vellore, Tamil Nadu, India; CSIR-Central Food Technological Research Institute, Mysore, India; Uttar Pradesh Drugs and Pharmaceutical Co. Ltd., Lucknow, India; and Indian Institute of Food Processing Technology (IIFPT), Thanjavur, Ministry of Food Processing Industries, Government of India. At IIFPT, Thanjavur, she was involved in a project funded by a leading pharmaceutical company, Dr. Reddy's Laboratories, and have successfully engineered microvehicles for model drug molecules. Her areas of interest include Micro/Nanomaterial fabrication and its applications in various fields – medicine, food, environment, agriculture, and biomedical.

She has published six edited books and one authored book in Springer, Switzerland, and two with CRC Press, USA. She has finished a contract for three book volumes in Elsevier, one volume with Wiley, two book volumes in CRC Press, and one volume in RSC (UK). She has authored many chapters and also published many scientific articles in international peer-reviewed journals. She has received the Certificate for 'Outstanding Contribution' in Reviewing from Elsevier, Netherlands. She has also been nominated for advisory panel for Elsevier Inc., Netherlands. She is the associate editor of *Environmental Chemistry Letters* – a Springer journal of 3.59 impact factor – and also serving as editorial board member and referee for reputed international peer-reviewed journals. She has received several awards and recognitions from different national and international organizations.

Dr. Shivendu Ranjan has expertise in Micro/Nano (Bio)technology and is currently working as Head R&D and Technology Development at E-Spin Nanotech Pvt. Ltd., SIDBI Incubation Center, IITKanpur, India. He has founded and drafted the concept for the first edition of the "VIT Bio Summit" in 2012, and the same has been continued till date by the university. He has worked in CSIR-CFTRI, Mysuru, India; UP Drugs and Pharmaceutical Co. Ltd., India; and IIFPT, Thanjavur, MoFPI, Govt of India. At IIFPT, Thanjavur, he was involved in a project funded by a leading pharmaceutical company, Dr. Reddy's Laboratories, and have successfully engineered microvehicles for model drug molecules

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Eric Lichtfouse born in 1960, is a geochemist working on carbon sequestration and climate change at the European Centre of Research and School in Environmental Geosciences. He has invented the ^{13}C-dating method allowing to measure the dynamics of soil organic molecules. He has published about 100 articles in organic synthesis, petroleum geochemistry, environmental chemistry, food chemistry, soil science and phytoremediation. He is Chief Editor and Founder of the journal *Environmental Chemistry Letters*, the book series *Sustainable Agriculture Reviews* and *Environmental Chemistry for a Sustainable World* and the magazine *Publier La Science*. His book *Scientific Writing for Impact Factor Journals* contains the micro-article, a new tool to identify the novelty of experimental results. He got awards in analytical chemistry and in science editing. He is also a triathlete who got the Bronze Medal in age groups at the World ITU Cross Triathlon Championships. He has qualified for the Word Ironman, Ironman 70.3 and XTerra Championships, finished 5 times in the top 3 of French Triathlon and Duathlon Championships, and completed 17 ironman competitions.

Chapter 1
An Introduction to Nanomaterials

Fatma Hadef

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Abstract Nanotechnology can be defined as the systematic study of materials that have properties critically dependant on length scales on the order of nanometers. Such novel and improved properties make nanoscale materials promising candidates for a wide range of applications that are expected to improve our lifestyles. Here, I review different aspects of nanotechnology. This paper describes first, definitions and classifications of nanomaterials reported in published research works. Then, I disscuss the most enhanced properties of manufactured nanomaterials. This will be followed by a description of the synthesis methods being used to obtain nanostructured materials. Nanotechnology applications in the energy, environment, nanomedicine, sensors, nanoelectronics, textile, food and agriculture fields are discussed in the last section.

1.1 Introduction and Historical Background

The first Industrial Revolution, at the end of eighteenth century, has triggered the development of technological research and the obtention of novel materials (Fajardo et al. 2015). The challenges today are the miniaturation of devices and instruments; smaller volume, lesser power consumption but greater performance. The progression relies upon the searching out new desirable materials and the ability of making tiny structures with high precision. However, the development is not so smooth and easy. One of the most brilliant methods created to answer such condition is the nanotechnology (Fajardo et al. 2015; Huyen 2011). In recent years, research involving nanoscale materials has generated a great deal of interest from scientists and engineers. They view nanotechnology as the revolutionary technology of the twenty-first century (The Royal Society 2004).

Visualize printing all 24 volumes of the Encyclopaedia Britannica on the head of a pin. In 1959, Richard Feynman articulated this reality in an insightful address at the annual meeting of the American Physical Society. In what became a prophetic speech, “There’s plenty of room at the bottom” (Feynman 1960). It was a masterly and provocative talk in which the problem of manipulating and controlling things on a small scale was discussed to its extreme limits. Points considered, several of which contained sound predictions, included: information on a small scale, comparisons with the biological systems, miniaturization by evaporation, making small machines, arranging the atoms one by one the way we want (Ferro and Saccone 2008). The tunable material properties that nanotechnology can provide were stated in Norio Taniguchi’s paper in 1974 where the term “nanotechnology” was first used in a scientific publication to explain precision engineering in semiconductor processes (Taniguchi 1974). However, the growing interest in nanosciences and nanotechnology emerged during the 1980s with the invention of the scanning tunnelling microscope by Binning and Rohrer. They received the Nobel Prize in Physics in 1986 (Binnig and Rohrer 1986). It was also used in the development of the atomic force microscope, invented by Calvin Quate and Christoph Gerber (Khun 2015). They

provided atomic resolution, three orders of magnitude better than the diffraction limit of optical microscopes, which more than fulfilled Feynman's request to make the electron microscope 100 times better (Roduner 2006). In 1985, fullerene, which is shaped like a ball and just 1 nm in diameter, was discovered by Kroto et al. (1985). In 1986, Eric Drexler published a book titled "Engine of Creation" which disseminates his provocative ideas on molecular nanotechnology to a general audience outside the scientific community (Drexler 1986). In 1991, Sumio Iijima discovered carbon nanotubes, which are tube shaped materials whose diameter measures on the nanometer scale (Iijima 1991). Ahead of schedule in 1995, S.Y. Chou and coworkers firstly proposed the nanoimprint lithography concept in Nanostructure Laboratory of University of Minnesota. Dr. T. Sasaki from National Institute of Research discovered nanosheets and investigation of nanosheets in photocatalytic activity in 1996 (Bashir and Liu 2015). As a strategic and distinct area of scientific inquiry, nanotechnology research began in the United States with the establishment of the National Nanotechnology Initiative (NNI) in 2001 (Eckelman et al. 2008). Actually, scientific journals that are focused specifically on nanotechnology have been started including: International Journal of Nanotechnology, Nano Letters, Journal of Nanoscience and Nanotechnology, Journal of Nanoparticle Research. . .etc. (Eckelman et al. 2008).

The term nanotechnology is derived from a Greek word 'nano' meaning 'dwarf', hence it relates to materials of very small size ranges (Nikalje 2015). Indeed, it is the creation of materials, components, devices and/or systems at near atomic or molecular levels. Usually, one of the dimensions of nanoproducts is between 1 and 100 nm length in scale. This emerging technology involves fabricating, imaging, measuring, modeling, and manipulating matter at individual atoms, molecules, or particles to significantly improve the physical, chemical, physico-chemical, and biological properties of materials and devices, for various purposes (Asmatulu et al. 2010). This definition has two parts. One is the part about engineering at dimensions of 1–100 nm, and the other is about properties of materials at the nanoscale that enable their use for novel applications. The size range that holds so much interest is typically from 100 nm down to the atomic level, because it is in this range that materials have radically different properties from their bulk counterparts. The main reasons for this change in behavior are an increased relevance of surface and interfacial area (Wardak et al. 2008). On the other hand, nanotechnology, is a new paradigm in fundamental thinking and understanding about the physical universe, where the bottom up approach is the norm and not an exception. In this new approach, one has to think in terms of atoms and how they interact to make useful materials, structures, devices and systems (Raza and Raza 2013; Rocco 2007; Rocco et al. 2011) (Fig. 1.1).

Nanotechnology has been moving from the laboratory environment into applications and consumer products for some time now (Barakat and Jiao 2011). Actually, nanotechnology is a highly multidisciplinary field, bringing together many fields, including: electrical and mechanical engineering, physics, chemistry, and biosciences. It will radically affect all these disciplines and their application areas. Economic impact is foreseen to be comparable to information technology and telecom

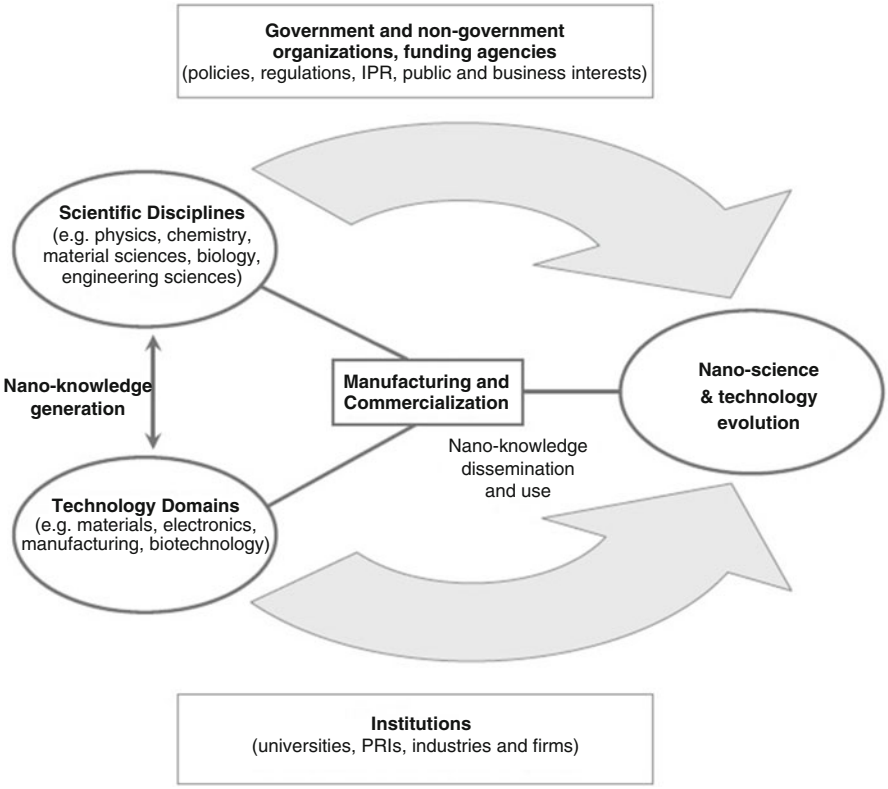


Fig. 1.1 General framework of nanoscience and technology evolution (Reproduced from Islam and Miyazaki 2010 Copyright (2010) Elsevier)

industries (Ermolov et al. 2007). As a result, demand has risen significantly for a workforce capable of supporting this promising technology (Barakat and Jiao 2011). The nanotechnology will create the new horizons for the human world and their promises have been realized to deliver the greatest scientific and technological advances in several areas including: environment, energy, health and medical care, information, communications, and electronics (Daryoush and Darvish 2013). This article addresses to fill current knowledge of manufactured nanomaterials, by providing a comprehensive review of recent developments in the nanotechnology field. It highlights the various definitions, classifications, fundamental properties and synthesis routes of nanomaterials. The review also focuses onto their potential applications in many fields.

1.2 The Nanoworld

The nanoworld is not new. Many important functions of living organisms take place at the nanoscale. The human body uses natural nanoscale materials such as proteins and other molecules, to control the body's many systems and processes. A typical protein such as hemoglobin, which carries oxygen through the bloodstream, is 5 nm in diameter (National Nanomaterial Initiative 2010).

Nanometal particle inclusions have been used for a long time, for example the famous Lycurgus Cup from fourth century AD, which was probably carved in Rome (Fig. 1.2). It appears red by reflexion and green by transmission (Daniszewska et al. 2006). The reason for this dichroism was unknown until detailed SEM analysis of the cup was performed in 1990. It was found that it was due to the presence of nano-sized particles of silver (66.2%), gold (31.2%) and copper (2.6%), up to 100 nm in size, embedded in the glass. Light absorption and scattering by these nanoparticles determines the different colours (Filipponi and Sutherland 2013). Another application of alloy nanoparticles is lustered pottery, which shows shining surfaces with particular optical properties. Lustering is one of the most sophisticated techniques used to decorate majolica. It was developed in Iraq and was then introduced in Italy via Spain. The studies showed that the beautiful iridescent reflections of various colors (especially gold and ruby-red) were obtained from a thin metallic film containing silver, copper, and other substances such as iron oxide and cinnabar. The differences in the luster nanostructures suggest how they are affected by not only the chemical composition of the recipes used but also the technological processes used (Pienpinijtham and Thongnopkun 2015).

The existence of nanomaterials has been known for centuries; examples of which are the carbon black, fumed silica, titania; their industrial applications dated since the 1900s (Charitidis et al. 2014). Nanomaterials are, also in the environment (Klaine et al. 2008):

Fig. 1.2 The Lycurgus cup dates from the Roman empire (British Museum)

1. In urban atmospheres: diesel- and gasoline-fueled vehicles and stationary combustion sources have for many years contributed particulate material throughout a wide size range, including nanoparticles, amounting to more than 36% of the total particulate number concentrations (Shi et al. 2001).
2. In aquatic systems: colloid is the generic term applied to particles in the 1–100 nm size range. Aquatic colloids comprise macromolecular organic materials, such as humic and fulvic acids, proteins, and peptides, as well as colloidal inorganic species, typically hydrous iron and manganese oxides.
3. In soils: natural nanoparticles include clays, organic matter, iron oxides, and other minerals that play an important role in biogeochemical processes.

Nanomaterials are in nature. We see hundreds of examples of nanoscience under our eyes daily. Natural nanomaterials are of interest not only to understand the amazing properties of biological materials but also to gather inspiration for the design and engineering of new materials with advanced properties (Filipponi and Sutherland 2013). These natural nanomachines are inspiring in their own right, and their existence and the detailed study of their mode of operation have driven efforts to mimic them using artificially designed and constructed systems – this is called bioinspired nanotechnology or biomimetic nanotechnology (Ramsden 2016).

1.2.1 Lotus Leaves (Self Cleaning)

In recent times there has been new understanding about how the hydrophobic (water hating) and hydrophilic (water loving) surfaces work. This effect has been there for millions of years and now scientists call it as the *Lotus effect*. Lotus (*Nelumbo nucifera* Gaertn) is an important freshwater aquatic plant within the family Nelumbonaceae (Fig. 1.3). Lotus is also commonly known as sacred lotus or Indian lotus (Zhu 2017). This flower, a symbol of beauty, has a superficial hydrophobic molecular layer made of nanometric-sized hairs on which the tiny water droplets slide, removing any dust particles; as a result the flower retains its shape (Nouailhat 2008). In fact, The surface properties of the lotus leaf were first investigated by Wilhelm Barthlott. In 1997, he published an important paper where he described for the first time the 'Lotus effect' (a term that he later copyrighted) responsible for the self-cleaning properties of the lotus leaves (Filipponi and Sutherland 2013). This self-cleaning behavior, called *superhydrophobicity*, is useful for many modern applications, including stain-resistant paints and roof tiles as well as coatings for fabrics and other surfaces that need to stay dry and repel dirt. Scientists are also studying this effect for lab-on-a-chip applications, in which hydrophobic and hydrophilic materials can be used to control the flow of liquids through microfluidic components (Risbuda and Bartl 2013; Ressine et al. 2007).

Fig. 1.3 Lotus flowers and leaves (Reproduced from Guo 2009 Copyright (2009) Springer)

1.2.2 Gecko Feet (Adhesive Materials)

Scientific interest in the gecko began when, more than 2000 years ago, the Greek philosopher Aristotle first coined the phrase "like the Gecko lizard" (Aristotle 1918). Since then, this lizard' s amazing ability to climb walls and run on ceilings has inspired a wealth of research studies, many of which have proposed reasons for the gecko's amazing adhesive abilities (Greiner 2010). Gecko feet is one of the attractive examples since these animals can climb vertical surfaces without the need of cleaning their feet (Hansen and Autumn 2005). It was not until the 1960s that the German anatomist, Uwe Hiller made a major breakthrough when, using electron microscopy, he revealed the bristle – like, hierarchical structure of the gecko' stoe pads (Hiller and Blaschke 1967; Hiller 1968) that today, are recognized as being responsible for the animal's climbing abilities (Greiner 2010). The gecko foot has a series of small ridges called scansors which contain numerous projections called setae. Each seta is about 100 μm long and has a diameter of about 5 μm. There are about half a million of these setae on the foot of a gecko. Each seta is further subdivided into about a thousand 200 nm-wide projections called spatulae (Fig. 1.4). As a result, the total surface area of the gecko's feet is enormous. The gecko spatulae are very flexible, so they essentially mould themselves into the molecular structure of any surface. The result is a strong adhesion which is entirely due to van der Waals forces (Filipponi and Sutherland 2013). Researchers are experimenting with using gecko tape on the feet of climbing robots (Kunkel Microscopy).

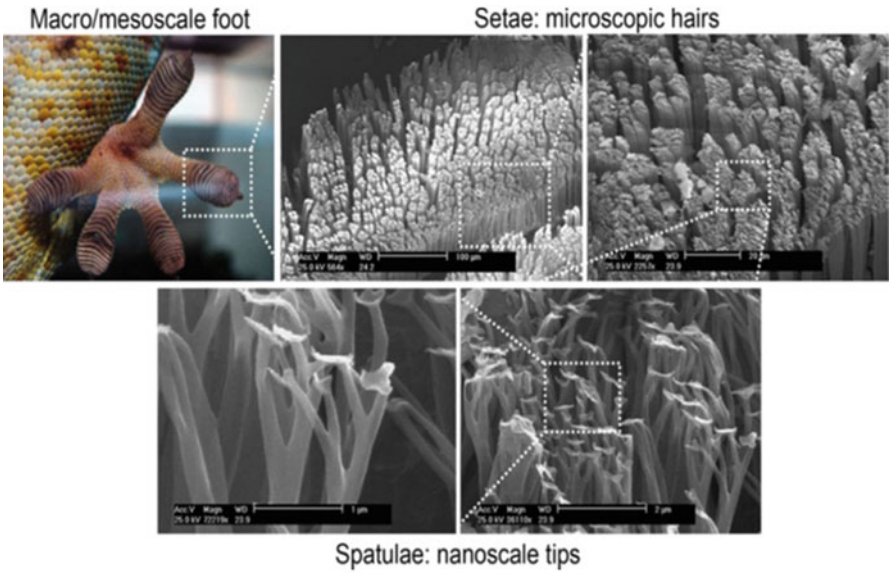


Fig. 1.4 Multi-scale combined hierarchical gecko foot hairs. As shown, millions of fine microscopic foot hairs (setae) on the attachment pads split into hundreds of nanoscale ends (spatulae) (Reproduced from Jeong and Suh 2009 Copyright (2009) Elsevier)

1.3 Nanomaterials

Nanomaterials and nano-manufactured goods represent areas of scientific research and industrial applications in full expansion (Gaffet 2011). Size reduction can lead to a whole range of new physico-chemical properties and a wealth of potential applications (Lehn 2006). These propertites strongly depends on size, shape, surface area and structure of particles. Nanomaterials can exist in single, fused, aggregated or agglomerated forms with spherical, tubular, and irregular shapes (Kumar and Kumbhat 2016). The major advantages of nanomaterial over bulk material include decrease in melting point and surface area, increase in dielectric constant and mechanical strength (Maddineni et al. 2015; Dasgupta et al. 2016; Ranjan et al. 2016; Pulimi and Subramanian 2016). In addition, size of nanoparticles enables them to absorb exceptionally on to other material (Dasgupta et al. 2015; Ranjan et al. 2015, 2016). Because of all these unique behaviour and properties, nanoparticles have wider application in textiles, clothing, and cosmetics, pharmaceutical, electronic and paint industry. Also, they are widely used for development of health care products and remediation of contaminated environment (Pulimi and Subramanian 2016).

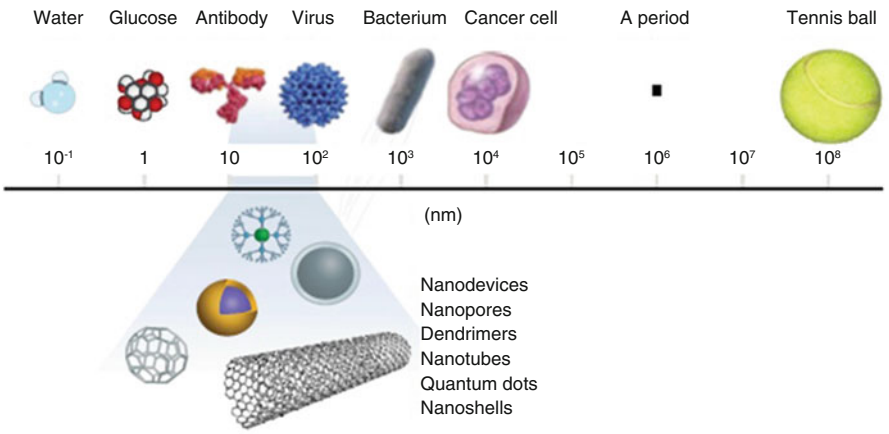


Fig. 1.5 A size comparison of nanoparticle with other larger-sized materials (Reproduced from Amin et al. 2014 Copyright (2014) Hindawi publishing corporation)

1.3.1 Definitions

Nanomaterials, once called by Paul Ehrlich as "Magic Bullets" (Kreuter 2007), are one of the most studied materials of the century that gave birth to a new branch of science known as nanotechnology (Nasir Khan et al. 2017). Nanomaterials are chemical substances or materials that are produced or used at a very small scale. In fact, the term material refers to an almost infinite number of constituents, collectivelly displaying an averaged statistical behavior. Therefore the behavior of nanomaterials is dominated by particular interface effects and exhibit characteristics affected by size and the limited number of constituents (Bahrami 2007).

But what is a nanometer? A nanometer is a thousandth of a micron and a micron is a thousandth of a millimeter, so a nanometer is a millionth of a millimeter or 10^{-9} m (Fig. 1.5). To date, there is no uniformly accepted definition of what in fact constitutes a 'nanomaterial'. To be classified as a nanomaterial, the material must be less than 100 nm in size in at least one direction. In 2008 and 2010, the International Standardization Organization has provided overarching technical definitions for nanotechnology-related terms: 'Nanomaterial' is defined as material with any external dimension in the nanoscale or having internal or surface structure in the nanoscale, with 'nanoscale' defined as the size range from approximately 1 to 100 nm (ISO/TS 27687 2008; ISO/TS 80004-1 2010). The European Commission has defined a nanomaterial as "Nanomaterial" means a natural, incidental, or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm (Official Journal of the European Union 2011). The definition, adopted in 2011, aims to provide a reference for determining whether a material should be considered as a nanomaterial for legislative and policy purposes in the European Union. This latter is

the only definition that includes natural or accidentally occurring nanoparticles, whereas all other definitions are restricted to 'intentionally produced, manufactured, or engineered nanomaterials (Cefic 2012).

The following microstructural features are considered to be the main factors on which the properties of the nanostructured materials are defined (Lemoine 2000):

1. Fine grain size and size distribution (less than 100 nm).
2. Presence of interfaces (grain boundaries, heterophase interfaces, free surface).
3. Interactions between constituent domains.

1.3.2 Classifications

A nanomaterial is a broad name given to all types of materials found at the nanoscale. Several names have been given to these new materials; nanostructured, nanometer-sized, ultrafine-grained . . .etc. They can be naturally occurring or chemically, mechanically, physically, or biologically synthesized with various structures (Saleh 2016). Nanomaterials can be classified based on different parameters including their origin (natural or anthropogenic); chemical composition (organic and inorganic); formation (biogenic, geogenic, anthropogenic, and atmospheric); size, shape, and characteristics; and applications in research and industry (Salah and Gupta 2016).

1.3.2.1 Classification of Nanomaterials Based on Their Origin

Nanomaterials can be of two types (Filipponi and Sutherland 2013):

1. Non-intentionally made nanomaterials, which refers to nano-sized particles or materials that belong naturally to the environment (e.g. proteins, viruses, nanoparticles produced during volcanic eruptions, . . .etc.) or that are produced by human activity without intention (e.g. nano-particles produced from diesel combustion).
2. Intentionally made nanomaterials, which refers to nanomaterials produced deliberately through a defined fabrication process.

1.3.2.2 Classification of Nanomaterials Based on Chemical Composition

On the basis of their chemical composition, they can be classified into various categories, Metal-based materials are mainly composed of metals (e.g, silver, gold, and copper nanoparticles). Metal oxide nanomaterials are made of metal and oxygen, such as titania, silica, and alumina. . .etc. (Saleh and Gupta 2016).

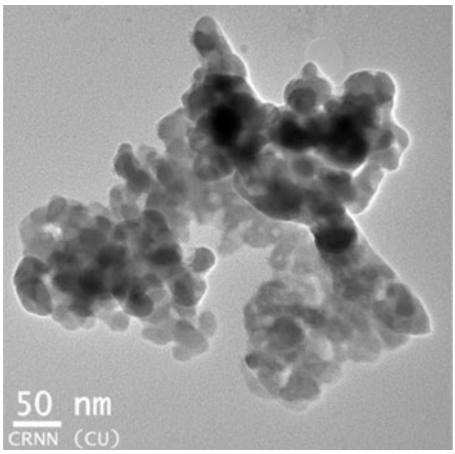


Fig. 1.6 Particle distribution of CdTe nanoparticles from TEM micrograph (Reproduced from Das et al. 2016 Copyright (2016) Elsevier)

1.3.2.3 Classification of Nanomaterials Based on Dimensionality

Nanomaterials with structural features at the nanoscale can be found in different forms. The materials of interest include metals, amorphous and crystalline alloys, semiconductors, oxides, nitride and carbide ceramics in the form of clusters, thin films, multilayers, and bulk nanocrystalline materials. According to this concept, nanomaterials can be classified as follows:

1.3.2.3.1 Zero-Dimensional (0-D)

They are crystalline clusters of a few hundred to a few thousand atoms with sizes of ranging from 2 to 100 nm (Wani 2015) (Fig. 1.6). Nanoparticles have been used in glass making since Mesopotamian and Roman times. However, it is only recently that nanoparticles and materials have been knowingly and deliberately manufactured (Royal Society of Chemistry 2011). In general, there are two broad types of nanoparticles: incidental and engineered. Incidental airborne nanoparticles (diameters less than 100 nm), also referred to as ultrafine particles, are common in indoor air. Engineered nanoparticles, on the other hand, are manufactured materials, and there are a growing number of concerns about the potential hazards associated with these particles (Jordan et al. 2014). Engineered nanoparticles cover a broad range of compounds, including both inorganic (elemental metals, metal oxides, metal salts, and aluminosilicates) and organic (fullerenes, micelle-like amphiphilic polyurethane particles, and dendrimers) compounds (Filella 2012).

Man-made/engineered nanoparticles have well-known applications in wide range of fields with the increasing demand in material science, electronic devices, biomedical research, food industry etc. Within the biomedicine industry, nanoparticle application has expanded to the areas of diagnostics and therapeutic purposes. The nano product demands in medicine and the pharmaceutical industry is expected to

rise by over 17% each year and at a much higher rate in the food industry (Jones and Grainger 2009, Jain et al. 2016). Metal nanoparticles are mainly used for drug delivery systems. These metals include silver AgNP, gold AuNP, titanium dioxide TiO_2 NP, and silica SiO_2.

Many techniques, including both top-down and bottom-up approaches, have been developed and applied for the synthesis of nanoparticles. The most traditional preparation method for nanoparticle synthesis is the sol-gel method (Brinker and Scherer 1990; Rajendran and Sen 2017). This technique allows the addition of all the dispersants in one synthetic step. In the spray-drying technique, a homogenized precursor solution and relevant additives are sprayed within a specially designed chamber at temperatures at or above the boiling point of the solvent leading to the quick formation of metallic nanoparticles. The ablation of a solid source with a pulsed laser can also yield nanoparticles, but the formation mechanism is at present not very clear. A micronsized aerosol droplet may also yield nanoparticles by evaporating a solute-containing droplet. Electrospray systems are often applied as droplet generators, as they produce very small droplets being quite monodisperse in comparison to other spray processes (Kruis 2001). Recently much attention was focused on green and biological synthesis of metallic nanoparticles using plants and microorganisms (Kumar et al. 2012, 2015; Kumar and Sen 2013).

Quantum Dots

Quantum dots or QDs, also known as nanocrystals, are another form of nanomaterial and are a specific type of semiconductor. They are 2–10 nm (10–50 atoms) in diameter (Salamon et al. 2010). The optical properties of nanocrystals are defined by their size and surface chemistry and they differ drastically from those of the bulk solids (Mohapatra et al. 2012). Indeed, QDs of the same element, are clusters of atoms less than tens of nanometers in size that emit different colors depending on their specific particle size (Kang 2010). In structure, quantum dots consist of a metalloid crystalline core and a 'cap' or 'shell' that shields the core. QDs cores can be formed from a variety of metal conductors such as semiconductors, noble metals and magnetic transition metals (Allsopp et al. 2007). The shells are also formed of a variety of materials. Therefore, not all quantum dots are alike and they cannot be considered to be a uniform group of substances (Hardman 2006). As quantum dots have such a small size they show different properties to bulk material. Hence the 'tunability', for example, sensitivity to different wavelengths of light, can be adjusted by the number of atoms or size of the quantum dot. They are typically made from CdSe, ZnS or CdTe compounds (Salamon et al. 2010). Quantum dots can be used for LEDs and solid-state lighting, displays, photovoltaics, transistors, quantum computing, medical imaging, biosensors, among many others (Material Matters 2012).

Fullerene

The first 0D graphite allotrope molecule to be discovered, and the family's namesake, buckminsterfullerene (C_{60}) (Fig. 1.7), was prepared in 1985 by Richard Smalley, Robert Curl, James Heath, Sean O'Brien, and Harold Kroto at Rice University. They named the molecule Buckminsterfullerene in honor of the

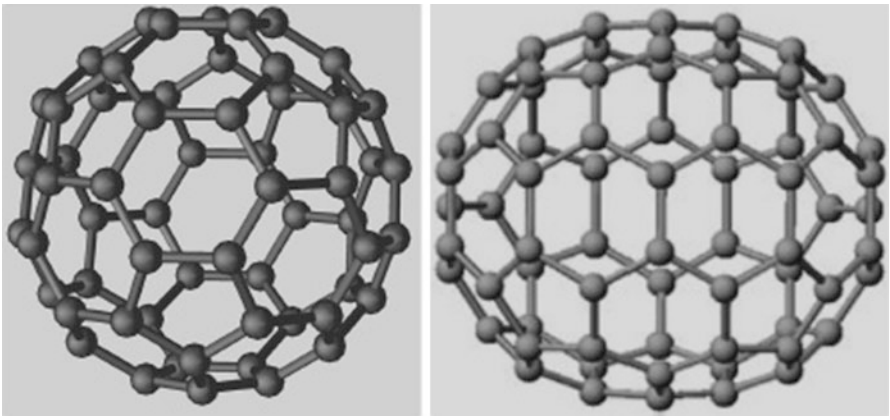


Fig. 1.7 The structures of C_{60} and C_{70} molecules (Reproduced from Wang 2015 Copyright (2015) Elsevier)

American architect R. Buckminster Fuller who introduced geodesic structures in architecture (Kroto et al. 1985). Its existance had been predicted before, in 1970, by the Japanese theoretician Eiji Ozawa (Ozawa et al. 1993). Fullerene or C_{60} is soccer – ball – shaped molecule, with a diameter around 1 nm, consisting of 20 hexagonal and 12 pentagonal rings as the basis of an icosahedral symmetry closed cage structure. In fullerenes, all the carbon atoms are sp^2 hybridized but they are not arranged on a plane like in graphite (Connell 2006; Meyyappan 2005). The unique morphology of these nanostructures possess large surface area to volume ratio and is suitable for a wide variety of applications (Cherusseri and Kar 2015). More than thirty higher fullerenes including C_{70}, C_{76}, C_{78}, C_{84}, C_{90} and C_{94} and their derivatives are synthesized along with C_{60} (Diederich et al. 1991).

1.3.2.3.2 One-Dimensional (1-D)

The second class of nanoscale materials, referred to as 1-D nanostructures, is reserved for those materials that have nanoscale dimensions that are equivalent in all but one direction (Balaz 2008). They are generally well understood and technologically advanced (The Royal Society 2003). One-dimensional nanoscale materials, such as nanowires and nanofibers, are extremely attractive as main elements for the first action of the sensors (Fig. 1.8). These nanoscale materials offer significant advantage over bulk or thin-film planar devices (Abdelsalam and Abdelaziz 2014). Nanofibers are slightly larger in diameter than the typical nanomaterial definition, though still invisible to the naked-eye. Their size ranges between 50 and 300 nm in diameter and are generally produced by electro spinning in the case of inorganic nanofibers or catalytic synthesis for carbon nanotubes. Nanofibers can be electrostatically aligned and biochemically aligned (Kumar and Kumbhat 2016). Similar to nanofibers are nanowires. In these systems, one dimension exceeds by an order of magnitude the

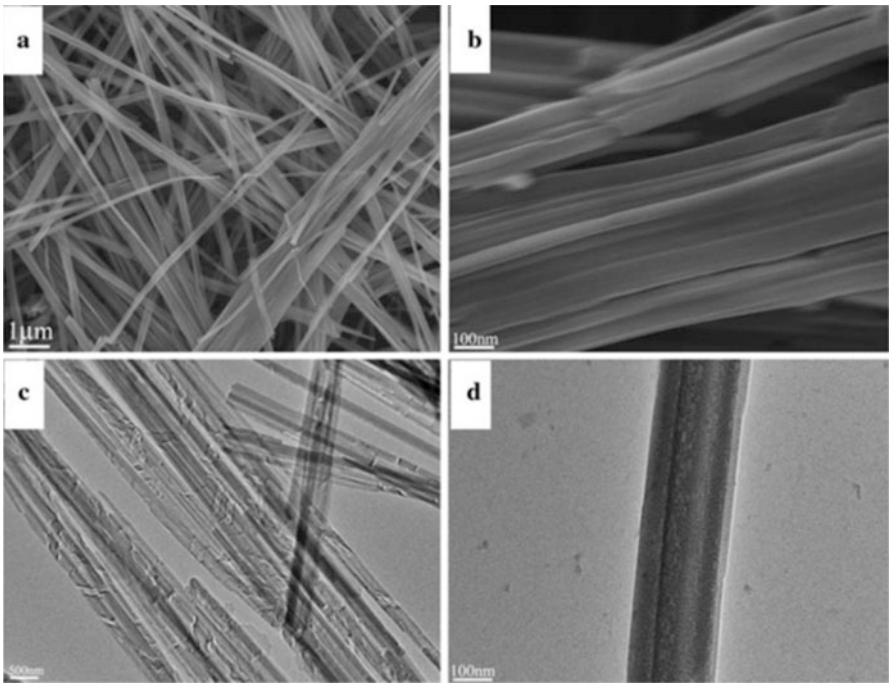


Fig. 1.8 SEM images (**a** and **b**) and TEM images (**c** and **d**) of FeC_2O_4 nanowires (Reproduced from Du et al. 2010 Copyright (2010) Springer International Publishing)

other two dimensions, which are in the nano-range (Gubin 2009). This class of nanomaterials can be potentially used in nanophotonics, laser, nanoelectronics, solar cells, resonators and high sensitivity sensors (Chellammal 2013).

Carbon Nanotubes

The discovery of carbon nanotubes is most often attributed to Sumio Iijima and his 1991 publication in Nature (Iijima 1991). Carbon nanotubes (CNTs, also called buckytubes in earlier days) are elongated cylindrical fullerenes with diameters of nanometers and lengths of microns even millimeters (Ren et al. 2013). There are two basic types of CNTs: single-wall carbon nanotubes, SWCNTs, which are the fundamental cylindrical structure and multi-wall carbon nanotubes, MWCNTs, which are made of coaxial cylinders (Fig. 1.9), having interlayer spacing close to that of the interlayer distance in graphite (0.34 nm) (Ajayan 2000). The walls of these tubes are constructed of a hexagonal lattice of carbon atoms and capped by fullerene-like structures (Ong et al. 2010).

The electrical conductivity of SWNTs may vary from metallic to semiconducting, depending on the way a graphene sheet is folded. For metallic SWNTs, the electrical conductance may exceed silver or copper by three orders of magnitude. Another electronic application for CNTs is for next-generation field-effect transistor, FET

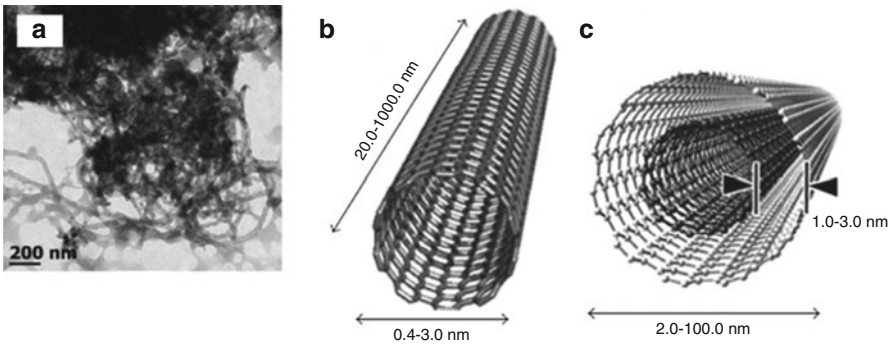


Fig. 1.9 (**a**) TEM micrograph of SWCNT (Reproduced from De la Luz-Asunción et al. 2015 Hindawi publishing corporation) (**b**) single walled carbon nanotube and (**c**) multiwalled carbon nanotube (Reproduced from Rastogi et al. 2014 Copyright (2014) Hindawi publishing corporation)

design. In addition to the above tunable conductive properties, CNTs are the strongest and stiffest materials known to date (Fahlman 2007).

1.3.2.3.3 Two-Dimensional (2-D)

They are the group of two-dimensional objects (2-D) in which two dimensions are an order of magnitude greater than the third dimension, which is in the nanometer range (Gubin 2009). 2-D nanomaterials exhibit platelike shapes (Thomas et al. 2014). They are moderately understood in terms of properties, but manufacture is much less advanced. These include: surface coatings, thin films, interfaces. . .etc. They are applied to structural bulk materials in order to improve the desired properties of the surface, such as wear resistance, friction, corrosion resistance and keeping the bulk properties of the material unchanged (Koch et al. 2007). Nanofilms are thin layers of material spanning from a fraction of a nanometer to several micrometers in thickness.

Graphene

Graphene is the most recent member of the multidimensional carbon-nanomaterial family, starting with fullerenes as a 0D material, SWCNTs as 1D nanomaterials, and ending with graphite as a 3D material (Du et al. 2014). Graphene was discovered in 2004 by Andre Geim and Konstatin Novoselov. They obtain graphene sheet by splitting graphite crystal into increasingly thinner units until individual atomic planes were reached. This remarkable contribution was felicitated by Noble prize in physics on 2010 and led to a sudden increase of research interest in graphene (Enoki et al. 2009; Liang et al. 2009). Graphene consists of a layer with π-conjugated structure of 6-atom rings which can be conceptually viewed as a planar aromatic macromolecule (Liu et al. 2013). The thickness of the graphene layer has been reported to be between 0.35 and 1.0 nm (Singh et al. 2011) (Fig. 1.10). Graphene can be readily doped with heteroatoms (e.g., nitrogen, boron) (Qu et al. 2010) or

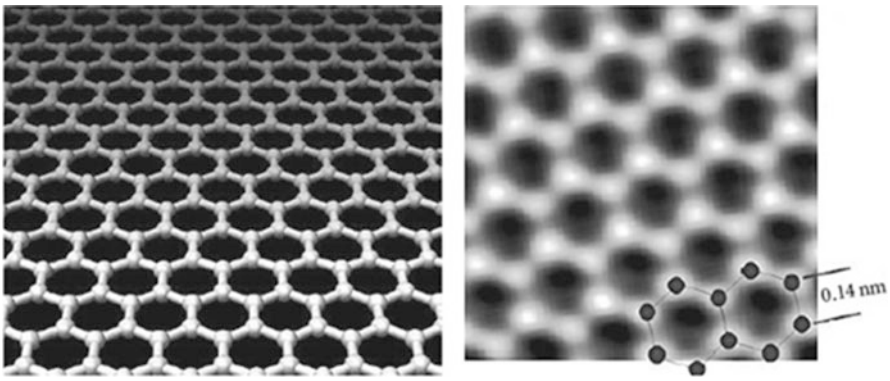


Fig. 1.10 The two-dimensional honeycomb structure of carbon atoms in graphene along with the high-resolution transmission electron microscopic, TEM image (Reproduced from Sur 2012 Copyright (2012) Hindawi publishing corporation)

modified with organic molecules, polymers, or inorganic components (Stankovich et al. 2006; Liu et al. 2012a, b). The single layer graphene, bi-layer graphene, multilayer graphene, graphene oxide or GO, reduced graphene oxide or rGO and chemically modified graphene are widely used graphene family nanomaterials (Zhang et al. 2016) (Fig. 1.11).

1.3.2.3.4 Three-Dimensional (3-D)

Three-dimensional (3-D) structures are materials having three arbitrary dimensions beyond the nanoscale (Saleh and Gupta 2016). However, these materials possess a nanocrystalline structure or involve the presence of features at the nanoscale (e.g. magnetic tunnel junctions, heterostructures, . . .etc.) (Law et al. 2004). They can be composed of a multiple arrangement of nanosize crystals, most typically in different orientations. 3-D nanosystems provide the great challenges in terms of both properties and controlled manufacture (Bahrami 2007).

Nanocomposites

The term nanocomposites is in the broadest sense referring to every type of material with fillers in the nanometer size range at least in one dimension (Roy et al. 1986). These are high performance materials that exhibit unusual property combinations and unique design possibilities and are thought of as the materials of the twenty-first century (Anandhan and Bandyopadhyay 2011). The bulk properties of nanocomposites are highly dependent on the properties of the filler, the host matrix, and the interfacial properties. The interface can be tailored using techniques such as

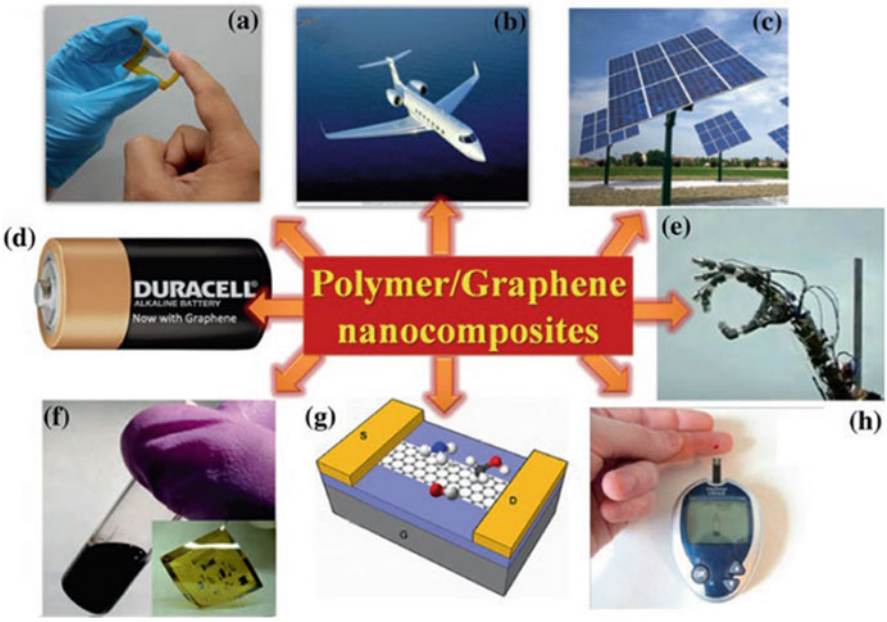


Fig. 1.11 Graphene uses and benefits: (**a**) Flexible transparent electronics, touch screen. (**b**) Aeronautical field. (**c**) Solar panels. (**d**) Batteries. (**e**) Actuators. (**f**) Conductive ink, flexible electrodes. (**g**) Gas sensors. (**h**) Biosensors (Reproduced from Ponnamma and Sadasivuni 2015 Copyright (2015) Springer International Publishing)

chemical functionalization and core-shell structuring to achieve desired properties (Irwin et al. 2010). There are three major classification of nanocomposites:

1. Ceramic matrix nanocomposites.
2. Metal matrix nanocomposites.
3. Polymer matrix nanocomposites.

1.3.3 Structure of Nanomaterials

The understanding of changes of nanomaterials properties requires a good knowledge of each of the constituents. The microstructural features of importance include: (a) grain size, distribution, and morphology, (b) the nature and morphology of grain boundaries and interphase interfaces, (c) the perfection and nature of intragrain defects, (d) composition profiles across grains and interfaces, and (e) identification of residual trapped species from processing (Suryanarayana 1994).

Two types of atoms can be distinguished in nanomaterials: crystal atoms with nearest-neighbor configuration corresponding to the lattice and the boundary atoms with a variety of interatomic spacings, differing from boundary to boundary

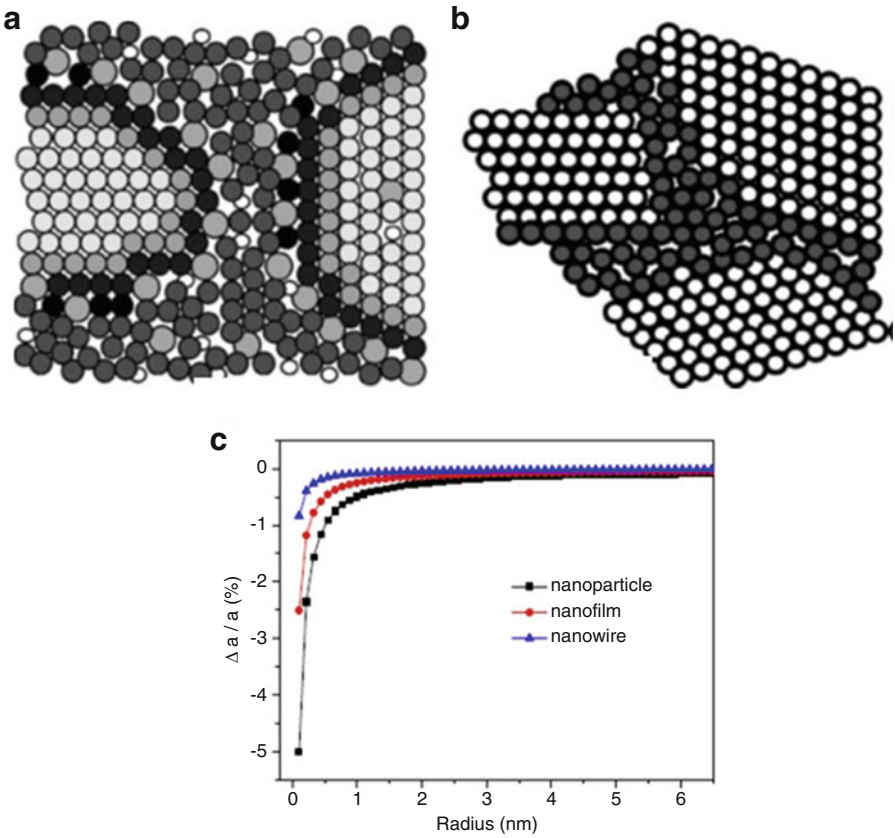


Fig. 1.12 2D schematic representation of the atomic structure in (**a**) nanocrystalline alloys, (**b**) nanostructured powders (Reproduced from Grenèche 2002 Copyright (2002) Springer Netherlands), (**c**) Variation of lattice distortion rates (Δa/a) with the size for a Au nanoparticle, nanowire, and nanofilm, respectively (Reproduced from Yu et al. 2015 Copyright (2015) Elsevier)

(Suryanarayana and Koch 2000) (Fig. 1.12a, b). It has been recently reported that the lattice distortion rates of nanoscale crystals and the nanosize exhibit an inverse proportional relationship when considering the atomic bond energy of a nanoscale crystal particle (Yu et al. 2015).

Nanomaterials are inherently heterogeneous on a nanometer scale consisting of nanometer-sized building blocks separated by boundary regions (Gleiter 2000). A nanocrystalline metal contains typically a high number of interfaces with random orientation relationships, and consequently, a substantial fraction of the atoms lies in the interfaces (Li 2000). As example, in a polycrystalline sample with 5 nm grain size, typically a fraction of 30% of all atoms are found within one lattice spacing, or less from a grain boundary of average thickness between 0.5 and 1 nm. If the average grain size is 10 nm, the above fraction falls as low as about 15% and for 100 nm grain size it falls to about 1% (Ossi 2006).

Grain boundary, GB, is the junction of two crystalline particles. They are characterized by the relatively large free volume, the great number of dangling or weakened bonds, and the extended GB width of ~1 nm. Therefore, the general GBs have the energy of near half of surface energy and greater than of special one. It is important to mention that the structure of grain boundaries in metallic systems is controversially debated: Gleiter assumed that nanocrystalline materials consist of perfect crystalline grains and completely disordered grain boundaries with low density (Gleiter 1993). Such a concept of a "gaslike" structure (Zhou et al. 1987; Grenèche 2002). The total intercrystalline region consists of grain boundaries, triple junctions, i.e., intersection lines of three or more adjoining crystals, and other interfaces (Suryanarayana 2004).

In general, grain boundaries in nanostructured materials have specific structural features, which are responsible for their specific behavior and properties (Gogotsi 2006). It has been reported that the structural distortions and symmetry breaking at the grain boundaries modify the nature of magnetic exchange interactions and induce a surface anisotropy and magnetostriction. Consequently, the ground-state magnetic arrangement of atoms located at the surface or in the interfacial region has to differ from that observed in the corresponding bulk material (Grenèche and Ślawska-Waniewska 2000).

1.4 Properties: The Physics at the Nanoscale

In fact, the fundamental properties of matter change at the nanoscale and nanomaterials manifested fascinating and useful properties. The physical and chemical properties of nanoparticles can be quite different from those of larger particles of the same substance. They are closer in size to single atoms and molecules than to bulk materials, and to explain their behavior, it is necessary to use quantum mechanics (Kumar and Kumbhat 2016). Quantum mechanics is a scientific model that was developed for describing the motion and energy of atoms and electrons. Altered properties can include but are not limited to colour, solubility, material strength, electrical conductivity, magnetic behavior, mobility (within the environment and within the human body), chemical reactivity and biological activity (Blackwelder 2007) (Fig. 1.13).

1.4.1 Confinement Effect

Quantum size effects are related to the "dimensionality" of a system in the nanometer range (Richards and Bönnemann 2005). The quantum effects are a consequence of quantum mechanics and of the particle wave duality. These arise in the case where the size of the system is commensurable with the de-Brogli wavelengths of the electrons, phonons or excitons propagating in them (Naseri and Saion 2012). Indeed,

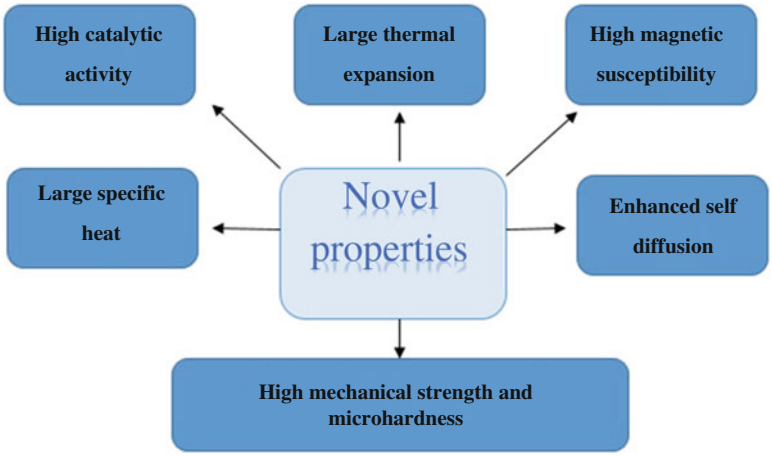


Fig. 1.13 Size-dependent properties

electrons behave at the same time as particles and as waves. As waves they explore the entire space in which they are free to move. The nanograin behaves like a kind of box, within which a specific property may or may not exist. Below a certain critical size, characteristics of the property directly and strictly depend on the grain size. This is called the confinement effect (Rezaie et al. 2013). Quantum size effects play a crucial role in determining the physical and chemical properties, e.g. electronic structure and charge-transport mechanisms. Optical and electron-tunnelling spectroscopies are essential for studying these systems (Van Keer 2015). Quantum tunneling is a nanoscopic phenomenon in which a particle violates the principles of classical mechanics by penetrating a potential barrier or impedance higher than the kinetic energy of the particle (Wikipedia 2017).

1.4.2 Surface Effects

1.4.2.1 The Fraction of Atoms at the Surface

Atoms at surfaces have fewer neighbours than atoms in the bulk. Because of this lower coordination and unsatisfied bonds, surface atoms are less stabilised than bulk atoms (Roduner 2006). The smaller a particle the larger the fraction of atoms at the surface, and the higher the average binding energy per atom. The surface-to-volume ratio scales with the inverse size, and therefore there are numerous properties which obey the same scaling law. Edge and corner atoms have an even lower coordination and bind foreign atoms and molecules more tightly. The coordination number is also limited in narrow pores (Lokhande and Pathak 2014).

1.4.2.2 Surface Structure Changes

The effect of size reduction is not without consequences for the atomic arrangement and the physical properties of materials. Actually, if the structure of the outer region of a particle is affected over the range of the particle size, a surface layer cannot be defined accurately (De Rogatis et al. 2008). It is known that the composition or the crystal structure is modified at the free surface of material. The volume of this surface layer becomes significant in nanoscale materials. The surface layer of nanoparticles in that case can be defined as the outer region where the composition or the crystal structure are different from those of the particle core (Wang et al. 2008). The clean surface of crystalline materials relaxes and reconstructs in order to minimize the total Gibbs energy, given the new chemical environment of the semi-infinite crystal (Pigozzi 2006).

1.4.2.3 Increasing of Surface Energy and Tension

Energy is a key physical characteristic because a knowledge of which give us a possibility to calculate a variety of derivative characteristics. Having the extended surface, the nanocrystals have therefore extended external free surface energy, Gibbs energy (Pokropivny et al. 2007):

$$\Delta G_s = \gamma S_f$$

where γ is a specific surface energy (the energy per surface unit), or a specific work to create the free surface area, or a specific tension. The surface energy gradually becomes the dominating contributor to the total energy of the material. Such a property will evolve monotonically with size and can be treated within the framework of thermodynamics. Among them are the melting and other phase transition temperatures (Rezaie et al. 2013).

1.4.3 Thermal Properties

Thermodynamics of nanosystems differs from the thermodynamics of macroscopic systems, where the number of particles tends to infinity (Labastie and Calvo 2007). As previously reported increasing of surface energy will evolve monotonically with size and can be treated within the framework of thermodynamics (Nièpce and Pizzagalli 2007). Among them are the melting and other phase transition temperatures. Figure 1.14 illustrates the general experimental variation of melting point of GaN spherical nanoparticles against the size of the particles (Antoniammal and Arivuoli 2012). Its physical origin is the increase of surface energy, the increase of amplitude of atomic vibrations, and the additional surface growth of thermal vibration energy in the result (Pokropivny et al. 2007). It has been reported that the

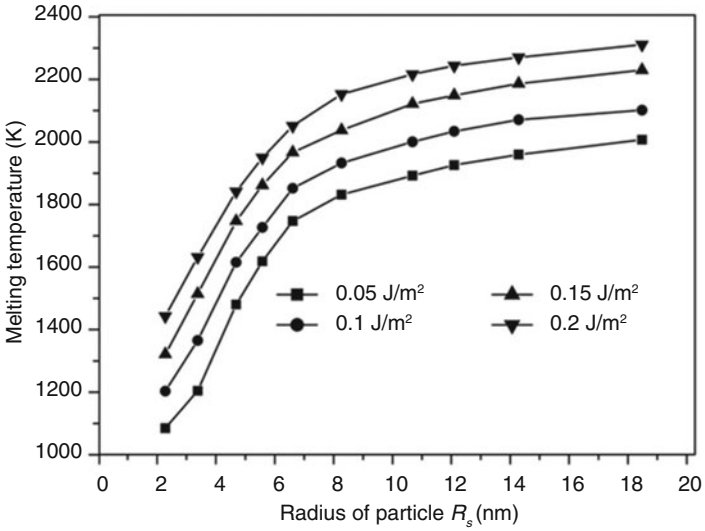


Fig. 1.14 Variation of melting point of GaN spherical nanoparticles against the size of the particles (Reproduced from Antoniammal and Arivuoli 2012 Copyright (2012) Hindawi publishing corporation)

specific heat increased with the decrease in particle size, whereas the melting entropy and enthalpy decreased as the particle size decreases (Singh et al. 2017).

The use of nanofluid to enhance the thermal transport is a promising application of the thermal properties of nanomaterials (Murty et al. 2013). Nanofluids are generally referred to the solid-liquid composite materials, which consist of nanomaterials of size in the range 1–100 nm suspended in a liquid (Obaid et al. 2013). Nanofluids hold increasing attentions in both research and practical applications due to their greatly enhanced thermal properties compared to their base fluids. Many type of nanomaterials can be used in nanofluids including nanoparticles of oxides, nitrides, metals, metal carbides, and nanofibers such as single wall and multi wall carbon nanotubes, which can be dispersed into a variety of base liquid depending on the possible applications, such as water, ethylene glycol, and oils (Gorji and Ranjbar 2017).

The most important features of nanofluids are the significant increase of thermal conductivity compared with liquids without nanomaterials, which have been proved by many experimental works (Han 2008) (Fig. 1.15). Nanofluidics based devices will enable the development of real-time, minimally invasive medical diagnostic systems to monitor astronaut health and aid in diagnosing and treating illness (Berger 2012).

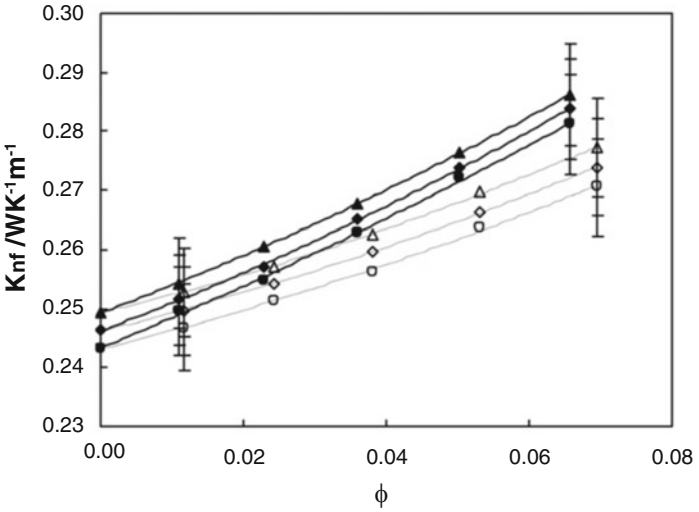


Fig. 1.15 Experimental thermal conductivity of iron oxide nanofluids in EG vs volume fraction concentration at different temperatures: (○, ●) 283.15 K; (◊, ⍰) 303.15 K, and (□, ■), 323.15 K. White symbols represents Fe_3O_4/EG and black symbols Fe_2O_3/EG nanofluids (Reproduced from Pastoriza-Gallego et al. 2011 Copyright (2011) American Institute of Physics)

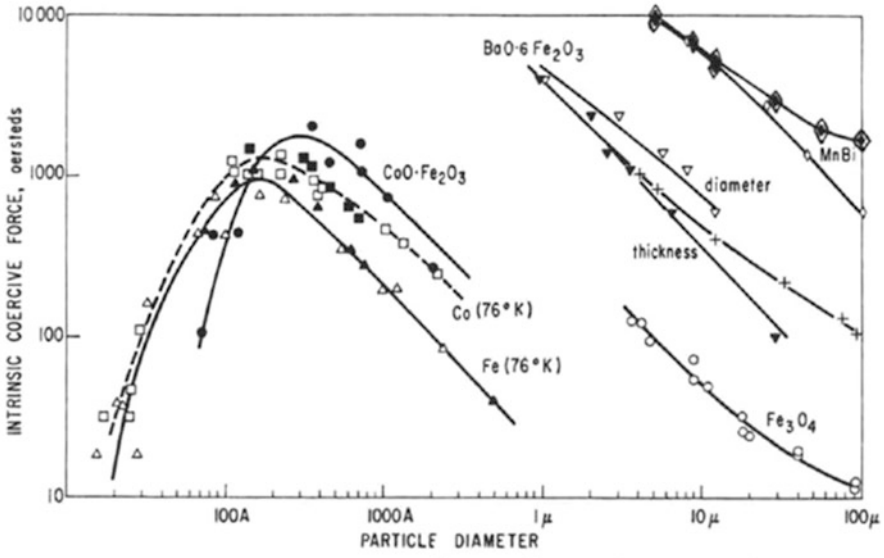
1.4.4 Optical Properties

The optical properties are connected with electronic structure, a change in zone structure leads to a change in absorption and luminescence spectra. Their characteristics such as spectral width and position, and sensitivity to light polarization, depend not only on the intrinsic properties of the nano-objects (e.g., composition, structure, size, shape), but also on their environment (Rezaie et al. 2013).

The appearance of color is caused by the partial absorption of light by electrons in that material; the unabsorbed part of light remains visibe. On most smoot metals surfaces, light is entirely reflected by the very high density of electrons; this is why the surfaces of slabs of metals have mirror-like appearance. In contrast, small particles absorb some of light, leading to the appearance of color (Kaur 2010). As example, bulk gold appears yellow in color however nanosized gold appears red in color. The particles are so small that electrons are not free to move about as in bulk gold, because this movement is restricted, the particles react differently with light. In 1857, Faraday reported that colloidal Au nanoparticles can be prepared by the reduction of gold salts with reagents including organic compounds or phosphorus (Faraday 1857). Faraday correlated the red color of Au colloid with the small size of the Au particles in metallic form. He concluded that gold is present in solution in a "finely divided metallic state" smaller than the wavelength of visible light that shows colors different from the original color (Niu and Lu 2015).

1.4.5 Magnetic Properties

Nanomagnetism is a vivid and highly interesting topic of modern solid state magnetism and nanotechnology (Petracic 2010). It is of paramount scientific interest and high technological relevance. Ferromagnetic nanomaterials have potential advantages over existing materials in numerous applications in soft magnets, hard magnets, magnetic recording,. . .etc. (Schwarz et al. 2004). It is well established, that the coercivity of magnetic materials has a striking dependence on their size (Fig. 1.16). It increases with the reduction of particle size in the nanometer range going through a maximum at the single domain size, and then decreases again for very small particles because of thermal effects and becomes zero at the superparamagnetic particle size. Iron, which is a soft magnetic material with coercivity about 20 Oe at room temperature, could be made "hard" with a coercivity of 540 Oe (Schwarz et al. 2004). Another example is the remarkable phenomenon of giant magnetoresistance (GMR) of magnetic multilayers that has been exploited to increase the capacity of hard discs by over a factor of a hundred in a small number of years (Mills and Bland 2006).



All measured at room temperature except Co and Fe. MnBí, ◇ Guillaud [C. Guillaud, thesis, University of Strasbourg (1943)], ◆ Shur [Ia. S. Shur, Trudy Inst. Fiz. Metall. Akad. Nauk S.S.S.R. **20**, 111 (1958)]; $BaO{\cdot}6Fe_2O_3$, ▽ ▼ Sixtus *et al.* [K. J. Sixtus, K. J. Kronenberg, and R. K. Tenzer, J. Appl. Phys. **27**, 1051 (1956)], + Brockman [F. G. Brockman, Eighth Progress Report, Signal Corps Project No. 32-2005D (1955)]; Fe_3O_4, ○ Gottschalk, see footnote 5; $CoO{\cdot}Fe_2O_3$, ● Berkowitz and Schuele [A. Berkowitz and W. Schuele, J. Appl. Phys. **30**, 134S (1959)]; Co, ■ Meiklejohn [W. H. Meiklejohn, Revs. Modern Phys. **25**, 302 (1953)], □ Luborsky [F. E. Luborsky (to be published)]; Fe, ▲ Meiklejohn [W. H. Meiklejohn, Revs. Modern Phys. **25**, 302 (1953)], △ Luborsky and Paine [F. E. Luborsky and T. O. Paine, J. Appl. Phys. **31**, 68S (1960) and an article to be published.

Fig. 1.16 Experimental relation between coercivity and diameter for particles deriving their coercive force principally from crystal anisotropy energy (Reproduced from Lubrosky 1961 Copyright (1961) American Institute of Physics)

1.4.5.1 Nanocrystalline Soft Magnetic Alloys

Soft magnetic nanocrystalline alloys have been a field of intensive research during the recent past decades. There are two main families of the soft magnetic nanocrystalline alloys: the FINEMET (Yoshizawa et al. 1988) and the NANOPERM (Suzuki et al. 1991). Generally, the microstructure of these systems consists of ferromagnetic crystals with grain sizes in the nanometer range, embedded in a ferromagnetic amorphous matrix. In an effort to extend the outstanding soft magnetic properties of these materials to higher temperatures, the HITPERM-type alloys have been developed (Willard et al. 1998; Franco et al. 2002).

1.4.5.2 Superparamagnetism

Magnetic nanoparticles behave very differently from bulk or thin film systems. When the size of the particles is reduced below the single domain limit (<15 nm for the common materials), they exhibit superparamagnetism behavior at room temperature (Tartaj et al. 2003). In fact, the first modelization of a nanometered-size particle was done by Kittel in 1946 (Kittel 1946). Bulky sized particles of magnetic materials display ferromagnetic properties due to their multi-domain structure of particles. Such materials are said to be ferromagnetic because they have magnetic properties regardless of the existing of an applied magnetic field (Shi 2006).

Superparamagnetism describes the state of a single-domain-sized grain when thermal energy is sufficient to overcome barriers to a reversal of magnetization. When the energy barriers are large with respect to thermal energy, the magnetization is "blocked" and the probability of spontaneous reversal becomes negligible. When the barriers are relatively low, thermal excitations can result in reversal of the magnetization over very short time scales, and the grain is in a superparamagnetic state (Bowles et al. 2009). This relaxation process was first proposed by Neel (1949) and further developed by Brown (1963) and Bedanta and Kleemann (2009). Superparamagnetic nanoparticles have a high potential as carriers for oligonucleotides and biomolecules, liver enzymes, antibodies and proteins in different life science applications such as magnetic cells separation, nucleic acid separation and magnetic resonance imaging (Rudershausen et al. 2002) (Fig. 1.17).

1.4.5.3 Magnetic Fluids: Ferrofluids

Ferrofluid is the only liquid that is magnetic, all other magnetic materials are solid. When there's no magnet around, ferrofluid is a thick fluid. But when a magnetic field is nearby, ferrofluid stiffens up and behaves like a solid (Kunkel Microscopy). Magnetic fluid is a stable colloidal system formed by the nanoscale (10 nm or less) strong magnetic particles highly dispersed in a liquid (Scherer and Neto

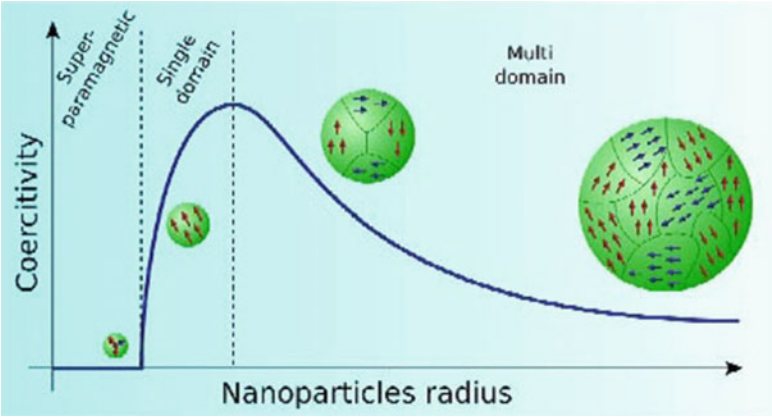


Fig. 1.17 Schematic illustration of the coercivity-size relations of small particles (Reproduced from Akbarzadeh et al. 2012 Copyright (2012) Springer)

2005). Ferrofluid was invented by NASA in the 1960s as a way to control liquids in space (Andrews et al. 2010). Nowadays, it's used in loudspeakers to dampen vibrations, in car brakes, and in the rotary seals of computer hard drives. In the future, ferrofluid might be used to carry medications to specific spots in the body (Kunkel Microscopy).

1.5 Nanomaterials Synthesis Procedures

Nanostructure fabrication is a formidable challenge and the subject of many studies (Rosei 2004). It is an interdisciplinary field covering physics, chemistry, biology, materials science and engineering. The interaction between scientists with different disciplines will undoubtedly lead to the production of novel materials with tailored properties. The success of nanomanufacturing depends on the strong cooperation between academia and industry in order to be informed about current needs and future challenges, to design products directly transferred into the industrial sector (Charitidis et al. 2014). The synthesis of nanomaterials and nanodevices can accommodate solid, liquid, and/or gaseous precursor materials. Nanoscale manufacturing involves one of two approaches: top-down or bottom-up (Fig. 1.18). However, some authors suggested virtual fabrication (computer simulations), as a third approach (Bader et al. 2007).

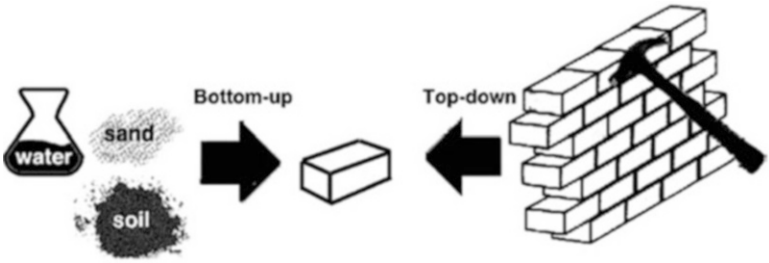


Fig. 1.18 Illustration of the concepts of bottom-up and top-down methods (Reproduced from Pacioni et al. 2015 Copyright (2015) Springer)

1.5.1 Bottom-Up Procedures

Bottom-up methods mimic nature by starting at the atomic or molecular level and building up through nucleation and/or growth from liquid, solid, or gas precursors by chemical reactions or physical processes (Dhingra et al. 2010). More typically, large numbers of atoms, molecules or particles are used or created by chemical synthesis, and then arranged through naturally occurring processes into a desired structure (Royal society 2004). The wide variety of approaches towards achieving this goal can be split into three categories: chemical synthesis, self-assembly, and positional assembly (Royal society 2004). Colloidal dispersions such as microemulsions are a good example of the bottom-up concept of nanomaterials synthesis (Yaya et al. 2012). Though the bottom-up approach is in its early development phase, it promises sweeping changes to current methods of production (Dhingra et al. 2010).

1.5.2 Top-Down Procedures

An area of nanotechnology that has been evolving for the last 40 years is the technique of micro- and nano-lithography and etching. These techniques are the source of the great microelectronics revolution, sometimes called "top-down" nanotechnology (Cornell and Heally 2005). The top-down approach starts with microsystems and miniaturizes them, through carving or grinding methods, such as lithography, etching, or milling (Upreti et al. 2015). This approach generally relies on physical processes, or a combination of physical and/or chemical, electrical or thermal processes for their production (Yaya et al. 2012). This is the most well established of all forms of nanotechnology but it is generally believed that top-down methods generate a lot more waste (Dhingra et al. 2010).

1.6 Applications

Nanoscale science and technology are fueling a revolution in manufacturing and production, creating new materials and novel processes (Murday et al. 2010). This miniaturization of devices and systems to sizes of the elementary units below 1 μm has revolutionized our daily life (Ihn 2010). Therefore, nanomaterials with such excellent properties have been extensively investigated in a wide range of applications and all fields below, are expected to undergo explosive developments.

1.6.1 Energy

The world energy demand is continuously growing and according to the forecasts of the International Energ Agency, it is expected to rise by approx. 50% until 2030. Currently, over 80% of the primary energy demand is covered by fossil fuels (Rhiel 2008). Therefore, there is an urgent need for energy resources alternative to fossil fuels. Such challenges have resulted in increasing attention being paid by policymakers, researchers, and corporations to new technologies, and the application of technologies in new ways (OECD 2013). Of these, renewable energy sources (solar, wind, geothermal,. . .etc.) are an opinion. However, tremendous technology breakthrough will need to occur in the next years to make the conversion of these energy resources efficient and economically viable option (Filipponi and Sutherland 2013). Recognizing the rapid progress in nanoscience and technology, it is timely to touch the nanoenergy theme (Lund 2009). Nanotechnology will offer huge opportunities for applications in the energy field and for the development of clean energy systems, which will be very important in the light of the enormous challenges ahead with the climate change and energy (Lund 2009). The most advanced nanotechnology projects related to energy are: storage, conversion, manufacturing improvements by reducing materials and process rates, energy saving and enhanced renewable energy sources (Arivalagan et al. 2011).

While it is critical to develop new renewable energy generation technologies such a solar, it will remain important to make the best use of the limited resources currently available (Brinker and Ginger 2011). Solid state lighting, SSL, encompasses technology to make lighting technologies more energy efficient, longer lasting and cheaper (Allsopp et al. 2007). The use of semiconductor-based light emitting diodes, LEDs, for general illumination is a rapidly developing technology that offers the potential of immense energy savings (Alivisatos et al. 2005). Quantum dots are nanoscale semiconductor particles characterised by emitting a specific colour based on the size of the nanoparticle. Light emission from a QD is monochromatic, therefore it is very pure. As a consequence, their use in displays would lead to images of exceptional quality. The most exciting property of QD-LEDs, however, is that they use much less power than the currently used LCDs (Filipponi

Fig. 1.19 (**a**) 2-mm-thick OLED monitor and (**b**) Concept for a future OLED screen, which could be rolled up like a scroll inside of a pen-sized device when not in use (Reproduced from Forrest 2004 Copyright (2004) Nature Publishing Group)

and Sutherland 2013) (Fig. 1.19). LEDs use less energy. Colored LEDs currently used in many applications, including display signs and trafic lights (Weiss Talk).

A fuel cell is a small power generating system used for various applications, including mobile, stationary, and portable applications (Fig. 1.20) (Abdelsalam and Abdelaziz 2014). It is a device used for electricity generation that is composed of electrodes that convert the energy of a chemical reaction directly into electrical energy, heat, and water. It produces electricity from an external supply of fuel and oxygen, rather than the limited internal energy storage capacity of the battery (Elcock 2007). The main primary obstacle is the high cost of fabrication. Nanotechnology is expected to contribute through miniaturization of all components (especially diminishing the thickness of the various laminar elements), simultaneously reducing inefficiencies and costs, and through realizing better catalysts for oxygen reduction and fuel oxidation. A particular priority is developing fuel cells able to use feedstocks other than hydrogen (Ramsden 2016). Carbon nanomaterials, including fullerenes, nanotubes and graphene as well as their N-doped derivatives, have been studied for a wide range of applications in energy conversion systems, such as fuel cells (Dai et al. 2012).

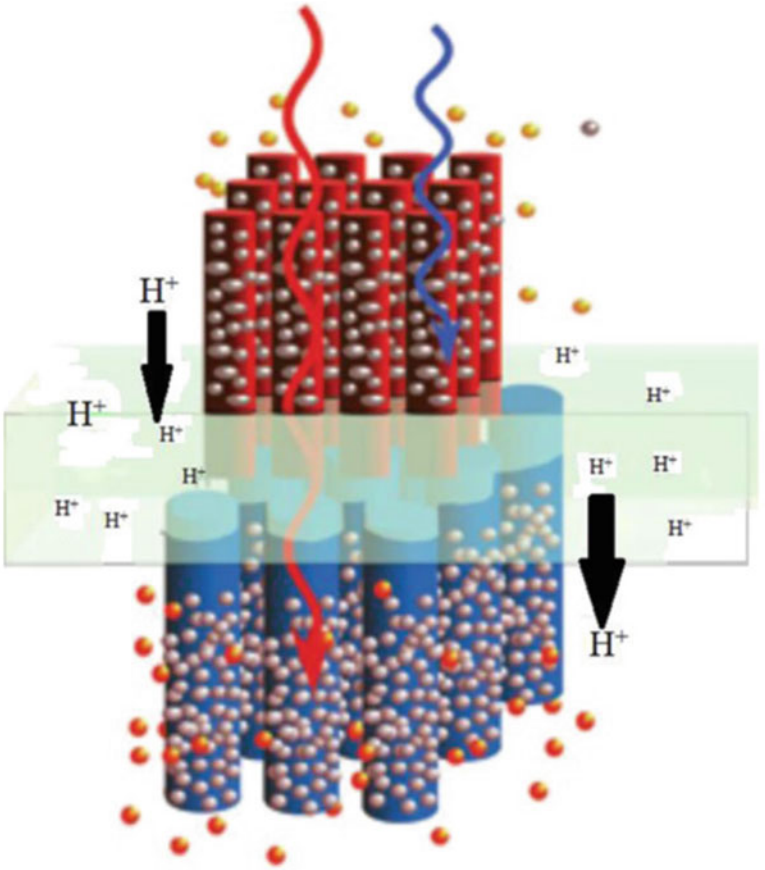


Fig. 1.20 A solar fuel cell (Reproduced from Gray 2009 Copyright (2009) Macmillan Publishers Limited, part of Springer Nature)

Dreams of a hydrogen-powered future, where the only emissions from cars are heat and water, have proven seductive to environmentalists, technophiles and politicians alike. Despite this, the reality is that today's hydrogen cars are powered by fossil fuels and release several times the greenhouse gas emissions of their petrol-powered counterparts (Illuminato and Miller 2010). Because hydrogen is the smallest element, many barriers need to be overcome for the hydrogen economy to become a reality. It can escape from tanks and pipes more easily than conventional fuels (Elcock 2007). There are two ways to store hydrogen in materials. One way involves absorption of the hydrogen within the material, and the other is to store the hydrogen in a container. The challenge for absorption is to control the diameter of the nanotube so that the absorption energy of hydrogen on the outside and inside of the tube is high enough to provide the desired storage capacity at an acceptable pressure (Elcock 2007). Nanotechnology may play a role in helping to meet these

challenges. High porosity materials seem to be promising, which are able to efficiently bind hydrogen in the pores through adsorption, or complex hybrids which sore hydrogen chemically reversible in the lattice structure (Luther 2008). Single-walled CNTs are a leading candidate for solving the storage problem for hydrogen-fueled cars and trucks (Elcock 2007). Nanoscale titanium (Ti) additive structures are crucial in both of these systems; to enhance the kinetics of hydrogen uptake and release in the complex metal hydride sodium alanate ($NaAlH_4$), and to increase the storage capacity of carbon nanotubes (Alivisatos et al. 2005).

Solar energy production is rapidly becoming a vital source of renewable energy being developed as an alternative to traditional fossil fuel-based sources of power (Suresh 2013). Photovoltaics involve the engineering expertise to generate electricity from light and recently it is developing into an important industrial product of the future. The low efficiency of solar cells and the expensive capital investments for large-scale electricity generation makes it a less popular option today (Ganguly et al. 2012). Possible avenues for nanotechnology are quantum dot structures providing an improvement of the conversion yield by shaping the solar spectrum, the improved use of high-tech light, optimised absorption properties (Chang et al. 2007). Moreover, nanostructured (hybrid) materials will make it possible to use very cheap materials by minimising the transport distances in the cell and through improved light housekeeping,. . .etc. (Roadmap Route 2013). Also, it has been reported that nanostructured materials are used to improve the efficiency of solar cells. The utilisation of nanostructures could allow for solar cell efficiencies of 10% in the medium term and over 60% in the long run (Luther 2008). Semiconductor nanocrystals are regarded as useful called third-generation solar cells. This utility is due to the fact that their optical band can be tuned by both material selection and quantum confinement and because advances in synthesis allow control over nanocrystal size and shape to optimize performance (Suresh 2013).

In addition to challenges in creating highly efficient energy-production systems, another hurdle facing the scientific community is energy storage (Liu et al. 2010). Types of electrical power storage devices include the flywheel, supercapacitor, and battery (Abdelsalam and Abdelaziz 2014). Supercapacitors and batteries are two important electrochemical energy storage devices that have been extensively developed for many applications. Improved energy storage capability, power delivery capability, and cycle life are highly desired for these devices to better satisfy the increasing performance demands (Dai et al. 2012).

Battery technologies face issues of internal surface area, electronic and ionic conduction, and phase-stability/reversibility that can benefit from the use of nanostructures (Brinker and Ginger 2011). Nanotechnologies help make more efficient, lighter and longer-lasting batteries for products such as laptops and electric cars. The next few steps in nano-based battery improvements are expected to increase power density over conventional lithium-ion batteries by five to ten times (Cefic). Nanostructured materials, such as these Si nanowires used as an anode in a Li ion battery before and after electrochemical cycling have the potential to increase the performance of batteries by ten times or more (Chan et al. 2008). Nanoscale capacitors made from multiwalled CNTs dramatically boost the amount of surface

area, and thus the electrical charge, that each metal electrode in the capacitor can possess. Smaller and more powerful capacitors may facilitate the development of microchips having greatly increased circuit density. Such nanoscale capacitors may also impact the development of compact and cost-effective supercapacitors (Elcock 2007).

1.6.2 Environment

In fact, environmental pollution especially toxic gases, heavy metal ions and organic pollutants in air and water, caused by heavy industrialization, agricultural activities, urbanization, and the changing life styles of people, severely threaten ecological balance and human health. These problems have received extensive attention worldwide (Lü et al. 2013).

Environmental remediation can be accomplished by means of different biochemical or physicochemical processes. Recently, the use of nanomaterials has been proposed as powerful tools that may improve the efficiency of remediation processes, as well as decrease their costs and ecological impact (Mendoza-Gonzalez et al. 2015). It is demonstrated that nanomaterials such as silica-titania nanocomposites are useful to remove elemental mercury from vapors. The application of nanomaterials in detection and removal of pathogen provides greater sensitivity, lower cost, shorter turnaround time, smaller sample size, in-line and real-time detection, higher throughput, portability in environmental remediation. They can be remove organic pollutants and metals by reduction or oxidation of nanomaterial and degree of removal can be enhanced through functionalization with chemical groups that can capture selectively target pollutants in water and air media (Khin et al. 2012). Water pollution has become the most severe dilemma in the entire world. Nanofiltration thin film composite membranes have been given tremendous attention over last two decades relative to conventional systems in desalination of sea water, waste water from industries and ultra pure water production (Mehwish et al. 2014) (Fig. 1.21).

Waste generation is proportional to the world's economic growth. Wastes, especially synthetic polymer waste, cause negative impacts on the environment. Materials are said to be green when they are biodegradable and renewable (Adeosun et al. 2012). However, most of the biodegradable polymers possess poorer mechanical properties and low heat distortion temperatures, which restrict their use in broad applications (Ong et al. 2010). Therefore, CNTs could act as nano-reinforcements for the biodegradable polymers. Another advantage offered by the green nanocomposites is the ability to recycle the incorporated CNTs due to the degradability of the biodegradable polymer (Ong et al. 2010; Grossiord et al. 2005; Vaudreuil et al. 2007).

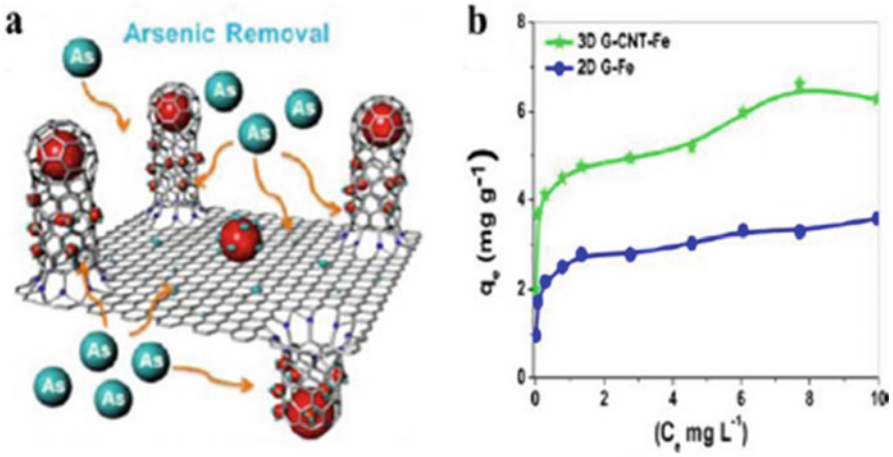


Fig. 1.21 (**a**) Schematic diagram of 3D G/CNT/Fe nanostructures. (**b**) Adsorption isotherms of 3D G/CNT/Fe nanostructures and 2D iron-decorated graphene for arsenic removal (Reproduced from Xiao et al. 2012 Copyright (2012) American Chemical Society)

1.6.3 Nanomedicine

Changes in lifestyle, food habits, and other environmental conditions resulted in the emergence of drug-resistant diseases. The existing health care system may not be sufficient to provide the necessities to cure emerging diseases. Besides the rapid rise in technological advancements, there is an urgent push toward the development of innovative (Sen and Pathak 2017). Nanomedicine has been defined as "the monitoring, repair, construction, and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures" (Morrow et al. 2007; Cirillo et al. 2014; Bao et al. 2016). It consists of application of nanotechnology to the diagnosis, prevention, and treatment of diseases and represents a useful instrument to understand specific underlying disease molecular mechanisms (Wan and Ying 2010; Cirillo et al. 2014). The nanomedecines are in the similar size-range as viruses, DNA and Proteins and they have some unique chemico-physical properties, such as ultra-small size, large surface area-to-mass ratio, and high reactivity, which can be used to overcome some of the limitations of the traditional therapeutic and diagnostic agents. Nanomaterials used in nanomedicine include a wide range of organic substances (e.g. liposomes, dendrimers, solid lipid nanoparticles, polymers). Some preparations based on inorganic materials (gold, iron oxides) have been approved or are in trial. Several other inorganic materials (quantum dots, metal or metal oxide nanoparticles, carbon nanotubes) are currently used for medical applications (Ghiazza and Vietti 2014). Figure 1.22, shows the most important medical applications of graphene.

Nanoparticles injected intravenously can be retained in the blood circulation for a longer period by appropriate surface manipulation. The particle escape from the

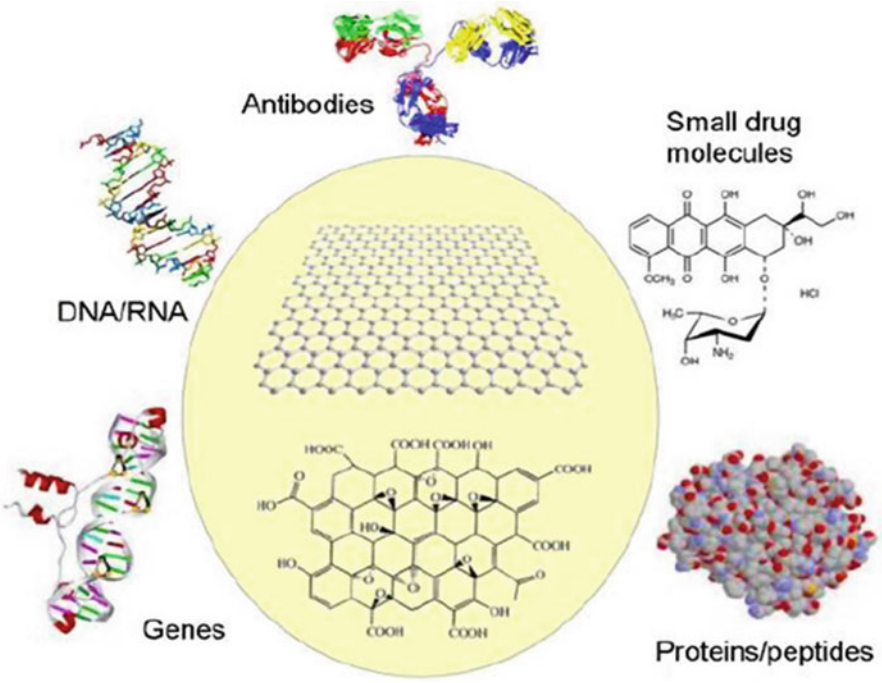


Fig. 1.22 Scheme of application of graphene and graphene oxide (GO) for drug delivery of various therapeutic agents and biomolecules (Reproduced from Liu et al. 2013 Copyright (2013) Elsevier)

vasculature is mainly restricted to sites where the capillaries have open fenestration, as in the sinus endothelium of the liver or when the integrity of the endothelial barrier is perturbed by inflammatory processes or by tumor growth which is the result of dysregulated angiogenesis (Schaefer 2010). The nanoparticles normally stay more in cancer cells than the normal cell due to the enhanced permeability and retention effect by virtue of passive intake (Kumar et al. 2017; Butler and Sadler 2013). Nanomaterials having large surface area and tiny size may empower the easy manipulation for definite and resolved purposes without or minimum unwanted issues (Li et al. 2011; Salata 2004).

Cosmeceutical is defined as a product between a drug and cosmetics. Cosmeceuticals are the fastest growing segment of the personal care industry (Fulekar 2010; Singh 2016). Cosmetics are intended to improve the appearance of the skin, the hair, or the teeth. Today many cosmetic products aim at hydrating the skin, reducing or slowing the signs of aged skin, or protecting the skin against the multitude of daily aggressions that it encounters (Schaefer 2010). Various nanotechnology-based cosmeceutical products are in the market used as moisturizer, cleanser, antiwrinkle, antiaging, sunscreen manufactured by Lancôme, Kara Vita, Nano-Infinity Nanotech, L'Oreal companies (Lohani et al. 2014; Singh 2016). Liposomes are used in a variety of cosmeceuticals because they are biocompatible,

biodegradable, nontoxic, flexible vesicles and can encapsulate active ingredients easily and liposomes can protect the encapsulated drug from external environment (Singh 2016). Liposomes can encapsulate water-soluble ingredients in their polar cavity and oil-soluble ingredients in their hydrophobic cavity (Schaefer 2010). These structures are useful in delivering incorporated components onto the skin surface and even transporting the drugs across it; in modifying the intercellular lipid lamellae by acting as penetration enhancers; or by controlling the release by creating a depot of active ingredients. Quite a few active components like vitamins A, E, K, including antioxidants such as Carotenoids, lycopene, and CoQ10 have been incorporated into liposomes, which amplified their physical and chemical stability when dispersed in water (Aparajita and Ravinkumar 2014; Lasic 1998).

1.6.4 Sensors

The quantitative and qualitative detection of chemical and biological molecules with high sensitivity and selectivity is crucial for a range of practical applications including determining and monitoring air/water/soil quality, medical diagnosis and chemical synthesis (Shearer et al. 2014; He et al. 2012). There is an ever increasing need for the development of miniaturized portable sensors. CNTs and graphene hold great promise for the development of such systems because of their high surface area (e.g. greater interaction zone), electrical properties (e.g. faster electron transfer), mechanical properties (e.g. robustness, flexibility) and their greater modulation of properties upon interaction with analytes (e.g. capacitance, resistance) (He et al. 2012; Ting et al. 2008; Liu et al. 2012a, b).

The CNTs-filled polymer composites used as an implantable sensor that is capable of transmitting information extracorporeally. Such a sensor made real time daterelated to the physiological relevant parameters such as pH, O_2 concentration, and glucose level available. In addition, the good biocompatibility with high electrical and electrochemical sensitivity assisted implantable biosensor applications (Qi et al. 2013a, b). The early research found that CNTs-filled polymer composites are able to detect serum proteins, as well as disease markers, autoantibodies, and antibodies (Julkapli et al. 2015; Grabowski et al. 2014). Functionalized graphene nanocomposites have shown promise for environmental applications, from environmental sensing and monitoring to remediation. Graphene and graphene nanocomposites can be used as general platforms for sensing inorganic ions, biomolecules and organisms (Wang 2006; Wang et al. 2013) and also as platforms for the removal of hazardous species in the environment (Chang and Wu 2013).

Sensing the biological responses has assumed great significance in the current scenario of ever dynamic environmental developments and corresponding altered homeostatic happenings occurring at both in vivo as well as ex vivo levels (Malik et al. 2013). Nanomaterials can be wonderful incumbents in this dimension as they have high surface area to volume ratios which allow the surface to be used in a better and far more diversely functional manner (Malik et al. 2013). The sensitivity and

performance of biosensors are being improved by using nanomaterials for their construction (Mendoza-Madrigal et al. 2015). Advances in nanotechnology have led to the development of nanoscale biosensors that have exquisite sensitivity and versatility (Touhami 2014). The most widely accepted definition of a biosensor is: "an analytical device which incorporates a biologically active element with an appropriate physical transducer to generate a measurable signal proportional to the concentration of chemical species in any type of sample" (Wilson 2005; Wilson and Gifford 2005; Warriner et al. 2014; Touhami 2014). The potential benefit of this emerging technology is receiving growing interest because nanotechnology-based sensors can rapidly detect pathogens, gases, aromas, freshness of processed product, flavour and food contaminants or toxins, and thereby reduce health risks and frequency of food-borne illness. The nanomaterial used in biosensor, such as magnetic nanoparticle, carbon nanotube, nanorods, quantum dots, nanowires, nanochannels, etc., have high capacity for charge transfer, large surface-to-volume ratio for immobilization of bioaffinity agents, high quantum yield and resistance to photo-degradation, i.e., excellent optical properties. All these tuneable properties of nanomaterial contribute to the improved performance of biosensors, making them suitable to reach lower detection limits and higher sensitivity values (Purkayastha and Manhar 2016). The ultimate goal of nanobiosensors is to detect any biochemical and biophysical signal associated with a specific disease at the level of a single molecule or cell. They can be integrated into other technologies such as lab-on-a-chip to facilitate molecular diagnostics (Touhami 2014). Biosensors encountered in the food sector are derived from those devices initially fabricated to meet the health care needs. Appropriately, the use of biosensors in food pathogen detection has been continuously growing in the last decade, with *Salmonella*, *Escherichia coli* and *Listeria monocytogenes* among the most studied microbial contaminants (Purkayastha and Manhar 2016).

1.6.5 Nanoelectronics

Microcomputers, microprocessors, mobile phones and MP3 players with a USB connection are available to the general public. For several decades now, this technology has been largely submicronic, and the idea of nanoelectronics was created in the laboratories (Nouailhat 2008). Nanoelectronics is defined as the ability to manipulate matter on a scale of less than 100 nm to create structures with many useful electronic properties. Nanoelectronics is a rapidly developing technological field with potential impact across a broad industry range (Anwar 2013). It is an interdisciplinary division which talks about the use of nanotechnology in electronic components. It targets to enable the use of new approaches and materials to build electronic devices with feature sizes at the nanoscale level. The materials and devices used in nanoelectronics are so small that the interatomic contacts and quantum mechanical properties of such materials need to be considered comprehensively. Even though much of this work has a long term explanation in the search for novel

devices, most of the results are having scientific significance instead of engineering (Pandey et al. 2016). Other developments such as the scanning tunneling microscope also helped further nanoelectronic technology. This equipment gave researchers the ability to see and control atoms and be able to work on the nanoscale. Researcher Don Eigler in 1989 took advantage of this technology and was able to using the microscope to arrange 35 xenon atoms to spell out the IBM logo (Karkare 2008). Another major historical event in nanoelectronics is the discovery of self-assembly nanomaterials such as electrostatic self-assembly (Karkare 2008). This technology was found to produce thin film materials with nanoscale-level molecular uniformity (Dahman et al. 2017). Integrating actuators and sensors based on nanomaterials device into existing control environments creates great demands on nanoelectronics. Nanodevices will not be used in isolation, but in systems of networks that may encompass tens of thousands of individual devices. The systems science alone in making such networks achievable is a challenge in itself, but there are also practical problems of energy supply and the dissipation of waste heat from nanodevice networks, as well as in the communications bandwidth required between thousands of networked devices. Large nanodevice networks will need to be self-organizing, managing their activity and communications to best effect and optimal energy consumption, without outside control and intervention (Ngô and Van de Voorde 2014).

As we mentioned earlier, miniaturization of microelectronics is limited. If we want the trend to continue, we must find something else. This is the field of nanoelectronics coupled with molecular and quantum computers. The field of molecular and biomolecular computers is currently booming. Simultaneously, some imagine using particles bigger than molecules of nanometric size: quantum dots. In this field, nanoparticles have specific electronic properties, Quantum dots could be used as single electron memory elements (Wu et al. 2016). There are many nanoscale electronic devices available now: Junctions with dimensions as low as 5 nm can be manufactured in a reproducible manner with e-beam lithography, and nanojunctions down to 2 nm have been obtained by electromigration (Technology Roadmap, Cholet et al. 1999). Devices with negative differential electrically configurable switches; carbon nanotube transistor; and single molecular transistor; ultra high density nanowires lattices and circuits with metal and semiconductor nanowires. . .etc. (Pokropivny et al. 2007). Devices have also been connected together to form circuits capable of performing single functions such as basic memory and logic function (Cao and Wang 2011). Hybrid molecular electronics holds the promise of self-assembly of circuits, both on a massive scale and cheaply, using chemical or biological reactions and to match the ultimate densities of CMOS (Technology Roadmap).

Graphene could be used in future nanoelectronic devices, taking advantage of its extremely high carrier mobilities and ambipolar behaviour. The absence of an energy gap in graphene, however, is problematic for logic applications, which require a sufficiently large ratio between the off and on-state current of the transistors. Such applications would thus require the use of other 2D materials, with complementary properties. Among these materials, semiconducting transition metal dichalcogenides

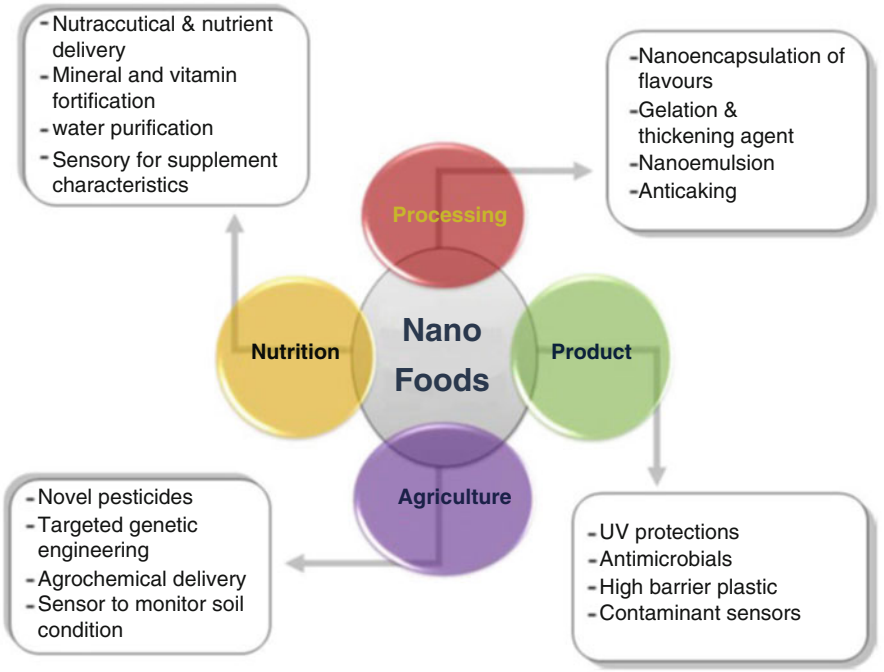


Fig. 1.23 Pictorial representation for some of the major applications of nanotechnology in different sectors of food and agriculture (Reproduced from Ranjan et al. 2014 Copyright (2014) Springer)

are gaining a lot of interest, due to the possibility to tune their energy band gap through their thickness, composition and applied mechanical strain (Houssa et al. 2016). On the other hand, nanoelectromechanical systems (NEMS) are devices at the nanoscale that integrate both electrical and mechanical functionality. Typically NEMS assimilate transistor-like nanoelectronics with mechanical actuators, pumps, or motors to form physical, biological and chemical sensors (Jasulaneca et al. 2018).

1.6.6 Food Industry

Food industries are always searching for new cheaper methods to produce and to preserve food and with this need we enter into the realm of nanotechnology (Ranjan et al. 2014) (Fig. 1.23). Understanding fundamentals of food nanotechnology represents a huge challenge for universities, industries and the public sector. The complex mechanisms involved in the research, development, production and legislation of food nanoproducts are studied under multi- and inter-disciplinary scopes (Ranjan et al. 2014).

Nanotechnology has revolutionized the entire food industry, from production to processing, storage, and development of materials, products, and innovative

applications (Cano-Sarmiento et al. 2015). The application of nanotechnology in the food sector has generated innovation in macroscale features of foods, such as texture, flavor, color, workmanship, safety, security, stability as well as reduction in the use of preservatives, salt, fat, and surfactants in food products (Cano-Sarmiento et al. 2015; Rajendran and Sen 2017). Moreover, nanotechnology may also improve food packaging, storing boxes, cooking equipment, crockery, coatings of machines and surfaces, or nano-sieves/membranes. The most important type of nanotechnology application in the food area for the near future is considered the incorporation of nanomaterials in packaging materials or storage containers in order to increase the storage time while keeping the products fresh (Donatella et al. 2013; Ramachandraiah et al. 2015; Silvestre and Cimmino 2013; Peters et al. 2016). Foods are nanostructured materials composed of hundreds of thousands of nanosized particles and molecules assembled in characteristic forms of the living organism. However, these arrangements are not considered within the nanofield unless the isolated materials and particles perform independently as nanomaterials by exhibiting characteristic properties that do not possess at the microscale (Hernández-Sánchez and Gutiérrez-López 2015). Nanofoods are differentiated from regular food products when the use of nanoparticles or nanotechnology techniques and tools are used during the cultivation, production, processing, or packaging of the products. It does not refer to food products that have been atomically modified or produced by nanomachines, as both of these ambitious options do not appear to be feasible for the the foreseeable future (Chauhan and Prasad 2017).

Within the last years, foods enriched with bioactive compounds such as nutraceuticals and nutrients have emerged with great strength in the markets worldwide. The application of nanotechnology includes the use of systems such as micelles, liposomes, nanotubes and nanoparticles for efficient bioactive compounds delivery and improved bioavailability (Kaya-Celiker and Mallikarjunan 2012; López-López et al. 2015). Important applications of nanotechnology in food and nutrition refer to the design and development of "novel functional food ingredients" with improved water solubility, thermal stability, oral bioavailability, sensory attributes, and physiological performance (Kakkar et al. 2016). Functional ingredients such as drugs, vitamins, and preservatives are essential aspects in many different products ranging from pharmaceuticals and health care products to food and cosmetics. The importance in these functional ingredients lies in their different characteristics including their polarity, physical states, and weights (Chauhan and Prasad 2017). Nanostructures of inorganic materials have also been studied as coating material to provide moisture or oxygen barrier (e.g.silicon dioxide (E551), magnesium oxide (E530), titanium dioxide (E171), and antibacterial 'active' coating, especially silver) (Chaudhry and Groves 2010; Dasgupta et al. 2015). Different products have been developed based on Nanoclusters™ system, such as Slim Shake Chocolate, which incorporates silica nanoparticles that are coated with cocoa to enhance the chocolate flavour (Dasgupta et al. 2015).

Approximately 500 nanopackaging products are in commercial use and in the near future, approximately 25% of all food packaging will be made of nanomaterials (Miller and Senjen 2008; Preuss et al. 2017). Recent trends in food packaging related

with nanoreinforcement, nanocomposite active packaging and nanocomposite smart packaging (Kuswandi 2016). Nanoreinforcement is mainly used to give extra tensile strength of food packets by different reinforcement method using nanoclays, cellulose.. etc. (Ranjan et al. 2014). Polymer nanocomposites integrated with metal or metal oxide nanoparticles such as silver, gold, zinc oxide, silica, titanium dioxide, and iron oxides have been developed for active packaging (Chaudhry et al. 2008; Rajendran and Sen 2017). Novel active packaging includes metallic nanoparticles with antimicrobial or oxygen scavenging properties (Momin et al. 2013). Intelligent, or smart, food packaging incorporates a nanobiosensor for sensing and signaling microbial and biochemical changes, release of antimicrobials, antioxidants, enzymes, flavors, and nutraceuticals to extend the shelf life of food and dairy products (Kalia and Parshad 2015; Rajendran and Sen 2017). Nanopackaging provides longer shelf life of food products by reducing gas and moisture exchange and UV light exposure (Sorrentino et al. 2007; Rajendran and Sen 2017).

1.6.7 Textile Industry

The textile industry is one of the most important consumer goods industries worldwide. Its mostly small and medium-sized enterprises produce textiles for various uses such as clothing, home textiles (such as bed and table linen, kitchen towels and cleaning rags), household textiles (such as curtains, furniture fabrics, textile floor coverings) and technical textiles (such as protective clothing, vehicle seat covers, tarps, tire fabrics, filter materials) (Appel et al. 2013). Textile industry is concerned with the design and production of textile fibres such as yarn, cotton, wool and silk. This industry plays a crucial part in providing the society with basic needs. It is also important in the economic perspective, providing employment and high industrial output (Senthil Kumar et al. 2017). The textile industry has already impacted by nanotechnology. Research involving nanotechnology to improve performances or to create unprecedented functions of textile materials are flourishing (Nelson 2013). Nanotechnology offers many advantages as compared to the conventional process in term of economy, energy saving, eco-friendliness, control release of substances, packaging, separating and storing materials on a microscopic scale for later use and release under control condition (David 2002; Singh 2016). Nanotechnology can provide durable solutions to the textile industry. The textile fabrics provide best suitable substrates where a large surface area is present for a given weight or a given volume of fabric. The synergy between nanotechnology and textile industry uses this property of large interfacial area and a drastic change in energetic is experienced by various macromolecules or super molecules in the vicinity of a fibre when changing from wet state to a dry state (Patra and Gouda 2013). The most significant early development of nano-finishes for textiles came through the research of Dr. David Soane. After almost 20 years at the University of California, Berkeley, Dr. Soane left academe and, using his garage as a lab, began devising ways of using nanotechnology to add unusual properties to natural and synthetic textiles, without changing a

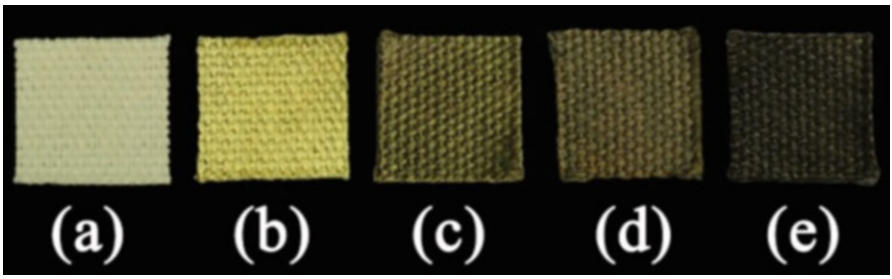


Fig. 1.24 Photographs of: (**a**) Untreated cotton fabric, the samples of blank cotton fabric and Ag/Cotton fabrics with different Ag loadings, prepared by argon glow discharge: (**b**) Ag/Cotton-1, (**c**) Ag/Cotton-2, (**d**) Ag/Cotton-5 and (**e**) Ag/Cotton-10. The formation of Ag NPs on cotton fabrics is visibly evident as the color is changed from colorless to yellow. Besides, the color of Ag/Cotton fabrics is light yellow at a low level of Ag loading (**b**). With the increase of loading amount, the color changes to dark yellow, brownish yellow and even to black, (**c**–**e**) indicating the coverage of Ag NPs expands since more Ag NPs are formed on cotton fabrics (Reproduced from Li et al. 2017 Copyright (2017) Elsevier)

fabric's look or feel. He floated the first nanotechnology-based company, Nano-Tex, in 1998, specifically catering to the textile industry (Gulrajani 2013).

Nanomaterials are expected to either improve the existing properties or bring new functionalities to textiles such as dirt and water repellence, breathability, UV protection, conductive and antistatic properties, wear and wrinkle resistance or resistance to stains, bacteria or fungi (Empa and TSV Textilverb and Schweiz 2011; Empa 2015). Nanoparticles can provide high durability for treated fabrics as they posses large surface area and high surface energy that ensure better affinity for fabrics and led to an increase in durability of the desired textile function (Singh 2016). The nanomaterials that are and soon will be used most frequently in textiles are: Silver, silicon dioxide, titanium dioxide, zinc oxide, aluminum (hydr)oxides, nanoclay (primarily montmorillo-nite), carbon nanotubes, carbon black. Copper, gold, iron (hydr)oxides, polypyrrol, and polyani-line are of secondary priority (Som et al. 2010; Appel et al. 2013). As exemples, some researchers employed nano-titanium dioxide and nano-silica to improve the wrinkle resistance of cotton and silk. Nano-titanium dioxide is used with carboxylic acid as a catalyst under UV irradiation to catalyse the cross-linking reaction between the cellulose molecule and the acid while nano-silica is used with maleic anhydride as a catalyst to improve the wrinkle resistance (Song et al. 2001; Wong et al. 2006). Silver nanoparticles are used in socks and sports clothing because of their ability to kill bacteria and inhibit unwanted odors (Medero 2013; Singh 2016) (Fig. 1.24).

Nanomaterials can be added to the textiles either during the fibre production or during the finishing, meaning being directly applied to the fibre surface or incorporated into fibre coatings (e.g. polymers). They can be applied as single, agglomerated (weakly bound) or aggregated (strongly bound) nanoparticles of different shapes or as part of a coating. It is also possible to produce nanotextiles without nanomaterials by creating nano-sized porosity in the textile's structure. New methods of application

of nanoparticles by nano-coating, electro-spraying, layer-by-layer deposition, chemical vapour deposition, sol-gel deposition and polymer film roughening are being researched and commercially exploited to impart super-hydrophobicity to textile substrates (Xue et al. 2010; Gulrajani 2013).

1.6.8 Agriculture

Agriculture is the basic activity by which humans live and survive on the Earth (Reddy 2015; Shalaby et al. 2016). Currently, the major challenges faced by world agriculture include changing climate, urbanization, sustainable use of natural resources and environmental issues like runoff and accumulation of pesticides and fertilizers. These problems are further intensified by an alarming increase in food demand that will be needed to feed an estimated population of six to nine billion by 2050 (Chen and Yada 2011; Dasgupta et al. 2016). Thus, implementation of new technology in agriculture sector is of extreme importance, particularly to deal with population growth, climate change, pest management and limited availability of nutrient (Chowdhury et al. 2016). There are many more important factors, with single aim to solve: how to increase crop production? Nanotechnology may play an effective role for this purpose. Already, there are many important developments on this aspect like enhancement of nutrients absorption by plants, protection of plants, nano-formulated food ingredients and water treatment processes (Chowdhury et al. 2016).

Uncontrolled and longer time application of different conventional fertilizers would be dangerous for the agriculture sector and will raise environmental issue near future. It has been reported that heavy use of phosphorus and nitrogen fertilizer raising the eutrophication problem into surface water bodies world-wide (Conley et al. 2009), provide nutrition to phototrophic microorganism and help them into developments of algal bloom (Chhipa and Joshi 2016). Application of nanotechnology has enhanced the delivery of fertilizers, pesticides, herbicides and plant growth regulators with the help of nanoscale carriers (Dasgupta et al. 2016). Reduction of chemical fertilizer and pesticide will be helpful in maintaining natural eco-balance of Geo-biological cycles, which have been destroyed or imbalanced by the use of synthetic chemicals (Alexander 1973; Chhipa and Joshi 2016). Cai et al. (2014), developed nanoclays which can be added to traditional fertilizer to improve the retention capacity of nitrogen. Thus, nitrogen loss is reduced and sufficient nutrition is provided to crops (Dasgupta et al. 2016). In fact, the use of nanoparticles as carriers of fertilizers and pesticides in agriculture increased the effectiveness of the active materials and reduce their volatilization. It also decreased the contamination of underground water resources (Aouada and de Moura 2015; Perez-de-Luque and Hermosín 2013; Chowdhury et al. 2016). One of the major advantages of nanoparticles is the gradual and controlled release of agrochemicals. The controlled release systems allow controlled delivery of active ingredients for a desired period in

Fig. 1.25 Application of nanotechnology in agriculture: nanotechnology applies in the form of nano-fertilizer, nano-pesticide, nanoherbicide and nano-sensor for controlling nutrition, pest detection and management (Reproduced from Chhipa and Joshi 2016. Copyright (2016) Springer International Publishing Switzerland)

the vicinity of the roots or the vegetative parts (Aouada and de Moura 2015; Chowdhury et al. 2016) (Fig. 1.25).

The soil characteristics can be improved by enhancing the water infiltration, aeration, availability of nutrients specially the liquid agrochemical and reducing the shear strength (Bandyopadhyay et al. 2009). Nanotechnology sector has contributed towards the soil improvement by way of producing nanomaterial products like zeolites and nano-clays which help in retention of liquid agrochemicals or water in the soil and allow slow release to the plants (Chowdhury et al. 2016). Biosensor, quantum dots, nanostructured platforms, nanoimaging and nanopore DNA sequencing tools have the potential to raise sensitivity, specificity and speed of the pathogen detection, facilitate high-throughput analysis, and can be used for high-quality monitoring and crop protection (Khiyami et al. 2014). Furthermore, nanodiagnostic kit equipments can easily and quickly detect potential plant pathogens, allowing experts to help farmers in the prevention of epidemic diseases (Kashyap et al. 2016). Nanoscience and nanotechnologies have vast applications in water quality managementas heavy metal removal, nano-bioremediation through nanolignodynamic metals, desalination, disinfecting process and the sensors to check the quality (Dasgupta et al. 2016).

1.7 Conclusion

Nanotechnology can be defined as the the understanding, control and manipulation of materials, having dimensions roughly within the 1–100 nm range, where conventional physics breaks down. Scientists view nanotechnology as the revolutionary technology of the twenty-first century. Nanomaterials refer to natural, incidental or manufactured materials containing particles in unbound or agglomerated/aggregated states. They are materials with basic structural units, grains, particles, fibers or other constituent components smaller than 100 nm in at least one dimension. The production of nanomaterials are achieved mainly through two approaches identified as

top-down and bottom-up methods. The first way, stands for breaking down the bulk material into smaller and smaller dimensions whereas the second one is based on consolidating the small clusters.

Nanoscience and nanotechnology have the potential to address many of the global challenges facing society today and improving the quality of life. The application of nanotechnology continues to make significant contributions to innovative and beneficial products across broad areas. Indeed, nanotechnology aims to design new functional smart materials and devices with a wide range of applications and it is important to emphasize the emergence of new topics such as nanoenergy, nanomedicine, nanoelectronics, nanofood . . .etc.

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Chapter 2
Nano-food Technology and Nutrition

Rasha M. A. Mousa and Deia Abd El-Hady

Contents

Abstract Applications of nano-technology to food have recently arisen, despite regulatory considerations, safety and environmental impact, and consumer acceptance. Indeed, nano-foods will have a new era in food technology and will have a huge impact on food sustainability accompanied by health and environmental benefits. Many of the benefits such as improvements in food quality, food safety or shelf life extension offer enormous potential for improvement of public nutrition and health. Several areas centered on nano-sizing micronutrients, using nano-materials to encapsulate and deliver bioactive food components, functionalising nano-particles for biosensing of food borne microbials and innovative packaging to enhance nano-food safety against pathogens have been emitted. The current level of nano-foods in the global food sector is, however, only small and most products are still at research and development stage. However, there may be a need for a

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pragmatic regulatory oversight in countries to ensure a case-by-case pre-market evaluation of the nano-technology-derived products to safeguard the consumer from any potential risks. There are also some major knowledge gaps in regard to our current understanding of the properties, behaviour and effects of nano-materials. Therefore, this chapter focused on the innovations of nano-based food technologies in terms of food processing, packaging and safety. It also discussed applications to nutrition, such as the design of nutrient delivery systems, nano-encapsulation of bioactive food components and nano-sensors to detect spoilage or infection.

2.1 Introduction

Nanotechnology is the creation of functional materials, devices, and systems through the manipulation of matter at a length scale of ~1 to 100 nm. On the other hand, food is any substance which contains nutritional value, when consumed they are ingested by the organism to produce energy. Healthier the food is, more energy is produced to maintain the metabolism of the body. The application of nanotechnology to the agricultural and food industries was first addressed by a United States Department of Agriculture roadmap published in September 2003. Food nano-technology has its history from Pasteurization process introduced by Pasteur to kill the spoilage bacteria, made the first step of revolution in food processing and improvement in quality of foods. Currently, the application of nano-technology in food production chain is focused on the development of nano-sized food ingredients and additives and innovative food packaging (Jain et al. 2017). As well, nano-technology has the potential to advance the science of nutrition by assisting in the discovery, development, and delivery of several intervention strategies to improve health and reduce the risk and complications of several diseases. Nano-technology applications may assist with obtaining accurate spatial information about the location of a nutrient or bioactive food component in a tissue, cell, or cellular component. Ultrasensitive detection of nutrients and metabolites, as well as increasing an understanding of nutrient and biomolecular interactions in specific tissues, has become possible. Nutrition and food science research areas that might benefit from applying or understanding nano-technology include research about molecular targets for bioactive food components; detection of food pathogens and spoilage microorganisms; enhancing nutrition quality of foods; and novel vehicles for nutrient delivery (Srinivas et al. 2010).

Despite rapid developments in food nano-technology, little is known about the occurrence, fate, and toxicity of nano-particles. Regulatory bodies around the world have established rules and guiding principles for nano-scale materials that have ramifications for use in food. Uncertainty exists over the regulation of nano-based products and is linked in part due to a lack of necessary safety data needed to inform regulatory bodies (Perspectives on FDA's Regulation of Nano-technology: Emerging Challenges and Potential Solutions 2016). Efforts to facilitate international collaboration and information exchange are underway to ensure acceptance and

utilization of the many benefits of nano-technology. Several published works and reviews discussed these issues scientifically in deep, but in our opinion, the availability of simple-way information could facilitate the public realization about nano-food products, its benefits and safety. Therefore, this chapter was designed in a simple manner to enhance knowledge and understanding about nano-technologies that may be utilized or are currently being employed for nutrition and food science research. It is hoped that by highlighting these technologies the potential benefit of nano-materials to revolutionize food and nutrition research is recognized.

2.2 Developments in Nano-food Technology

Foods are structurally composed of a complex assembly of nano-sized compounds with varying physical and chemical characteristics that determine the overall stability and properties of the interfacial colloidal mixture containing lipids, proteins, carbohydrates, artificial additives and surfactants (Sonkaria et al. 2012). Although nano-materials are universally accepted to be between 1 and 100 nm, their dimensional size varies significantly beyond this scale particularly in regulating nano-based food products (Rao 2008). Controlling how nano-particles, form assemble and interact with each other using nano-technological tools provides a means to design foods from scratch. Therefore, food is nano-food when nano-particles or nano-technology techniques or tools are used during cultivation, production, processing, or packaging of the food (Fig. 2.1). It does not mean atomically modified food or food produced by nano-machines (Sekhon 2014). Although there are ambitious thoughts of creating molecular food using nano-machines, this is unrealistic in the foreseeable future. Instead nano-technologists are more optimistic about the potential to change the existing system of food processing and to ensure the safety of food products, creating a healthy food culture. They are also hopeful of enhancing the nutritional quality of food through selected additives and improvements to the way the body digests and absorbs food.

Nano-food technology has its history from Pasteurization process introduced by Pasteur to kill the spoilage bacteria, made the first step of revolution in food processing and improvement in quality of foods. Later, Watson and Crick's model of DNA structure which is about 2.5 nm opened the gateway of applications in biotechnology, biomedical, agricultural and food production processes. Further, the invention of carbon nano-tubes "buckyball fullerene" which is 1.0 nm in size served as the cutting edge discovery to the world of innovation and led to the era of nano-food (Pray and Yaktine 2009). There are several interested applications of nano-technology in nano-foods that will describe further in this part.

The range of the length scales of food elements that already exist, either in nature or as a result of processing, has been figured in some events (Fig. 2.2), emphasizing again that in fact many elements that play very important structural roles in foods that we already eat exist on the nano-scale. We don't notice them because not only are they invisible to the naked eye, most things smaller than about 80 μm cannot be seen by the human eye, but they are imperceptible by taste as well, as most things

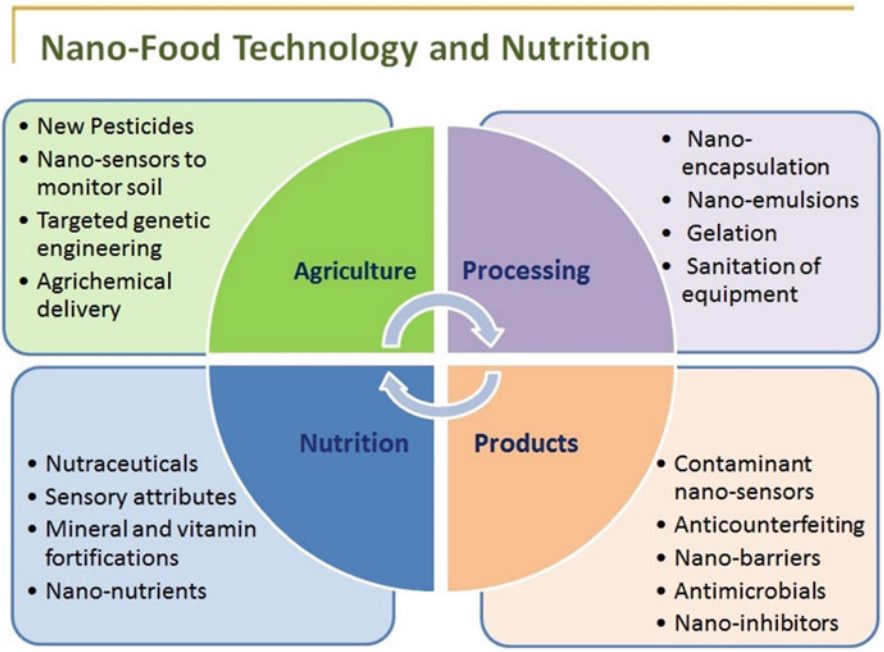

Fig. 2.1 Nano-food technology applications during cultivation, production, or processing of the food and nutrition

smaller than about 40 μm cannot be sensed in the mouth. In fact, some of food's most important raw materials—proteins, starches, and fats—undergo structural changes at the nano-meter and micrometer scales during normal food processing (Fig. 2.3).

1. Food proteins, e.g., native beta-lactoglobulin, which is about 3.6 nm in length, can undergo denaturation, via e.g. pressure, heat, and pH, and the denatured components reassemble to form larger structures, like fibrils or aggregates, which in turn can be assembled to form even larger gel networks, e.g. yogurt.
2. Starch granules expand when heated and hydrated releasing biopolymers that can be recrystallized into nano-sized structures, e.g., recrystallized amylose regions may be about 10–20 nm; dextrins and other degradation products of extrusion can be used to encapsulate bioactive substances in micro-regions, etc.
3. Fats: While many people think of fats as being homogeneous liquids or solids, in fact some fats have a lot of structure. Monoglycerides, for example, can self-assemble into many morphologies at the nano-scale level, and hierarchically structured into tryglicerides can be crystallites e.g. 10–100 nm, followed by arrangement into large clusters, then flocs, and finally, fat crystal networks.

Therefore, some nano-structures occur naturally in food; others can be added by food manufacturers. But there's another way that nano-technology can get into the food chain—from the ground up. The areas of key focus for the future development of food governed by the size and functional nature of nano-particles broadly center

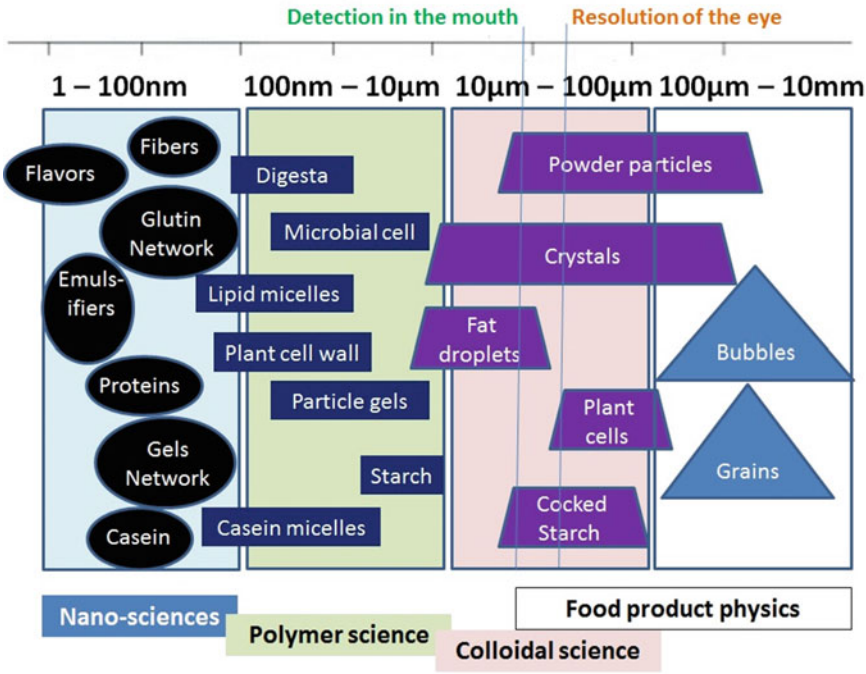

Fig. 2.2 Length scale of some food elements that already exist, either in nature or as a result of processing

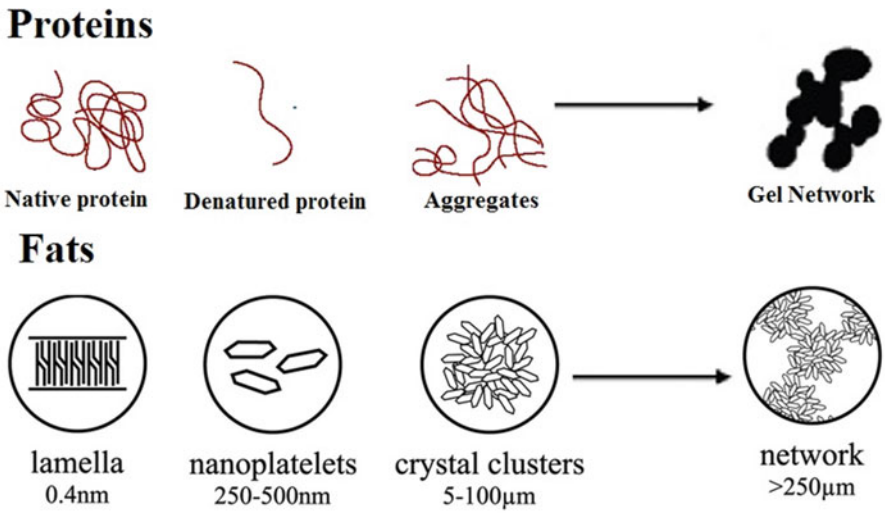

Fig. 2.3 Schemes of the structural changes that proteins and fats naturally undergo during normal food processing

Table 2.1 Nano-food products currently identified on the market

Company	Product name	Functionality
Tip Top®	Tip Top UP® omega-3 fatty acid docosahexaenoic acid	Fortified with nano-capsules containing omega-3 fatty acid docosahexaenoic acid rich tuna fish oil
Shemen industries	Canola Activa oil	Fortified with nonesterified phytosterols encapsulated via a new nano-encapsulation technology
RBC Life Sciences®, Inc.	Nanoceuticals™ Slim Shake Chocolate	Nano-scale ingredients that scavenge more free radicals, increase hydration, balance the body's pH, reduce lactic acid during exercise, reduce the surface tension of foods and supplements to increase wetness and absorption of nutrients
Shenzhen Become Industry & Trade Co., Ltd.	Nanotea	Nano-fine powder produced using nano-technologies
Aquanova	NovaSOL Sustain	Nano-carrier that introduces CoQ1O to address fat reduction and alphalipoic acid for satiety

on (a) nano-sizing micronutrients as nano-particles and incorporating novel functional properties to form novel nano-materials (b) using nano-materials to encapsulate and deliver bioactive food components to enhance their nutritional value in the body (c) functionalising nano-particles for biosensing of food borne microbials (d) innovative packaging to enhance nano-food safety against pathogens by increasing the shelf-life of products. These developments will have a huge impact on processing from agricultural growth to catering of nano-food products for consumers in an interactive way. For example, nano-foods are being designed to react to consumer's choice of colouring and flavouring in their food by activating their release from 'programmable' nano-capsules' via 'smart functional' materials. Nano-particles also have the potential to deliver a multitude of textures in food by using nano-emulsions that affect their taste and colour. Table 2.1 summarized the information about some nano-food products that already existed in the market (Nano-technology in the food industry: applications, opportunities and challenges 2012). Therefore, one can say that the word "nano-food" is relatively new but the concept is not.

2.3 Nano-food Products and Nutrition

A variety of nano-technology to be used in food is in development, and a few products have hit the market. But experts say that the traditionally food is unlikely to adopt nano-technology on a large scale unless it has compelling benefits for their customers. One of the main uses could be to deliver more vitamins and minerals

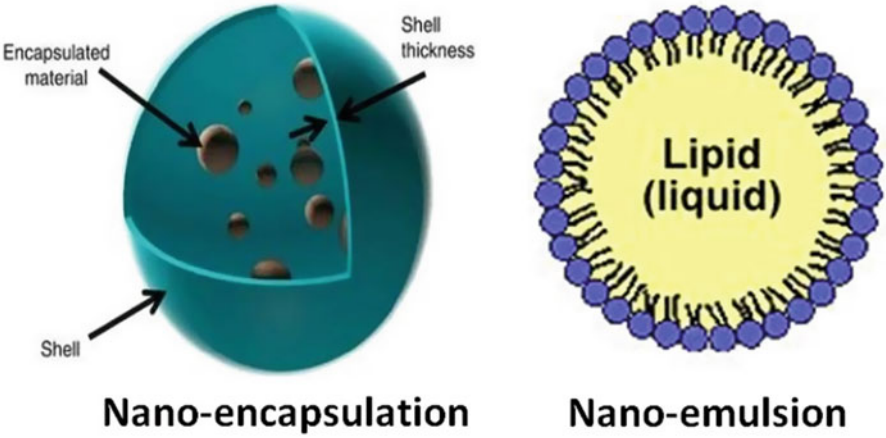

Fig. 2.4 Nano-encapsulation and nano-emulsion with supplements such as vitamin or minerals which could be added to everyday foods

through the food we eat. Nano-particles could encapsulate vitamin or minerals supplements, which could be added to everyday foods (Fig. 2.4). Food technologists have taken advantage of a number of nano-encapsulation delivery systems including nano-emulsions, surfactant micelles, emulsion bilayers and reverse micelles and functionally designed nano-capsules.

A number of potential advantages of using nano-emulsions rather than conventional emulsions for this purpose (McClements 2011) that include the following: (a) they carry the ingredient to the desired site of action; (b) they control the release of the ingredient in response an external trigger e.g., pH, temperature, ionic strength, enzymes, etc.; (c) they greatly increase the bioavailability of lipophilic substances; (d) they can be used to modulate the product texture; (e) a high stability to particle aggregation and gravitational separation and (f) they protect the ingredient from chemical or biological degradation.

Incorporation of functional ingredients in functionally coated nano-materials to drive the development of functional nano-foods is another area of major active interest in the food industry. In pursuit of this technology, a number of coating methods like physical and chemical vapour deposition, pyrolysis, sol-gel processes and supercritical carbon dioxide have been used (McClements 2011). Nutritive nano-particle sized compositions may also be mixed with surface compatible agents that interact with nano-particles and promote the assembly of non-agglomerated stable suspensions by reducing the attraction of inter-particle forces between neighboring particles. One approach based on this principle involves suspending large sized nutritive compositions in solvents that are designed to be broken into smaller particulates (Ahn 2010). There are some important applications including nano-technology-based GuardIN Fresh such as Fayetteville, AR, USA benefits perishable produce and floral products by scavenging the ethylene gas that hastens ripening (Nano-technology products and applications 2014). TopScreen DS13 i.e. TopChim,

Wommelgem, Belgium is an easily recyclable water-based coating that contains a biopolymer with a monodisperse distribution of nano-particles with a regular shape. By its very nature, this biopolymer has no negative impact on the recyclability or biodegradability of the packaging. NanoCeram-PAC from The Aquarian Environmental Group Pty Ltd., Sydney, Australia offers a much greater external surface area that results in much more rapid adsorption of soluble contaminants that may cause unpalatable taste and odor.

Further, foods among the nano-technology-created consumer products coming onto the market include a brand of canola cooking oil called Canola Active Oil from Shemen Industries-Tel Aviv-Israel, a tea called Nanotea from Qinhuangdao Taiji Ring Nano-Products Co., Ltd.-Hebei-People's Republic of China, and a chocolate diet shake called Nanoceuticals Slim Shake Chocolate from RBC Life Sciences Inc., Irving-TX-USA. The canola oil contains an additive called "nanodrops" designed to carry vitamins, minerals, and phytochemicals through the digestive system and urea (Sekhon 2014). The shake, according to its manufacturer, uses cocoa-infused "NanoClusters" to enhance the taste and health benefits of cocoa without the need for extra sugar. Nano-technology will replace many fields with tremendous application potential in the area of dairy and food sectors (Qureshi et al. 2012).

Nano-technology has also the potential to impact food processing significantly (Huang 2012). A combination of antibacterial agents and nano-silver could prove to be more potent due to broadened antibacterial spectrum with possibly lower doses. To achieve this, a facile single-step green method of synthesizing silver nanoparticles functionalized with an antibacterial peptide from a food-grade lactic acid bacterium has been reported. The synthesized enterocin-coated silver nan-oparticles showed broad-spectrum inhibition against a battery of food-borne pathogenic bacteria without any detectable toxicity to red blood cells (Sharma et al. 2012). Moreover, nano-porous ceramic pellets can be added to the frying oil to prevent oil molecules from clumping together while in use. Moreover, they extend the useful life span of the oil (Sunnyvale 2008, 2014). In addition, imperm from Eastman Chemical Co., Kingsport-TN-USA), a nano-composite of nylon and nano-clay (Lan 2012) can help keep the oxygen out and the carbonation in. Furthermore, nanoparticles added to feed mimic cell surfaces inside the chicken. This may be due to the fact that tiny pathogens get confused and bind to the nano-particles instead of real cells, then "flush" out as they go through the digestive system—keeping chickens safer and healthier for human consumption (Chaudhry and Castle 2011). The combined effect of food preservative agent with nano-particles against food spoiling organisms such as *Micrococcus luteus*, *Bacillus cereus, Staphylococcus aureus, and Escherichia coli* was reported. Here, results revealed that the producer organism producing peptides have more antimicrobial activity against the above mentioned food-spoiling organisms, when used in combination and alone, than commercially available nisin with gold nano-particles (Thirumurugan et al. 2013). Therefore, we can say that there are a little of trials to produce nano-food products having nutritive value, but these products are still limited and the consumer is still afraid of using these products.

2.4 Marketing of Nano-food Products

The application of nano-technologies in the food industry is at an early stage, and to the best of our knowledge some of the international food manufacturing industry does not currently use engineered nano-materials in food products, their processing or their packaging. For example, Nestlé says that it is keeping a watchful eye on developments in nano-food technology, but not doing any of its own research. As well, Heinz takes the same line, saying that it is monitoring the field but not actively participating. Why have these international companies become so coy since then? It may reflect a genuine decline in interest, perhaps due to regulatory challenges. The nano-technologies used to deliver food supplements, for example, will first make their way into medical applications, an arena where new products go through more rigorous testing. In 2010, the House of Lords committee on science and technology conducted an in-depth investigation of nano-food, and its report criticized the food industry for its secrecy on the subject. The Food and Agriculture Organization of the United Nations issued a report on food and nano-technology which raised similar concerns about a lack of transparency about what the food industry was doing with nano-technology. From an international marketing perspective, a restrictive regulation may discourage the innovation and marketing of nanotechnology, leading to an impediment to the growth and development of nano-food industry. As an oversight of nano-technology is to nurture beneficial technologies rather than stifle them, it is important to keep a balance between "too strict" and "too loose" in developing the standard, definition and regulation for nano-foods. However, public perception may differ from the experts' assessments. Public perception of nano-technology is very limited. A number of studies have examined on public perception of nano-technology in the US and in Europe. Results of these studies showed that public knowledge about nano-technology is very limited. In Europe, the public seems to be less optimistic about nano-technology. However, most studies focusing on public attitudes toward nano-technology have examined attitudes toward nano-technology in the abstract. Introducing such novel foods is unlikely to result, generally, in more positive attitudes toward nano-food. It is more likely that, for some products, nano-food is safe, but not for other products.

2.5 Safety of Nano-food Technology

As with any new technology that offers significant benefits to humankind, there are risks of adverse and unintended consequences with nano-technology. The risk is due to the small size and large surface area of nano-particles, which allow easy dispersion, might cross membrane barriers and capillaries, therefore can lead to different toxico-kinetic and toxico-dynamic properties due to unexpected and unanticipated consequences on interaction with biological systems (Oberdorster et al. 2005). The interaction of nano-particles with cells forms a solid-liquid interface (Jain et al.

2017). For engineered nano-particles, crossing the lipid bilayer is difficult and only cationic nano-particles can penetrate by creating pores in the cell membranes. This results in toxicity by generating an imbalance in intracellular and extracellular ions, proteins, and other macromolecules that are required to protect the integrity of a cell. Some nano-particles interact with protein and enzymes leading to induction of oxidative stress and generation of reactive oxygen species (ROS) free radicals, thus destruction of mitochondria and causing apoptosis following the administration of nano-particles (Hajipour et al. 2012). This destruction could be due to different cellular and acellular factors like metal ions and their reactivity, cellular interactions, immune response generation etc. Moreover, the small size, and subsequent larger surface area of nano-particles, endows them with some highly useful and specific properties. These apprehensions have generated concerns about the potential adverse effects of engineered nano-materials on human health. Furthermore, it was observed that nano-particles could penetrate red blood cells due to that red blood cells have no phagocytic receptors on their surface. However, their exact mechanism of entering into the red blood cell is still not known properly (Rothen-Rutishauser et al. 2006).

Government and regulatory authorities are realizing the importance of nano-material risk assessment. A thorough understanding of the mechanisms of nano-particles entering and leaving the cells could also lead to a better understanding of nano-particles toxicity as well as improvement in their bio-medical applications. Unfortunately, there are limited human studies on potential toxicity of nano-particles, although preliminary studies on animal have shown potential toxicity for liver, kidneys, and immune system. Therefore, risk assessment studies to show the adverse effect of nano-particles on human health should be critically investigated. Thus any concerns over consumer safety mainly relate to long term, or new/unforeseen harmful effects of exposure to nano-materials. Nano-additives in food are also likely to undergo various transformations in food and the *gastrointestinal* (GI) system due to agglomeration, aggregation, binding with other food components, and reaction with stomach acid, enzymes, and other biotransformation in the body.

This will enable the formulation of regulatory rules to reduce the risks involved in the field. But even if they wanted to, food companies are not allowed to use clever new nano-technologies in their products without regulatory approval. All foods that include nano-materials, or are processed using nano-technology, fall under the same regulations as conventional food. The next challenge is to find out how effective existing regulatory frameworks are for looking at any novel effects associated with nano-technologies. This is still an open, and highly debated, question. Until recently, industry has not been required to label products containing nano-materials. But that is changing. The European Union recently introduced new regulations for cosmetics and food labeling. From the end of 2014, it became a legal requirement to clearly label food products that contain nano-materials—although the regulations do not cover manufacturing processes. Recommendations by the Royal Society and the Royal Academy of Engineering, commissioned by the UK government to assess the potential impact of nano-technology, included a call for identification of the use of nano-particles in ingredient lists. The UK government agreed that this was necessary

for consumers to make informed decisions and that modifications to current labeling requirements would be necessary. It was suggested that when nano-particles are used as food additives, the conventional E-numbering system for labeling be used along with the subscript "n" (Institute of Food Science and Technology 2006).

Therefore, it is vital to investigate and debate the use of nano-technologies in food now, rather than waiting until there is a consumer backlash. Countries such as the US, the UK, the European Union more generally, Australia and New Zealand have been extremely proactive in examining the effectiveness of their regulatory frameworks for dealing with nano-technologies. Halliday (2007) mentioned that the European Union regulations for food and food packaging have recommended specific risk assessment and safety standards should be met before introduction of nano-food to market. In United States, nano-foods and most of the food packaging are regulated by the USFDA (Badgley et al. 2007). While in Australia, nano-food additives and ingredients are regulated by Food Standards Australia and New Zealand under the Food Standards Code (Bowman and Hodge 2006). The raising regulatory issues enforced many countries to establish regulatory systems capable of managing any risks associated with nano-food (Tinkle et al. 2014). In many other countries, incomplete food safety regulations are introduced due to poor information about exposure, availability and toxicity to human. In fact there is urgent need for international regulation system for use of nano-particles.

With the introduction of nano-particles in foods, methods for the identification and quantification of nano-sized particles in food matrices are being developed for future regulatory testing in terms of the distribution and migration of engineered particles in food stuffs. These devices will be necessary to instill public confidence in nano-particle based products to ensure that shelf products are quality assured and safe. A lack of analytical assessment tools in this area has been met by efforts to establish methodologies and instrumentation for food analysis. However, this area will require further attention as regulatory authorities may implement restrictions on the use of nano-particles as food components in the future (Sonkaria et al. 2012).

Whatever the impacts of nano-technology on the food industry and products entering the market, the safety of nano-food will remain the prime concern. This need will strengthen the adoption of nano-technology in sensing applications, which will ensure food safety and security, as well as technology which alerts customers and shopkeepers when a food is nearing the end of its shelf-life. New antimicrobial coatings and dirt repellent plastic bags are a remarkable improvement in ensuring the safety and security of packaged food.

2.6 Packaging of Nano-food Products

Recent trends in food packaging related with nano-reinforcement, nano-composite active packaging and nano-composite smart packaging (Fig. 2.5) have been discussed in details by Ranjan et al. (2014). Nano-reinforcement is mainly used to give extra tensile strength of food packets by different reinforcement method using

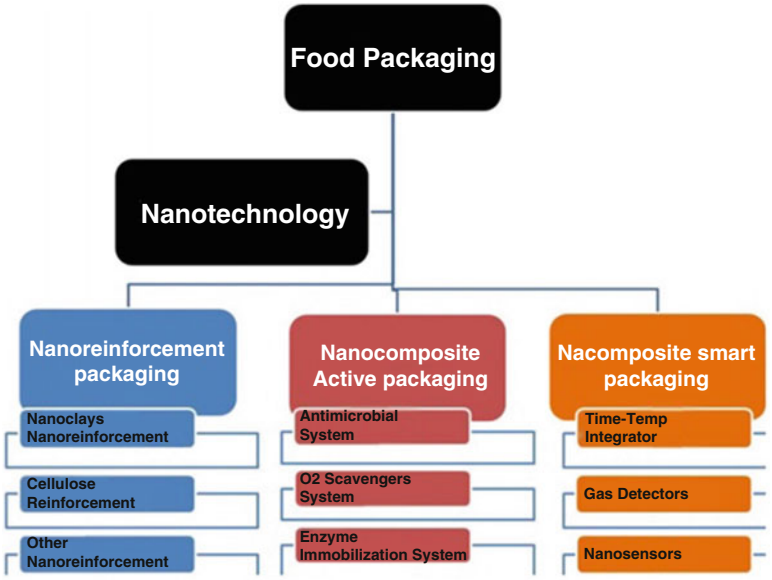

Fig. 2.5 Research trends of food packaging with the help of nano-technology (Ranjan et al. 2014)

nano-clays, cellulose, carbon nano-tubes, multiwalled nanotubes or silica nano-particles. Nano-composite active packaging is the integration of many useful systems along with the food packets. An active food packaging unlike conventional food packaging may be defined as a system that not only acts as a passive barrier but also interacts with the food in some desirable way, e.g. by releasing desirable compounds such as antimicrobial or antioxidant agents, or by removing some detrimental factor such as oxygen or water vapour. The consequences of such interactions are usually related to improvements in food stability. Furthermore, Enzyme immobilization has been considered for packaging applications (Soares and Hotchkiss 1998). The incorporation of enzymes like lactase or cholesterol reductase to packaging materials could increase the value of food products and answer the needs of consumers with enzyme deficiencies. Similarly, nano-composite smart packaging mainly involves sensors, e.g. time–temperature integrator, gas detectors and other nano-sensors. Nano-sensors incorporated into the nano-food packaging materials might help in track of any physical, chemical or even biological modification during nano-food processing phase. Smart packaging with specialized nano-sensors and nano-devices were designed to detect toxins, food pathogens and chemicals (Bereka 2015; Li and Sheng 2014; Mihindukulasuriya and Lim 2014). This smart packaging might increase efficiency of information transfer during distribution. Potential nano-sensors could indicate temperature, freshness, ripeness, and contaminant/pathogen status on the package (Chaudhry and Castle 2011; Brody et al. 2008). The response generated due to changes related with internal or external environmental factor, will be recorded through specific sensor. Nano-particles added

to feed mimic cell surfaces inside the chicken. This may be due to the fact that tiny pathogens get confused and bind to the nano-particles instead of real cells, then "flush" out as they go through the digestive system—keeping chickens safer and healthier for human consumption (Tzeng 2014). Therefore, nano(bio)sensors are expected to enable multi-analyte detection of pathogens and food contaminants. They are also expected to be low-cost, and usable in the field by relatively little training. The potential benefits of these sensors will include microbial and chemical safety of foods to protect consumer health (Chaudhry and Castle 2011). An optimized amperometric immunobiosensing strip was developed to detect foodborne pathogens. Conjugating secondary enzyme-labeled antibodies with gold nanoparticles had the ability to detect *Listeria* exhibited and *Salmonella typhimurium* (Davis et al. 2013). Others include zinc oxide and *monocytogenes* at 2 log colony-forming unit CFU/g in wild blueberry samples and significant specificity over other enteric pathogens such as *Escherichia coli* O157:H7 titanium oxide nanocomposites for the detection of volatile organic compounds. Furthermore, nanobarcodes are used for tagging and also for security. Thus the use of smart sensors is beneficial to the consumers in terms of better quality identification and producers for rapid distribution and authentication of the nano-food products.

2.7 Conclusion

Through improved knowledge of nano-food and the realisation of their potential in the food industry, the introduction of nano-foods will provide solutions for persisting problems associated with foods and will offer long-term economic benefits. Globally, nations will profit from increased food productivity with cost effective returns, innovative products with tunable properties to deliver smarter and healthier foods and equally intelligent packaging systems with enhanced storage properties for better food protection. Nano-foods will have a huge impact on sustainability and will be accompanied by health and environmental benefits if regulated properly. Many of the benefits such as improvements in food quality and hygiene, shelf life extension, water decontamination/desalination etc., offer enormous potential for improvement of public nutrition and health. The current level of nano-foods in the global food sector is, however, only small and most products and applications are still at research and development (R&D) stage. There are also some major knowledge gaps in regard to our current understanding of the properties, behaviour and effects of nano-materials. The challenge in assessing the safety of nano-foods becomes more complex with the arrival of novel nano-materials for use in the food industry, greater cooperation is required to ensure that human concerns are not compromised as new products are released. The existence of stringent regulatory controls in many countries provides reassurance that only safe products and applications of nano-technologies will be permitted on the market. However, there may be a need for a pragmatic regulatory oversight in countries to ensure a case-by-case

pre-market safety evaluation of the nano-technology-derived products to safeguard the consumer from any potential risks. Possible ways to achieve this could be through:

- Establishment of international research collaborations and networks that can address different aspects of the existing and new nano-foods. Industry sponsored research also needs to be encouraged.
- Internal collaborations within a country between different research and development (R&D) institutions, industry and government departments can overcome many of the current barriers.
- The presence of standardised protocols for the assessment of the toxicological profiles of nano-particles in vitro and in vivo.
- Reliable analytical methods to detect nano-particles in nano-foods or the migration of nano-particles from food contact materials such as packaging into food.
- Promote the programs and talks concerning the public realization about nano-food products, its benefits and safety.
- Where nano-particles are incorporated in food or food packaging, labeling of these products should be to inform the consumer.
- Urgent consideration should be given to whether additional controls are required on the disposal and/or recycling of nano-particle-containing food contact

This essentially means that innovation in nano-food must be balanced by regulatory guidelines through the availability of reliable and robust risk-assessment tools which currently do not exist for nano-foods. Also, if nano-foods are to be implemented successively in our food cycle, the benefits of nano-foods must be accompanied by greater transparency of the risks of such foods publicly to build consumer confidence.

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Chapter 3
Nanoparticles for Heavy Metal Removal from Drinking Water

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Abstract The implementation of nanotechnology in drinking water treatment is a very promising field for applied research. A major part of this effort focuses on reducing the building units dimensions in the existing inorganic adsorbents used for the purification of water versus heavy metal species. The development of engineered nanoparticles has the potential to provide improved uptake efficiencies and sustainability if issues related to cost, technical incorporation and environmental safety will be overcome. We reviewed (1) the technical and economic conditions for potential implementation of inorganic nanoparticles as alternative adsorbents of heavy metals from drinking water, (2) the reported studies referring to the capture of heavy metals ionic forms by inorganic nanoparticles giving emphasis to those succeeding residual concentrations below the maximum contaminant level and (3) the indirect health and environmental risk related to the application of nanosized materials in a water treatment line. In particular, a separate section is devoted to the identification of an optimum nanoparticle profile that fits the unique characteristics of each class of emerging heavy metals with respect to the chemical affinity, charge interactions, aqueous speciation, redox reactions and ion-exchange processes. Importantly, in order to bridge fundamental research with the requirements of the technical and commercial sector dealing with water treatment plants, we introduce an evaluation path for the preliminary qualification of candidate nanoparticulate materials, based on a universal index which is derived by adsorption isotherms recorded under realistic conditions of application.

3.1 Introduction

Water treatment has become a major field of interest during expansion of nanotechnology to more traditional sectors of human applications. In general, it involves a variety of separation, catalytic, sensing and quality controlling processes aiming to secure health or environmental protection, water resources management and sustainable development. Based on recent research and technological trends, the development of nanomaterials capable to remove heavy metals from water appears as the most pronounced case of nanotechnology's incorporation in water treatment. During last decades, the presence of elevated heavy metals concentrations in aqueous resources raised as a problem of worldwide concern related to the risk of severe health implications and increased mortality rates. Particularly, the aqueous soluble forms of elements such as arsenic, cadmium, lead, antimony, chromium, mercury and nickel are considered as emerging water pollutants regulated by strict legislation especially referring to their long-term exposure through drinking water consumption. Therefore, whenever the problem comes up, a water purification method oriented to the removal of heavy metals should be included as an extra task into the conventional treatment sequence. Such need is usually addressed by proper adsorbents which show high affinity and selectivity to specific heavy metals as a result of their surface configuration. To this point, owed to their small dimensions and tunable surface features, the possible use of nanostructured materials is rather

challenging as a way to overcome limitations and improve efficiency of conventional adsorbents.

Nanoparticles are the most representative type of nanostructured materials. Met at a wide variety of shapes, nanoparticles are characterized as self-existent material units completely isolated from other adjacent particles with a uniform size lying in the nanoscale. According to the strict definition of nanoscale range, only material units below a critical dimension (lower than 30 nm for most crystal phases) resulting in a dramatic modification of bulk properties should be called nanoparticles. However, it is common to use the term for particles with sizes at least up to 100 nm with regards to their elevated specific surface area which is evaluated as the main advantage for many applications. During the last two decades, plenty of research work has been devoted in the synthesis of engineered nanoparticles and their optimization for various technology fields including electronics, biomedicine and catalysis. More frequently, nanoparticles consisting of inorganic phases (metals, alloys, oxides, composites) are preferred due to the offered diversity of advanced electronic, optical, magnetic and mechanical properties and the further opportunities arising by nanoscale coupling effects. From another point of view, inorganic nanoparticles appear to be very compatible to the aqueous chemistry which is the base of most industrial, environmental and biological processes.

Nanoparticles were also suggested as potential heavy metal adsorbents during drinking water purification. Numerous preliminary studies support the ability of particles with specific compositions to irreversibly capture one or more heavy metals from the aqueous phase. As shown in Fig. 3.1, the number of nanoparticles-relevant articles for water remediation has maintained an increasing trend over the last 10 years. However, it is not always clear if such observations are reproducible under realistic water treatment conditions and even worse, if nanoparticles application can fulfil all technical/economic limitations and regulations for drinking water. Becoming competitive to conventional adsorbents requires at least an equal efficiency and a similar production cost for nanoparticles. Furthermore, the benefit from the small dimensions may turn into a serious drawback considering the need to design a different application setup followed by a corresponding recovery process.

This chapter summarizes the current state of the art related to the potential of inorganic nanoparticles to be used as efficient adsorbents for heavy metal ionic forms able to comply with the drinking water regulations. Importantly, it emphasizes into reported technologies and research studies which provide sufficient data allowing their evaluation under realistic terms of water treatment. Furthermore, it attempts to give an approach for facing common heavy metal pollutants providing the optimum nanoparticle profile for each case.

3.2 Synthesis of Engineered Nanoparticles

Despite the ancient origin of the term “nanoparticle” -*νάνο*=dwarfish and *ἀπάρτησις*=detachment (Liddell et al. 1996)- use of this term exclusively refers to modern science and technology. Nevertheless, materials with identical texture were

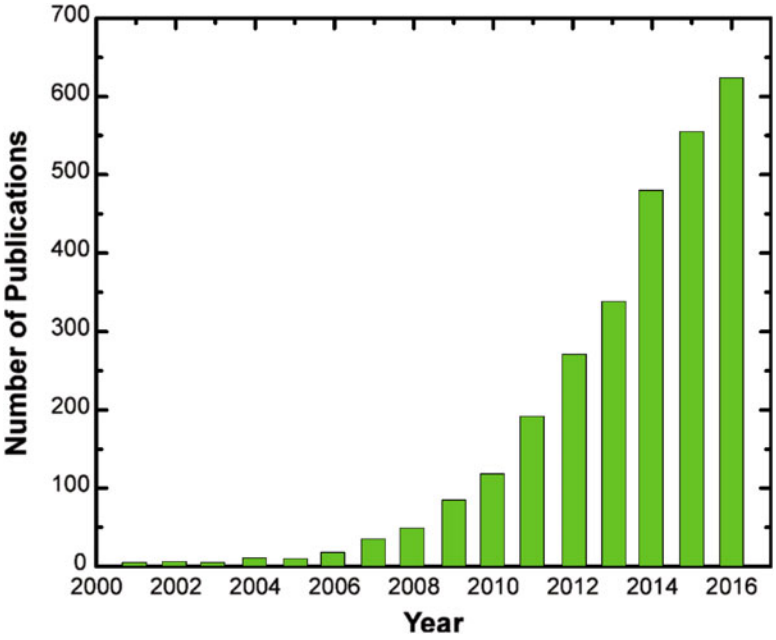

Fig. 3.1 Scientific papers published per year including the terms "nanoparticles", "water" and "heavy metal" for the search. (Data obtained from the Thomson Reuters Science Citation Index). The increasing trend signifies the turn of scientific community to adopt nanoparticulate materials for heavy metals removal practices

developed throughout human history or even found naturally as a result of biological or anthropogenic procedures. The roman cup with the figure of Lycurgus is the most prevalent case of metal nanoparticles incorporation in human technique for the preparation of dichroic glass. On the other side, many bacteria, fungi or plants involve bioreduction and biosorption mechanisms resulting in the formation of inorganic nanoparticles. Large quantities of nanoparticles are also released to the environment as byproduct of industrial, mining or combustion activities.

All these cases are separate to the engineered nanoparticles, those intentionally designed and produced to cover the specifications of technological applications. Synthesis of engineered nanoparticles may be realized by two routes: (i) bottom-up, building nanoparticles from small nuclei in the atomic scale, and (ii) top-down, splitting coarse materials to smaller dimensions. Chemical wet methods are classified in the bottom-up approach where nanoparticles are formed after the oversaturation of soluble species triggered by the controllable modification of specific parameters defining their stability. In general, thermal or solvothermal decomposition and sonication are methods based on the destabilization of metal complexes by introducing high energy amounts by means of heating, pressure elevation or supersonics, respectively. Working in aqueous medium offers further possibilities for nanoparticles synthesis through the variation of the pH or the redox potential (aqueous precipitation, electrocoagulation). Mechanical treatment and

Table 3.1 Evaluation of commonly applied methods for nanoparticles synthesis with respect to their potential for large-scale production oriented for drinking water purification systems

Method	Cost	Production rate	Water compatible	Energy demands	Special facilities	Eco-friendly
Thermal decomposition	High	Medium	No	High	Yes	No
Solvothermal	High	Medium	Can be	High	Yes	No
Precipitation	Low	High	Highly	Low	No	Yes
Electrochemical	Medium	High	Highly	High	No	Yes
Ball milling	Low	High	Can be	Medium	Yes	Yes
Vapor condensation	Very high	Low	Yes	High	Yes	Yes

vapor condensation processes are the most important top-down techniques for nanoparticles preparation. High-energy ball milling is considered as a convenient way to achieve the size reduction of any phase down to the nanoscale. Finally, physical vapor condensation, whether performed by thermal-, laser-, electron- or even solar- assisted reaction, is a set of modern and rather challenging techniques but with many requirements for energy and specialized instrumentation.

Ideally, a successful synthetic route should be able to provide well-defined nanoparticles with respect to chemical composition, structural stability and sufficient segregation. For this reason, preparation of nanoparticles usually involves their protective coating by organic molecules or inorganic phases and ions. Another common procedure is the size separation of nanoparticles which is applied in order to obtain good monodispersity and uniform properties. In practice, a compromise between the degree of surface activity, aggregation tendency and resistance against phase changes should be considered according to the targeted application of nanoparticles. More importantly, proportionality between the cost of the selected production method and the added value by nanoparticles incorporation in the corresponding technological field, should be always maintained. For instance, drinking water treatment requires nanoparticles with extremely low cost, ton-scale availability, water compatibility, zero toxicity and high surface activity. Therefore, in the majority of cases, the available synthesis methods are limited to those operated in a simple and scalable setup, using low temperatures and pressures, in an environmentally friendly process free of any toxic reagents (Table 3.1).

3.3 Traditional Drinking Water Purification

As the management of drinking water is a priority for the sustainable development of organized societies within the centuries, controlling the water quality by treatment facilities remains an achievement of high importance. Water intended for consumption by human is obtained by underground aquifers or surface reservoirs. The long-term contact of water with the surroundings cause the dissolution or the drift of

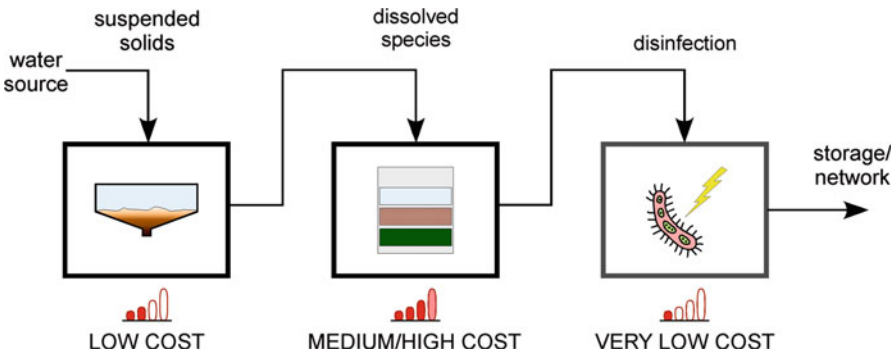

Fig. 3.2 Sequence of typical drinking water treatment steps indicating the height of expected cost for each one. Depending on the water quality, a medium to high cost could be affordable for the removal of dissolved species like heavy metals

components originating by the earth background or anthropogenic byproducts. Suspended solids, dissolved species and microorganisms are considered as the main categories of such components. Nowadays, the regulation or elimination of such parameters with respect to their impact in human health is usually accomplished by the application of conventional technologies based on physical or chemical effects (Fig. 3.2).

3.3.1 Suspended Solids

The colloidal stability of suspended solids is related to the electrostatic repulsion developed by an excess of anions or cations on the particles-water interface. Therefore, a typical process for the removal of suspended solids includes (i) the destabilization of the colloid dispersion by coagulation using chemical reagents, (ii) the flocculation of solids by adding polyelectrolytes and (iii) their separation by gravity sedimentation followed by depth (sand) filtration. The coagulation-flocculation methodology is widely preferred due to the facile design of the unit operating in continuous flow, the acceptable fixed and operational cost as well as the absence of limitations in upscaling. In addition, the simultaneous contribution of the process in the removal of other pollution species such as heavy metals, humus and pathogens, is also appreciated as an advantage. However, the addition of chemical reagents, the demand for pH adjustment and the large volume of produced sludge that should be handled are the main disadvantages. Beyond this conventional method, recent advances in micro- and nano- filtration suggest the gradual incorporation of membranes for the separation of suspended solids. In the near future, engineering of membrane materials and their morphology at the nanoscale is expected to increase the impact of nanotechnology at this water treatment step.

3.3.2 Dissolved Species

Dissolved water pollutants may be captured by non-selective or species-oriented methods. Reverse osmosis is the most representative case of a non-selective technique that completely removes the majority of soluble water constituents resulting in quality parameters very close to those of deionized water. Thus, produced water is practically non-potable while the process has an overall high cost. On the other side, ion-exchange, air-stripping, chemical precipitation and adsorption by solids are characterized by relatively high selectivity and much lower cost for application.

Ion-exchange involves synthetic resins usually consisting of styrene-divinylbenzene copolymers hosting active groups which appear selective in the uptake of particular water species. The ion-exchange resins are traditionally applied for softening and deionization but more specialized uses, for example capturing nitrates, chromates, arsenate or boron have been also developed. Their regeneration allows a significant decrease of operation cost, although the need for byproducts treatment and the difficulty to achieve sub-ppb concentrations are important disadvantages. Air-stripping addresses the removal of dissolved gases like CO_2, H_2S, NH_3, chloroform, trichloroethylene etc., by modifying the dissolved gas equilibrium through air pumping. Chemical precipitation is based on the solubility modification of water constituents by varying ions valence or the pH value. The removal of Fe (II) and Mn(II) after oxidation to Fe(III) and Mn(IV), the reduction of Cr(VI) to the insoluble Cr(III) form and the precipitation of Ca^{2+} as $CaCO_3$ by modification of HCO_3^- to CO_3^{2-} through pH elevation are widely applied processes of this category.

The major class of selective methods for the removal of dissolved pollutants from water is adsorption by various solids. The general mechanism of adsorption is described by the initial approach of the solid/water interface by soluble pollutants and their attachment to the solid's surface by means of van der Waals (physisorption) or chemical (chemisorption) bonds. Adsorption processes are usually adapted to column bed filter setups which are very popular for large-scale and point-of-use water treatment solutions due to their simplicity and low cost. Although activated carbon is referred as the most common example of adsorbent solid, numerous inorganic materials were promoted as high-capacity adsorption media to achieve selective removal of pollutants below ppb-levels of residual concentration. Since the increase of specific surface area is a critical task for the improvement of adsorption efficiency, the development of nanomaterials for adsorption comes as an obvious sequence in the evolution of the field especially if low-cost availability and recycling are achieved. Based on the principles of nanoscale engineering, tuning adsorbents' surface configuration and charge density may be also realized.

3.3.3 Disinfection

Water offers a favorable nutrient substrate for the growth of various microorganisms. For this reason a disinfection process that eliminates pathogens is always a necessary step before drinking water is supplied to the consumers site. Whether it is carried out by the application of electromagnetic irradiation or chemical reagents, disinfection may provide a short or a longer-term effect. For instance, UV irradiation (260 ± 20 nm) is strongly and mainly absorbed by the nucleic acids of microbial cells and, therefore, has the best potential ability to destroy bacteria but it remains active only during contact time unless support by chemical disinfection (e.g. NaOCl, ClO_2) is combined. An important advantage of irradiation techniques is the absence of byproducts. On the opposite, disinfection using chemical oxidizing agents is always accompanied by the formation of byproducts but this drawback is balanced by the very low cost of the process.

Chlorine (Cl_2) and sodium hypochlorite (NaOCl) appear in the form of ClO^- or HClO in water generating a high oxidative potential with extended lifetime at a very low cost. However, their interaction with natural organic matter produces either carcinogenic compounds (halomethans) or organic molecules with unpleasant smell (chlorophenols). These issues are partially solved by the use of chlorine dioxide (ClO_2) which is also considered as a more efficient disinfectant. For safety reasons, chlorine dioxide has to be prepared on-site introducing a higher capital, operating and labor cost to the process. Finally, cutting down on the introduction of harmful disinfection by products and foul tastes or odors associated with chlorination, ozone is the most effective disinfectant currently in use, very oxidant for both bacteria and viruses, though the disadvantages of high operational cost and low lifetime should not be ignored.

3.4 Implementation of Nanoparticles in Water Treatment

The small dimensions of nanoparticles may turn into a serious drawback for their successful implementation into water treatment units. More specifically, it is almost impossible to get the benefit of utmost in specific surface area without meeting severe difficulties in the design of the proper operation setup with respect to their separation. In summary, there are three potential approaches able to employ nanoparticles-based processes in a water purification line:

(i) Dispersion of nanoparticles in water and separation by filtration,
(ii) Use of nanoparticles aggregates or composites in typical column beds and
(iii) Supported on substrates like membranes, porous materials and graphene oxide.

Which one of these application schemes is the most appropriate would be defined by a number of parameters like the size of the treatment unit, the added value of the performed process, the cost of the nanoparticles and their efficiency.

In the first case, nanoparticles are initially added in the water under treatment in the form of dried product or highly concentrated suspension. This part requires a simple but relative large continuous-stirred vessel in which contact of nanoparticles with water for sufficient time results in the removal of the targeted pollutant. However, the outflowing water still contains the dispersed nanoparticles that need to be completely separated. The recovery of solids with dimensions lying in the nanoscale should be accomplished by nanofiltration in order to be on the safe side against possible leakage. But referring to common water purification strategies, the introduction of nanofiltration may become the cost-determining step of the whole process. This is an obvious limitation for using nanoparticles in direct dispersion although theoretically this approach predicts the maximum removal efficiency for the pollutant. For specific kinds of nanoparticles (iron and its oxides), their magnetic response to external fields enables their recovery by a more sophisticated way with significant impact in the cost reduction. In particular, magnetic nanoparticles can be easily captured by placing an electromagnet or permanent magnet in the side of the outflowing stream from the contact vessel.

The filtration bed, which operates as a plug-flow reactor, is considered as the best way to bring an adsorbent in contact with the polluted water resulting in high removal efficiency within short time. A large quantity of the material is packed in a column being able to operate for a long period without the need for any maintenance until replacement. However, to ensure the normal flow of water through the filter and avoid occlusion problems the applied adsorbent should be in the form of granules (>200 μm). From this aspect, nanoparticles cannot be used in a filtration process as fine powder but instead should be arranged in larger units whether by self-aggregation or by their attachment to other phases (composites). Of course, this approach is equivalent to a partial loss of their activity proportional to the decrease of the active surface area. However, when applicable, it is still a compact, flexible and easy way to introduce nanoparticles in everyday life for water treatment with respect to point-of-use and point-of-entry home solutions and portable facilities.

In specific systems, nanoparticles are used in secondary processes to integrate a main water treatment step. For instance, a small quantity of an adsorbent may be introduced as a filtration step to face the periodical or possible appearance of a pollutant in the treatment line. Here, there is an option to apply highly-activated nanoparticles supported on substrates or immobilized on membranes, porous materials or graphene oxide. Such methodology exploits the maximum efficiency of nanoparticles but probably has a limited lifetime. This case also refers to relative expensive nanoparticles for specialized treatment processes, protection or sensing setups designed to guard the operation of water purification units from specific pollutants.

3.5 Removal of Heavy Metals

3.5.1 Mechanisms

When used in water purification, nanoparticles are conventionally considered as adsorbents with nanosized units regarding that final loading of pollutants occurs on their surface. However, adsorption is not the only possible mechanism of heavy metals uptake by nanoparticles. Various processes involving electron or ion exchange, optical activation, release of free radicals, precipitation or even alloying may participate and determine capture of soluble heavy metal species.

Adsorption is a favorable mechanism for heavy metals removal as, under optimized conditions, it can achieve both high capacities and non-reversible binding of the pollutant on the nanoparticle. It comes as the result of surface energy and the tendency of atoms on the nanoparticle surface to link to other atoms from the surrounding phase. The presence of the adsorption mechanism is signified through isotherm curves that usually follow a Langmuir (monolayer) or a Freundlich (multiple layers) equation model. There are numerous parameters that determine the nature of adsorption. The chemical affinity between the adsorbent and the adsorbate, which is associated to the geometry and the charge distribution of the solid and the ionic phase, mostly defines the classification of adsorption as physisorption or chemisorption. Chemisorption is characterized by the formation of strong covalent bonds usually through oxygen bridges when the process takes place in aqueous environment. A representative system for chemisorption is the case of As (V) adsorption by ferric oxy-hydroxides where a variety of complexation types (mononuclear monodentate or bidentate and binuclear bidentate inner-sphere complexes shown in Fig. 3.3) may appear according to the proximity of Fe octahedra and As(V) oxyanions (Cornell and Schwertmann 2003). The surface charge of the adsorbent is proved critical for the exact geometry of the binding. Positively-charged adsorbents not only favor the attraction of As(V) oxy-anions but also induce a corner/edge-connectivity of the Fe octahedra while a face-connectivity is promoted when surface charge is negative (Pinakidou et al. 2015).

Direct adsorption is not always spontaneous especially when the targeted heavy metal form is very mobile or uncharged. In this occasion, modifying metal's oxidation state is a sophisticated approach to enable its removal. This can be realized by using adsorbents which potentially act as reducing or oxidizing intermediates and exchange electrons with aqueous species. For example, MnO_2 is used in synergy with ferric oxy-hydroxides to oxidize As(III) to As(V) before adsorption of the last (Moore et al. 2008). Tetravalent Mn can be also incorporated into a single-phase adsorbent by substituting iron in feroxyhyte which then works both as an oxidizing and adsorbent material as shown in Fig. 3.3d (Pinakidou et al. 2016b).

A number of phases can act as heavy metal adsorbents when activated by photons through solar or UV-lamp radiation. Titanium dioxide is the most pronounce case while ZnO, ZrO_2, CeO_2 and Ag are also known for their photocatalytic properties. Photocatalysis is initiated by the excitation of an electron from the valence band

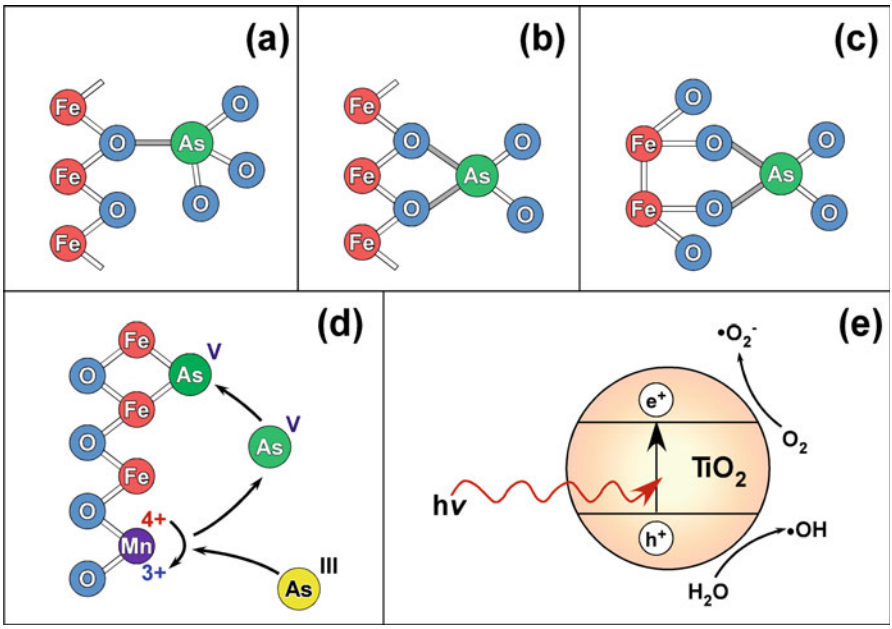

Fig. 3.3 Representative scheme of possible uptake mechanisms of heavy metals by inorganic nanoparticles. Monodentate (**a**) bidentate-mononuclear (**b**) and bidenate-binuclear adsorption complexes of As(V) on an iron oxy-hydroxide. Oxidation-mediated adsorption of As(III) in a Mn(IV)-substituted iron oxy-hydroxide (**d**). Photocatalytic mechanisms releasing free radicals on TiO_2 nanoparticles (**e**)

which is promoted to the conduction band producing a pair of electron and a hole. The photo-excitation results in the release of electrons, hydroxyl radicals (•OH), superoxide anions ($•O_2^-$) and other forms depending on co-existing compounds (Fig. 3.3e), and therefore, can provide multiple mechanisms for the removal of heavy metals for water by involving direct or indirect reduction and oxidation processes (Litter 2015). Typically, TiO_2 nanoparticles are used for the oxidation of As(III) to the less mobile As(V). However, although a large debate is still open on the exact role of free radicals in the oxidation part, it is not clear how the formed As(V) is adsorbed on the solid's surface (Yoon et al. 2009; Choi et al. 2010). To support the As(V) adsorption step, the combination of TiO_2 with iron oxide phases was suggested (Fu et al. 2015). Iron-based materials can also activate free radicals release through Fenton reactions indicating the possibility of secondary mechanisms than direct adsorption to contribute for heavy metal removal. The reactive oxygen species (•OH, $HO_2•/O_2•^-$, Fe(IV)) may be produced either by a homogeneous process triggered by iron dissolution at acidic conditions or a heterogeneous catalysis route (He et al. 2016).

Another common mechanism which results in the removal of heavy metals from the aqueous phase is the modification of their solubility by a change in the oxidation state. For instance, Cr(VI) is a soluble state of chromium whereas Cr(III) has the

tendency to form insoluble hydroxides. Therefore, electron donors can be employed as adsorbents to favor such reduction step with the grown solid to be precipitated on adsorbent's surface. In some cases, the reduction process is enhanced by a dynamic equilibrium between dissolution of metal ions from the bulk structure of the adsorbent to the aqueous phase and their precipitation back to the surface (Gorski et al. 2012). Finally, amalgamation refers to the purification of water from soluble mercury through the formation of insoluble solid solutions with various metals or alloys. In this mechanism, divalent Hg is first reduced to Hg^0 and then diffused to the metal structure resulting in a very stable alloy.

3.5.2 Evaluation Methodology

The performance of adsorbents oriented to meet the drinking water specifications should be initially evaluated by bench-scale experiments followed by their validation in pilot operational units. However, an overview of the literature indicates the absence of a common approach to determine the efficiency of heavy metal adsorbents while in most cases tests are done under "ideal laboratory conditions" very different to those found in drinking water treatment processes. The same issue occurs for engineered nanoparticles developed for heavy metals removal. The dissimilar evaluation criteria applied among research efforts studying nanoparticles as adsorbents hinder the direct classification of removal properties compared to conventional materials or other purification methods. In the following, the prerequisites which ensure the reliable estimation of nanoparticles efficiency are analyzed whereas a universal quality evaluation index specified for heavy metals removal in compliance to drinking water limitations is introduced.

A major modification observed during the transition from wastewater treatment to drinking water purification is related to the much lower initial concentrations of the pollutant that need to be handled. Particularly, a polluted groundwater source hardly provides concentrations of heavy metals higher than 100 μg/L. Proportionally, the permissible concentration after purification should be at most equal to the corresponding drinking water regulation limit for each heavy metal which is usually below 10 μg/L. Therefore, considering that recording of adsorption isotherms is the common methodology to estimate adsorption efficiency of a material, the bench-scale experiments should deliver detailed results in a range of residual concentrations starting from zero (practically as low as the detection limit of analytical method) up to 100–200 μg/L. In addition, the conditions during a laboratory experiment should be as close as possible to those met in natural water. A parameter which is critical for the determination of the removal efficiency for heavy metals is the pH. The pH is directly involved to the effective surface charge of nanoparticles while it also defines the exact speciation of heavy metal ionic forms. For this reason, any study should be carried in the pH range 6–8 which is compatible with drinking water purification processes. Furthermore, the collective interfering effect of the common constituents of natural water should be also taken into account. Anions like HCO_3^-, Cl^-, SO_4^{2-},

SiO_2^-, PO_4^{3-} and cations like Ca^{2+}, Mg^{2+}, Na^+, may act in competition to the targeted heavy metal forms and cause a significant reduction of the removal efficiency. It is known that a decrease of around 50% in the overall efficiency is expected when adsorption experiments are carried out in natural water compared to similar tests in deionized water. Accordingly, the investigation of nanoparticles performance should consider a representative water composition of ions at their average levels of concentration.

After ensuring that nanoparticles efficiency for heavy metals removal will be estimated under conditions similar to those found in drinking water samples, an important task is the proper evaluation of obtained results with respect to the need for direct comparison with other studies and the compliance to the maximum contaminant limit (MCL) for each pollutant. Unfortunately, in the majority of bench-scale experiments, the efficiency of adsorbents is judged through the maximum adsorption capacity (Q_{max}) which is defined by the plateau of the recorded isotherm observed at extremely high residual concentrations (see curve A in Fig. 3.4). In some other cases, the percentage of decrease in initial pollutant concentration after treatment is given as a criterion for the successful adsorbent's performance (see curve C in Fig. 3.4). The weakness of both approaches is that they usually point to high initial and residual concentrations which indeed bring high adsorption capacities and percentage removals but provide no data for the ability to reach low concentrations such as the regulation limits. Depending on the heavy metal removal mechanism, the risk of

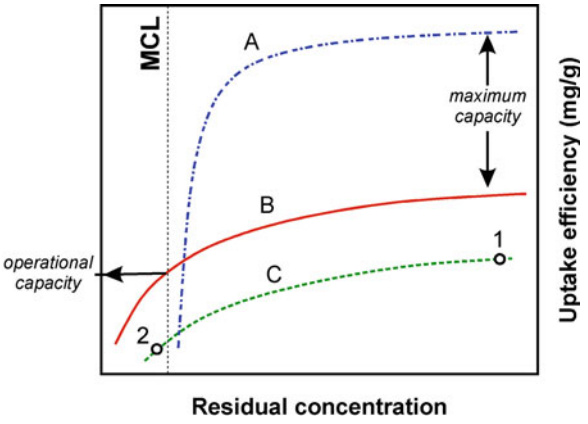

Fig. 3.4 Simplified approach to evaluate applicability of nanoparticles in drinking water purification by adsorption isotherms. *Case A*: material succeeding high maximum capacity but completely fails to decrease pollutant concentration below the MCL. *Case B*: high performing material in the concentration range of the MCL; effective operational capacity is pointed at the section of the curve with the MCL. *Case C* is an example of mistaken use of percentage removal for the evaluation of nanoparticles independently to the residual concentration. Point 1 indicates the removal of 95% of an unrealistic initial pollutant's concentration (e.g. >10 mg/L) succeeding a high residual concentration. Point 2 corresponds to the removal of 70% of a realistic initial pollutant's concentration (e.g. 40 μg/L) reaching residual concentration below the MCL. (Reproduced after modification by Simeonidis et al. 2016 with permission of The Royal Society of Chemistry)

using such evaluation criteria is related to the possible failure of specific nanoparticles to reduce concentration below legislation demands although they achieve very high maximum adsorption capacities. For this reason, a better way to monitor the efficiency of various nanoparticles is by the introduction of an index defined after the adsorption capacity that corresponds to a residual concentration equal to the regulation limit of each pollutant (Q_{MCL}). In practice, this index directly indicates the operational capacity and lifetime of the material and it is estimated by the projection of adsorption isotherm to the MCL of the studied heavy metal (see curve B in Fig. 3.4). For example, the evaluation index for nanoparticles used to remove arsenic should be determined by the adsorption capacity from isotherms at the residual concentration of 10 μg/L. The value of this index is expected to provide a good estimation of the nanoparticles efficiency during the operation of a large-scale unit indicating the maximum operational capacity before their replacement.

The bench-scale adsorption experiments is the best way to get a fast preliminary overview of nanoparticles performance for heavy metal removal and collect important information about their capacity, kinetic and thermodynamic features. However, not always the employment of nanoparticles in water purification is done by their dispersion in contact to the flowing polluted water, a process which is mostly simulated by shaken flasks during typical adsorption experiments. As explained, nanoparticles may be implemented as granulated aggregates or immobilized on supports. Depending on the type of application setup, a much different contact surface and duration would be available suggesting that other kinds of laboratory tests should be carried in order to safely predict the efficiency in large scale. In particular, running rapid small-scale column tests, identical to those used for conventional granular adsorbents, should be an essential step for the evaluation of nanoparticles aggregates under realistic conditions of operation.

3.5.3 Kinetics

The kinetic mechanism of heavy metals uptake on adsorbents is a rather interesting aspect, both for scientific understanding and implementation into real applications. In this regard, the adsorption rate for a specific pollutant is not just a determinant parameter for the qualification of studied phases but it can also dictate the design parameters for scale-up such as the contact configuration, the installation's capacity and the treatment rate. In addition, modelling of kinetic data initiates the deconvolution of the occurring uptake mechanism; a primary milestone for the optimization of an adsorbent.

Ideally, adsorption refers to the chemical interaction between the adsorbent's surface and the pollutant's species resulting in the formation of complex structures. For this reason, adsorption reaction models, which are derived from the kinetics of chemical reaction equations, are very popular among those studies which aim to

provide batch kinetic data as complementary information during the development of novel adsorbents. The major adsorption reaction models are described by the pseudo first-order and the pseudo second-order equations, $\frac{dQ}{dt} = k_i(Q_e - Q)^i$, with i taking the values 1 and 2, respectively, Q the adsorption capacity, Q_e the adsorption capacity at equilibrium, t the contact time, k_i the rate constant. In general, the vast majority of works reporting on the kinetic of heavy metals adsorption by inorganic nanoparticles fit experimental data using the pseudo first-order and pseudo second-order equations with the second model always showing better correlation coefficient (Tan and Hameed 2017). At first thought, this implies to the domination of surface reaction step in the control of overall adsorption rate for nanoparticles. Therefore, the use of nanoparticles in water treatment is supposed to enhance the uptake rate compared to conventional adsorbents due to the higher specific surface area. This assumption is not always validated by the experimental results of comparative adsorption studies involving nanoparticles and aggregates of the same phase. For instance, the adsorption rates of As(III) and As(V) by hematite nanoparticles (~120 nm) showed no significant difference compared to those for large aggregates (>700 nm) when fitted by a the pseudo second-order equation (Dickson et al. 2017). Another interesting finding, which probably explains the similar rates, is that nanoparticles tend to aggregate and sedimentate during the initial fast adsorption stage.

On the other hand, it is to be noted that both adsorption reaction models are just empirical expressions showing good fitting performance for any kind of adsorbent (nanosized or conventional granular) but lacking of any obvious physical and theoretical basis (Qiu et al. 2009). Even worse, the usually followed linearization of initial equations enhances the error of calculated parameters (Tran et al. 2017). According to these remarks, the commonly delivered fitting of adsorption rate on nanoparticles by a pseudo-second-order equation can be excellent to describe the experimental curves but appear completely meaningless in the effort to predict the kinetic mechanisms. On the same rationale, the calculated constants of these models (k_1, k_2) cannot be safely used for direct comparison between nanoadsorbents or the design of large-scale adsorption systems, especially if a configuration setup different than a batch stirring tank is employed. Despite the aforementioned difficulties to evaluate adsorption reaction kinetic modelling, an overview of the literature indicates higher k_2 values for nanoparticles as compared to adsorbents with conventional dimensions (Ho et al. 2000).

As explained, adsorption reaction models represent a mere routine to describe the complexity of liquid adsorption kinetics. However, a general course of the adsorption process includes also a number of mass transfer steps able to modify the adsorption rate. The class of adsorption diffusion models are based on the kinetic modelling of these steps. Among them, film diffusion refers to the transport of the pollutant from the bulk phase to the external surface of the adsorbent while pore diffusion corresponds to the sequential transport to the adsorbent's pores. Considering that the pore diffusion step does not occur and the external mass transfer is eliminated under the intense mixing of batch kinetic experiments, the diffusion

model should be simplified in the case of isolated nanoparticles. But since aggregation of nanoparticles is a very common effect, the small contribution of intraparticle diffusion in the voids formed between particles cannot be neglected. A number of works indicate the important role of intraparticle diffusion in the adsorption of heavy metals on iron-based nanoparticles (Jiang et al. 2013; Simeonidis et al. 2017b).

Last, it should be mentioned the recent development of a phenomenological model that takes into account the physics of the adsorption process and the specific structure of the adsorbent (Tresintsi et al. 2015). This approach represents a step beyond the typical evaluation of kinetic experiments for nanoadsorbents. The model considers the structure of a highly efficient arsenic adsorbent (Mn-feroxyhyte nanoparticles), the special characteristics of the heavy metal (As(III) or As(V)) and the theories of pore and surface adsorption to describe adsorption kinetics in small and large aggregates. In particular, fitting of the kinetic data for small aggregates, which present an initial very high adsorption rate followed by a slower part, requires the assumption of two types of adsorption sites. The first type corresponds to the adsorption on the external nanoparticles surface while the second type is located into the structure's vacancies of the nanoparticles (solid state diffusion). The extension of similar material-specific approximations for more nanoadsorbent/pollutants systems is expected to shed light in the mechanisms defining the dynamics of heavy metal adsorption in nanoparticles.

3.5.4 Categories

The qualification of the proper adsorbent for a particular heavy metal is based on a number of conditions defined by the uptake mechanism of pollutant's species. High chemical affinity, proper adjustment of surface charge, and incorporation of ion or electron exchange potential are commonly mentioned as possible directions of optimization. This section discusses the most favorable approaches for the removal of heavy metals from drinking water following a preliminary classification to divalent cations (Pb, Cd, Ni, Hg), high-valent ions (Cr, Mo, Se, U) and oxy-ionic species (As, Sb). An ideal profile of a nanoparticulate adsorbent is described particularly for each separate heavy metal, with respect to its speciation in natural water environment, including representative studies from the literature. It should be underlined that the current review focuses on cases were potential implementation for purposes in drinking water purification is supported, at least indirectly. A thorough overview of recent progress in the research related to nanoparticles and heavy metal removal is given in Tang and Lo (2013), Gómez-Pastora et al. (2014), Ray and Shipley (2015), Adeleye et al. (2016), Lata and Samadder (2016), Santhosh et al. (2016), Simeonidis et al. (2016), and Gómez-Pastora et al. (2017).

3.5.4.1 Divalent Cations

3.5.4.1.1 Lead

Dissolved lead in water is usually correlated to the flow through lead-containing pipes which stayed in use till recently. The leaching mechanism includes the oxidation of Pb^0 by dissolved oxygen or chlorine to Pb^{2+} followed by the reaction of intermediate complexes with carbonates or hydroxides to produce deposits like $PbCO_3$ and $Pb(OH)_2$ (Xie et al. 2010). The gradual dissolution of corrosion products enriches water with Pb ionic forms. Lead appears in the positively charged forms Pb^{2+} and $Pb(OH)^+$ in the pH range of natural water, with the percentage of the hydroxylated form increasing at higher pH values. Therefore, the incorporation of an adsorbent with negatively charged surface would provide such conditions that favor the approach of lead species by electrostatic attraction. Accordingly, applied solids should preserve a point of zero charge (PZC) located in the acidic range. Divalent lead has a first-shell coordination with 3–12 oxygens implying to an effective ionic radius up to 1.49 Å (Krauskopf and Ernst 2002). Depending on the chemistry of the solid's surface, the adsorption of lead species may proceed by the formation of inner sphere complexes or by physisorption. For metal (oxyhydr)oxides, the binding of Pb^{2+} at neutral pH values involves the exchange of H^+ and the formation of a mononuclear bidentate type complex ($\equiv(FeOO)_2Pb$) especially at low surface coverages. This kind of complexation is enhanced at higher pH values where deprotonation is favored although the partial appearance of lead precipitates cannot be excluded.

A number of works studied different kinds of inorganic nanoparticles for the removal of lead from water providing indications about their potential efficiency under drinking water treatment conditions that comply also with the regulation limit of 10 μg/L (Table 3.2). Titanium dioxide nanoparticles with a size of 8.3 nm were examined for the removal of Pb and other divalent metals (Engates and Shipley 2011). Due to the low point of zero charge, TiO_2 nanoparticles appear efficient to adsorb at least 4 mg Pb/g from polluted tap water with pH 8, while keeping a residual concentration well-below MCL. Authors suggest that TiO_2 nanoparticles also introduce a much faster adsorption kinetic rate compared to the bulk material being also many times more efficient than Fe_3O_4 nanoparticles or activated carbon. Hematite nanoparticles were found with a smaller capacity (2 mg Pb/g) though they still succeed to achieve residual concentrations below MCL (Shipley et al. 2013). The adsorption of lead on hematite is a spontaneous endothermic process which is enhanced as the pH moves from 6 to 8 since PZC of nanoparticles is located at 6.8. On the other side, Pb adsorption on electrochemically synthesized Fe_3O_4 nanorods is possible only at high concentrations but capacity approaches zero when dealing with the common concentrations of polluted natural waters (Karami 2013). Finally, adsorption data for zirconia-based nanoparticles ($ZrSiO_4$) cannot support their use for drinking water treatment although they showed some weak

uptake capacities at extremely high concentrations of solid and Pb (Mahmoud et al. 2015).

3.5.4.1.2 Cadmium

The presence of cadmium in natural water is usually attributed to anthropogenic activities and especially to the leaching from galvanized pipes, fittings and water coolers. Unlike lead, cadmium appears exclusively in the form Cd^{2+} in the whole pH range of natural water, thus presenting more or less the same requirement of negatively charged surface by potential adsorbents. The hydroxylation of Cd^{2+} initiates above pH 9 and for this reason solvation effects are more favorable than in the case of Pb implying to a lower tendency to approach adsorbents surface (Zhao et al. 2016). At neutral pH values, cadmium ions are normally hydrated by six water molecules $Cd(H_2O)_6^{2+}$ keeping an ionic radius of 0.95 Å (Tansel 2012). The same coordination number is preserved during cadmium adsorption on inorganic (oxyhydr)oxides where cadmium forms inner-sphere bidentate or even tridentate complexes without any significant effect from occurring pH values (Krauskopf and Ernst 2002).

In most cases, cadmium adsorption by inorganic nanoparticles is discussed in comparison to that of lead (Table 3.2). Among published works, TiO_2 nanoparticles offered the highest uptake capacity for Cd according to the drinking water standards reaching a capacity of around 4.5 mg Cd/g at pH 8 using polluted tap water (Engates and Shipley 2011). Zirconia nanoparticles with a mean diameter of 13 nm showed also some weak tendency to capture Cd at low concentrations (Gusain et al. 2016). On the opposite side, the estimated capacity at the MCL of 5 μg/L for other systems like α-Fe_2O_3 (Shipley et al. 2013), Fe_3O_4 (Karami 2013) and $ZrSiO_4$ (Mahmoud et al. 2015) is equal or very close to zero. Disappointingly, relevant research performed by applying zero valent iron (Boparai et al. 2011) and ZnO (Sheela et al. 2012) nanoparticles cannot be evaluated due to the absence of any information on the adsorption pH and the extremely high concentrations of Cd test solutions. However, given thermodynamic data for uptake at high concentrations describe a spontaneous endothermic adsorption on Fe and an exothermic process on ZnO.

3.5.4.1.3 Nickel

Nickel appears in water supplies as a result of corrosion processes on steel construction but under specific conditions has the potential to dissolve from the soil. Although nickel's naturally occurring forms are highly insoluble hydroxides or sulfides, whenever nickel becomes soluble it is very stable at neutral pH. Nickel speciation is very similar to that of Cd with Ni^{2+} being the dominant species at the pH range 6–8. The hydroxylation is observed at a pH above 9.5 slightly higher than that for Cd signifying a higher mobility and a proportional difficulty to be adsorbed by solid surfaces. Divalent Ni also appears in hexaaquo- ions at neutral pH values

Table 3.2 Summary of research studies on Pb, Cd, Ni, Hg adsorption by nanoparticles with potential interest for drinking water treatment

Phase	Type	Size (nm)	Heavy metal	PZC	pH	Water	Estimated Q_{MCL} (mg/g)	References
TiO_2	Particles	8.3	Pb	5.2	8	Tap	4.0	Engates and Shipley (2011)
			Cd				4.5	
			Ni				1.8	
α-Fe_2O_3	Particles	30	Pb	6.8	8	Tap	2.0	Shipley et al. (2013)
			Cd				0.2	
Fe_3O_4	Rods	60 × 950	Pb	4.2	5.5	Distilled	~0	Karami (2013)
			Cd					
			Ni					
$ZrSiO_4$	Particles	40	Pb	ND	7	Distilled	~0	Mahmoud et al. (2015)
			Cd					
ZrO_2	Particles	13	Cd	6.8	7	Distilled	0.2	Gusain et al. (2016)
Au	Particles	13	Hg	ND	7	Groundwater	20	Lo et al. (2012)
Fe_3O_4@SiO_2	Particles	50	Hg	4	6	Tap	5	Hakami et al. (2012)
(Fe,Mn)OOH	Spheres	200	Hg	7.6	7	Tap	2.5	Kokkinos et al. (2017)

ND not defined by authors

and low concentrations. However, during its adsorption on metal (oxyhydr)oxides, Ni^{2+} forms inner-sphere complexes coordinated with six atoms at pH >7 but may give weakly bound outer-sphere complexes at pH <7. The ionic radius for Ni^{2+} is 0.70 Å very close to that for Co^{2+}, Zn^{2+} and Cu^{2+} (Tansel 2012).

A very limited number of works is focused on the removal of nickel from water employing nanoparticles of inorganic phases (Table 3.2). Even worse, none of them clearly examines the possibility of their use as drinking water adsorbents. The most promising result comes from the negatively-charged TiO_2 nanoparticles of Engates and Shipley (2011). A capacity of 1.8 mg Ni/g was estimated from the given data as the efficiency of this material to remove Ni from tap water below the residual concentration of 20 μg/L which stands as the current MCL. In comparison to the corresponding values for Pb and Cd, it is clear that Ni shows a significant lower affinity for adsorption. Magnetite nanorods are practically inefficient to remove Ni in terms of drinking water treatment demands (Karami 2013). Finally, alumina nanoparticles (20 nm) indicate some good removal efficiencies at large concentrations but given data indicate a very low performance at concentrations below 1 mg/L which is attributed to the high PZC (7.9) of the material (Srivastava et al. 2011). In addition, critical parameters for the evaluation, like the adsorption pH, are not mentioned by the authors.

3.5.4.1.4 Mercury

Mercury's presence is not so frequent in natural water resources, however, its removal from drinking water is a very challenging field taking into consideration the high toxicity of mercury species and the low MCL of 1 μg/L. The origin of its presence can be both natural and industrial (volcanos, fires, combustion processes). The hydroxylated and chlorinated forms of mercury ($Hg(OH)_2$, HgClOH) are dominant in the pH range of natural water with some precipitation appearing in the weak alkaline region. After that, their adsorption in negatively charged metal hydroxides is more favorable. The coordination of Hg^{2+} is the distorted octahedral one with the two bonds being shorter than the other four. For this reason the formation of both inner-sphere monodentate and bidentate complexes is possible during adsorption of Hg^{2+} species on metal (oxyhydr)oxides.

A variety of nanoparticle systems have been tested for Hg removal from water (Table 3.2). Gold nanoparticles embedded on activated Al_2O_3 adsorbent show high selectivity against Hg^{2+} species explained by the formation of Au-Hg amalgams (Lo et al. 2012). The study was performed using low concentrations of Hg (200 μg/L) but still a capacity of 20 mg Hg/g (reduced to the mass of Au) was achieved for total removal of Hg. Nevertheless, the high cost of Au restricts the application of such systems only for analytical purposes rather than large-scale water purification. A better expectancy comes from functionalized silica-coated Fe_3O_4 nanoparticles which gave relative good efficiency for the removal of Hg below its MCL when tested in polluted tap water (Hakami et al. 2012). The observed efficiency of 5 mg Hg/g is mainly attributed to the selectivity of thiol groups while

nanoparticles are considered as a carrier for the application and magnetic separation of the nanoadsorbents. Mercury adsorption by thiol-functionalized nanoparticles is an exothermic process slightly affected by the pH or coexisting anions providing also the possibility for the regeneration and recovery of Hg. In another case, TiO_2 nanoparticles (9.1 nm) were studied for their ability to capture Hg when exposed to UV irradiation (Dou and Chen 2011). Unfortunately, published data refer only to high Hg concentrations, thus, the estimation of possible implementation in drinking water purification is not feasible. So far, the study of Mn-substituted iron oxy-hydroxide nanospheres is the best established case for the development of mercury adsorbents (Kokkinos et al. 2017). In particular, synthesis in an alkaline and highly oxidizing environment favors the enhancement of the negative surface charge density maximizing the efficiency for Hg^{2+} uptake. Mercury adsorption is exothermic involving both doubly and triply coordinated oxygen atoms. The application of negatively-charged (Fe,Mn)OOH as granules (aggregated nanospheres) in a column filter setup, showed a capacity of 2.5 mg Hg/g while keeping residual concentration below the MCL.

3.5.4.2 High-Valent Ions

3.5.4.2.1 Chromium

Hexavalent chromium is by far the most studied form in this category of heavy metal species. Such interest was triggered by the recent extended discussion on its toxicity by the drinking water consumption path in combination to the practical absence of any specific regulation beyond the total chromium MCL of 50 or 100 μg/L. Furthermore, studies indicated the intensity of the problem by revealing a high frequency of Cr(VI) presence among drinking water resources. Both anthropogenic and geological procedures have been accused for chromium release to water (Kaprara et al. 2015). Chromium is a naturally occurring element found as Cr(III), which is considered as nutrient, and Cr(VI) a very oxidative and toxic compound. In groundwater, Cr(VI) is the dominant form due to its high mobility and weak tendency to be adsorbed. Aqueous speciation of Cr(VI) indicates CrO_4^{2-} as major species in the pH range of drinking water (Kazakis et al. 2015). However, in practice, the exact speciation and hydration of CrO_4^{2-} is not critical for its removal at concentration levels below 10 μg/L. Testing of several inorganic materials suggests that CrO_4^{2-} adsorption increases with decreasing pH and maximizes when the PZC is reached. This is a strong indication of an outer-sphere complexation favored by the high valence of Cr(VI). Redox-active solids are more favorable to uptake Cr(VI) since they provide an intermediate reduction step to the insoluble Cr(III) hydrolysis products. Therefore, an ideal adsorbent for the uptake of Cr(VI) should have a positively charged surface to attract chromate anions combined by high electron donation ability to cause their reduction.

In this direction, much research effort has been attributed in the development of redox-active nanoparticles able to eliminate Cr(VI) concentration by the reduction-

precipitation of Cr(III). Numerous studies refer to zero-valent iron (ZVI) (Shi et al. 2011; Petala et al. 2013; Nahuel Montesinos et al. 2014; Zhou et al. 2015; Poguberović et al. 2016; Toli et al. 2016; Wang et al. 2016a) and Fe_3O_4 (Luo et al. 2013; Kumari et al. 2015; Rajput et al. 2016) nanoparticles, whether as pure nanomaterials or embedded on supports, due their potential to provide electrons for the reduction of Cr(VI) in combination to their magnetic behavior which enables easy separation. However, the obtained results are only of fundamental research interest since extreme Cr(VI) concentrations and adsorption pH values are applied. Similarly, not much information can be extracted for the potential of other nanoparticles consisting of γ-Fe_2O_3 (Hu et al. 2005a), $MnFe_2O_4$ (Hu et al. 2005b; Ahalya et al. 2014), ZnO (Khan et al. 2013), TiO_2 (Paul et al. 2014), Al_2O_3 (Paul et al. 2014; Dubey et al. 2016), CeO_2 (Recillas et al. 2010), CuO (Gupta et al. 2016), MgO (Oladoja et al. 2016) and many bimetallic oxides and hydroxides (Jaiswal et al. 2015; Wang et al. 2015) to operate sufficiently for drinking water treatment, as a consequence of the improper evaluation carried out.

There are hopefully a bunch of works that successfully face Cr(VI) removal from drinking water or at least provide enough data for an indirect estimation of developed nanoparticles potential (Table 3.3). For instance, ZVI nanoparticles supported on mesoporous silica (Sun et al. 2014), mesoporous carbon (Dai et al. 2016) or humus (Fu et al. 2017) were tested at pH values 5–6.3 in distilled water presenting a significant ability to decrease Cr(VI) concentration below the 50 μg/L. Although such pH range cannot be directly assigned to the drinking water conditions, values such as the 118 mg Cr(VI)/g of ZVI content supported on mesoporous silica should be taken into serious consideration. Recently, a series of studies discussed the impact of inorganic nanoparticles for Cr(VI) uptake under the prism of their use in representative conditions of a drinking water purification unit aiming to comply to the current and the upcoming regulation limits. Magnetite nanoparticles with a size of 30 and 80 nm either dispersed or as aggregates were evaluated according to their capacity corresponding to residual Cr(VI) concentrations equal to the current MCL or even lower (Simeonidis et al. 2013, 2015; Kaprara et al. 2016). Their efficiency is proportional to the diameter following a decreasing trend upon size increment. However, water/solid contact configuration is another important parameter defining Cr(VI) removal. In particular, granules formed by particle aggregates and used in column filters almost doubled the removal capacity compared to that from the dispersion of the separated counterparts. X-ray absorption spectroscopy analysis on the uptake mechanism of Cr(VI) by Fe_3O_4 nanoparticles indicated that Fe^{2+} ions work as electron donors to activate the precipitation of Cr(VI) to Cr(III) (Pinakidou et al. 2016c). The Cr(III) oxy-anions are then adsorbed on the nanoparticles surface forming bidentate binuclear or monodentate complexes. At the same time, the consumption of Fe^{2+} causes the stabilization of a γ-Fe_2O_3 layer which, together with the precipitated Cr(III), is responsible for the gradual passivation of the nanomaterial. A similar passivation effect is the main drawback of ZVI nanoparticles when applied for Cr(VI) reduction. Despite their higher Cr(VI) uptake capacity compared to Fe_3O_4, the inhibition of surface oxidation even before their contact with polluted water, is practically unattainable. On this, tin-based nanoparticles

Table 3.3 Summary of research studies on high-valent ions Cr(VI), Mo(VI), Se(IV), Se(VI) and U(VI) uptake by nanoparticles with potential interest for drinking water treatment

Phase	Type	Size (nm)	Heavy metal	pH	Water	Estimated Q_{MCL} (mg/g)	References
ZVI/SiO_2	Supported particles	25	Cr(VI)	5	Distilled	118	Sun et al. (2014)
ZVI/C	Supported particles	25	Cr(VI)	5.6	Distilled	8.3	Dai et al. (2016)
ZVI/humus	Supported particles	100	Cr(VI)	6.3	Distilled	10	Fu et al. (2017)
Fe_3O_4	Particles	30	Cr(VI)	7	Tap	1.8	Simeonidis et al. (2015)
Fe_3O_4	Aggregated	30	Cr(VI)	7.2	Tap	4.5	Kaprara et al. (2016)
Fe_3O_4	Particles	80	Cr(VI)	7	Distilled	0.9	Simeonidis et al. (2013)
ZVI	Particles	45	Cr(VI)	7	Distilled	3.5	Simeonidis et al. (2013)
$Sn_6O_4(OH)_4$	Particles	30	Cr(VI)	7	Tap	7	Pinakidou et al. (2016a)
Fe_3O_4	Particles	6	Se(IV)	5.6	Distilled	0.02	López de Arroyabe Loyo et al. (2008)
Fe_3O_4	Particles	27	Se(IV)	6	Distilled	0.04	Gonzalez et al. (2012)
			Se(VI)			–	
Fe_3O_4	Particles	15	Se(IV)	6	Distilled	0.5	Wei et al. (2012)
Fe_3O_4	Particles	ND	Se(IV)	5.3	Distilled	0.06	Kwon et al. (2015)
Fe_3O_4	Supported particles	15	Se(IV)	7	Distilled	1.9	Fu et al. (2014)]
			Se(VI)			–	
Mn_3O_4	Particles	25	Se(IV)	6	Distilled	0.04	Gonzalez et al. (2011)
			Se(VI)			0.03	
ZVI	Particles	5	U(VI)	7	Groundwater	300	Li et al. (2015)
(Fe,Mn)OOH	Spheres	200	U(VI)	7	Tap	4	Dimiropoulos et al. (2015)

ND not defined by authors

includes a high perspective for a redox-active material able to overcome passivation problems (Pinakidou et al. 2016a). The developed $Sn_6O_4(OH)_4$ nanoparticles are advantageous not only because of the large number of electrons delivered by the Sn^{4+} for Cr(VI) reduction but also due to their surface stability against secondary oxidation processes. Produced Cr(III) species are directly adsorbed on tin oxy-hydroxides surface by an inner-sphere non-reversible complexation.

3.5.4.2.2 Molybdenum

For the time, hexavalent molybdenum is not a heavy metal form of high priority for drinking water treatment. This is signified by the absence of a MCL whereas some advisory guidelines for 40 or 70 μg/L are only valid according to the essential daily requirement for human. Even though it appears very similar to Cr(VI), Mo(VI) is a weaker oxidant with only few evidence existing on possible health effects caused by its consumption through the drinking water path. However, its presence is very common in both ground and surface waters mainly originating from industrial activities like nuclear, electricity or petroleum plants. Furthermore, considering the fast-growing use of molybdenum in many products and the fact that the Mo (VI) species have a lifetime of thousands of years, it can be predicted that much attention will be given for the development of its removal or recovery in the near future. The aqueous speciation of Mo(VI) is identical to that of Cr(VI) with the MoO_4^{2-} appearing as the dominant form above pH 6.

The research related to the removal of Mo(VI) from water is rather limited (Table 3.3). Direct adsorption or reduction to less soluble forms at a lower oxidation state e.g. Mo(IV) are potential ways for its uptake by adsorbents. Adsorption of Mo (VI) on inorganic oxy-hydroxides is mentioned to take place by ligand exchange with hydroxyl ions resulting in inner-sphere complexation (Goldberg et al. 1996). Proportionally, a small number of works refers to the use of nanoparticles oriented for Mo(VI) removal from water. Suggestively, γ-Fe_2O_3 (Afkhami and Norooz-Asl 2009), $ZnFe_2O_4$ (Tu et al. 2016) and $CuFe_2O_4$ (Tu et al. 2014) were tested in this direction but under evaluation conditions and concentration levels much different than those met in drinking water treatment. Thus, the validity of such works should be considered more for wastewater treatment or molybdenum recovery procedures.

3.5.4.2.3 Selenium

Selenium is dissolved in water resources by the weathering of calcareous sedimentary rocks or by agricultural activities. It is controversial that at the same time selenium is a nutrient and a toxic trace element for human depending on its concentration and oxidation state. For this reason, in some countries its concentration in drinking water is regulated by the strict MCL of 10 μg/L while in others a guideline is unnecessary estimating that selenium deficiency is a greater problem than its toxicity. Things become more complicated as the presence of Se(IV), Se

(VI) or a mixture of these species is almost equally possible in natural water. Selenite appears more toxic but shows a higher tendency for strong adsorption than the Se (VI) form. Under oxidizing conditions, Se(VI) dominates in the form of SeO_4^{2-} whereas a more reducing environment favors Se(IV) species and particularly a coexistence of $HSeO_3^-/SeO_3^{2-}$ in the pH of natural waters. Adsorption of Se (IV) on inorganic (oxyhydr)oxides involves the formation of bidentate binuclear complexes while Se(VI) sorption is performed through outer-sphere or inner-sphere monodentate complexes.

An increasing number of publications are dealing with nanoparticles implementation for the removal of selenium species from water with few of them providing sufficient data to be evaluated for drinking water purification (Table 3.3). In general, Se(VI) is strongly captured only after its reduction to insoluble Se^{2-} compounds with Se(IV) species to be preferably removed by direct adsorption. Magnetite nanoparticles are frequently tested as potential selenium adsorbents but only with poor efficiency (López de Arroyabe Loyo et al. 2008; Gonzalez et al. 2012; Wei et al. 2012; Kwon et al. 2015). It is estimated that, in most cases, the removal capacity for Se(IV) hardly reaches 0.5 mg Se/g at the pH range 5.5–6 while Fe_3O_4 nanoparticles are practically inefficient to decrease Se(VI) below the MCL. An exception appears for the composite consisting of Fe_3O_4 nanoparticles embedded on graphene oxide which gave a capacity of 1.9 mg Se(IV)/g of Fe_3O_4 at the MCL (Fu et al. 2014). Another system which was evaluated at residual concentrations below the MCL but still indicated a low removal capacity for both Se(IV) and Se(VI) was Mn_3O_4 nanoparticles (Gonzalez et al. 2011). Several other nanoparticulate phases including TiO_2 (Zhang et al. 2009; Jordan et al. 2011), ferrites (Gonzalez et al. 2010; Sun et al. 2015) and iron oxides (Jordan et al. 2014; Lounsbury et al. 2016) were studied for the adsorption of selenium from water, but presented results whether refer to extremely low pH values and high concentrations or the estimated adsorption capacity is zero. Redox-active nanoparticles consisting of ZVI (Olegario et al. 2010; Ling et al. 2015) and FeS (Mitchell et al. 2013) were introduced as alternatives for the reduction of Se(VI), however, carried experiments were not focused on drinking water treatment conditions.

3.5.4.2.4 Uranium

Regarding its radioactivity, dissolved uranium is not as dangerous as the metallic form. However, when ingested in human beings by drinking water, hexavalent uranium can cause severe damages especially to the kidney. Mining activities is the main origin of groundwater pollution by U(VI). In general, U(IV) from minerals gets oxidized upon exposure to the atmosphere producing U(VI) which is then released to water streams. In well-oxygenated water resources, there is a higher frequency of U(VI) appearance usually in the form of anionic carbonate complexes, $UO_2(CO_3)_2^{2-}$ at pH <7 and $UO_2(CO_3)_3^{4-}$ at pH >8. Uranium concentration in drinking water is currently regulated by a guideline of 30 μg/L which is equivalent

to a radioactivity of 30 pCi/L. The same value is expected to become worldwide the MCL for uranium.

Not many research works have been reported for U(VI) uptake by inorganic nanoparticles (Table 3.3). In some of them, ZVI is used in order to introduce a reduction mechanism to the less mobile U(IV) form. Under anoxic conditions, ZVI nanoparticles were found to provide extremely high U(VI) capacities reaching 300 mg U(VI)/g (Li et al. 2015). However, during the process huge amounts of iron corrosion products are released to water; at the same time, in the presence of dissolved oxygen the ZVI surface is rapidly passivated and the precipitated U(IV) is easily redissolved. The reducing precipitation of U(VI) by ZVI nanoparticles is also described in other studies but under pH values far from those met in drinking water (Crane and Scott 2014; Sheng et al. 2014). Magnesium oxide nanoparticles indicated limited potential to decrease U(VI) concentration below the MCL (Camtakan et al. 2012). On the opposite, Mn(IV)-substituted feroxyhyte nanospheres tested under conditions simulating a drinking water treatment unit were able to capture around 4 mg U(VI)/g keeping the residual concentration below 30 μg/L (Dimiropoulos et al. 2015). Aggregated particles of the same nanomaterial were also applied for column experiments illustrating the potential for implementation in existing water purification units. Adsorption of U(VI) on Mn-feroxyhyte nanoparticles is a spontaneous endothermic process involving physisorption due to the presence of carbonate ions.

3.5.4.3 Oxy-Ionic Species

3.5.4.3.1 Arsenic

Through drinking water, more than 200 million people globally are exposed to higher than safe levels of arsenic. Clearly, water treatment for arsenic is the most discussed subject related to heavy metals removal and not only for nanoparticles but any kind of adsorbents and methods. The frequency of appearance in ground and surface water, the significant decrease of the MCL from 50 to 10 μg/L at the beginning of this century and the remarkable chemistry and complexation of its aqueous species are some of the reasons explaining such interest. The high request for arsenic adsorbents is also demonstrated by the numerous available commercial products usually based on iron oxy-hydroxides, activated alumina and titania. Arsenic usually enters water resources by geological deposits or even from agricultural and industrial activities on the surface. Depending on the oxygenation of the reservoir, arsenic is met in two oxidation states, the As(III) and the As(V). In well-oxygenated waters, As(V) is the dominant specie while in fewer occasions elevated As(III) may also appear introducing a more intense problem due to its higher toxicity and mobility. These species have rather different behavior since As(III) hydrated forms are neutral (H_3AsO_3) in the pH range of natural waters and As(V) is distributed between $H_2AsO_4^-$ and $HAsO_4^{2-}$ oxy-anions. As a general rule, As(V) -oxy-anions have high affinity to solids containing Fe^{3+} in their structure forming very stable inner-sphere complexes through oxygen bridges. For this reason, iron

oxy-hydroxides are considered as the best class of As(V) adsorbents. Apart from the chemical affinity, another critical parameter for an efficient As(V) adsorbent is the surface charge density. Particularly, positively-charged materials provide a good substrate for the attraction of $H_2AsO_4^-$ or $HAsO_4^{2-}$. Furthermore, ion-exchange with similar ionic forms like SO_4^{2-} may increase adsorption capacity by providing highly-active sorption sites. However, these features does not have any impact to the removal of uncharged As(III) species and as a consequence, none of the defined as good As(V) adsorbents manage to offer a similar performance against As(III). The pre-oxidation of As(III) to As(V) is the usual strategy to overcome this weakness. Materials working as electron acceptors are combined with common arsenic adsorbents in order to favor an oxidation step followed by the adsorption of formed As(V).

On this approach, expectations by inorganic nanoparticles mainly arise from the possibility of tuning their surface charge and morphology. It should be noted that compared to the cases of other heavy metals, the field of arsenic removal is rather competitive since commercial adsorbents are offered at a very low cost achieving high efficiencies while alternative methods (coagulation) are also applicable. A wide variety of phases, usually metal oxides or their hydrated counterparts, has been tested for As(III) and As(V) removal in the form of nanoparticles (Table 3.4). Iron-based nanoparticles are a frequent choice due to the relative low cost and the good affinity to arsenic species. In this category, the best results are coming from phases like iron oxy-hydroxides (FeOOH) and α-Fe_2O_3 due to the high specific surface area, the positive charge and the strong sorption binding through inner-sphere complexes. More specifically, schwertmannite nanospheres consisting of small nanoparticles showed an enhanced capacity, especially for the uptake of As(V), reaching a value of 13.5 mg As(V)/g (Tresintsi et al. 2012). Column experiments with the same material indicated the superiority of this adsorbent as compared to conventional commercial iron oxy-hydroxides. Such efficiency is attributed to the synthesis conditions using acidic environment with high redox and excess of sulfate ions which bind strongly to the particles offering an ion-exchange mechanism with As(V) oxy-anions (Tresintsi et al. 2014b). In order to combine high As(V) removal with sufficient As(III) adsorption, the same nanoparticles were modified by partial substitution of Fe^{3+} by Mn^{4+} (Tresintsi et al. 2013). This increased As(III) adsorption up to 6.7 mg As(III)/g while keeping residual concentration below 10 μg/L by adding an oxidation step to As(V) after reaction with Mn^{4+} (Tresintsi et al. 2014a). Hematite-coated magnetic nanospheres also appear capable to decrease As(III) and As(V) concentrations below the MCL but without achieving the capacities of iron oxy-hydroxides (Simeonidis et al. 2011).

Not very high but competitive capacities are provided by zero-valent iron, Fe_3O_4 and γ-Fe_2O_3 nanoparticles, which are nonetheless many times preferable for their magnetic properties. Under drinking water treatment conditions, zero-valent nanoparticles usually succeed efficiencies below 2 mg/g for both As(III) and As(V) (Kanel et al. 2005; Zhu et al. 2009; Gupta et al. 2012). However, an exceptional value of around 5 mg As(V)/g was reported for 15 nm Fe nanoparticles (Kanel et al. 2006). In any case, the spontaneous oxidation and hydration of iron's surface indicates that adsorption is always carried out on the formed surface oxides or

Table 3.4 Summary of research studies on As(III), As(V), Sb(III) and Sb(V) uptake by nanoparticles with potential interest for drinking water treatment

Phase	Type	Size (nm)	Heavy metal	PZC	pH	Water	Estimated Q_{MCL} (mg/g)	References
FeOOH	Spheres	200	As(III)	3.1	7	Tap	1.9	Tresintsi et al. (2012)
			As(V)				13.5	
(Fe,Mn)OOH	Spheres	200	As(III)	2.9	7	Tap	6.7	Tresintsi et al. (2013)
			As(V)				11.7	
α-Fe_2O_3@Fe_3O_4	Spheres	300	As(III)	7.7	7	Distilled	2.1	Simeonidis et al. (2011)
			As(V)				1	
ZVI	Particles	15	As(III)	7.8	7	Groundwater	0.4	Kanel et al. (2005)
ZVI	Particles	80	As(III)	ND	7	Distilled	0.4	Gupta et al. (2012)
			As(V)					
ZVI	Needles supported	200 × 1500	As(III)	ND	6.5	Distilled	1.6	Zhu et al. (2009)
			As(V)					
ZVI	Particles	15	As(V)	7.8	7	Groundwater	5	Kanel et al. (2006)
Fe_3O_4	Particles	12	As(III)	ND	8	Distilled	1	Yavuz et al. (2006)
			As(V)					
Fe_3O_4	Particles	15	As(III)	ND	7	Distilled	2	Lunge et al. (2014)
γ-Fe_2O_3	Particles	23	As(V)	7.9	7	Distilled	1	Park et al. (2009)
$MgFe_2O_4$	Particles	3.7	As(III)	5.2	7	Tap	9	Tang et al. (2013)
			As(V)				10	
TiO_2	Aggregated particles	6	As(III)	5.8	7	Groundwater	4	Jing et al. (2009)
			As(V)				3.5	
TiO_2	Particles	21	As(V)	ND	7.8	Tap	1.2	Sun et al. (2007)
γ-Fe_2O_3/TiO_2	Particles	35	As(V)	6.7	7	Distilled	2	Yu et al. (2013)
CeO_2	Particles	4	As(III)	2.7		Distilled	13.5	Li et al. (2012)
			As(V)				12	

ZrO_2	Spheres	600	As(III)	ND	7.2	Distilled	5	Cui et al. (2013)
			As(V)				4.5	
ZrO_2	Particles	8	As(III)	3	7	Distilled	0.6	Hang et al. (2012)
			As(V)				3.6	
CeO_2/ZrO_2	Spheres	90	As(III)	7.8	7	Distilled	9.2	Xu et al. (2013)
			As(V)				27.1	
α-Fe_2O_3@Fe_3O_4	Particles	20	Sb(III)	6.8	7	Distilled	1	Shan et al. (2014)
FeOOH	Spheres	200	Sb(III)	7.2	7	Tap	3	Simeonidis et al. (2017b)
			Sb(V)				–	
TiO_2	Particles	15	Sb(III)	ND	10–5	Distilled	0.8	Nishad et al. (2014)

ND not defined by authors

oxy-hydroxides. Magnetite and maghemite nanoparticles whether as single or surface-modified do not show significant adsorption capacities against arsenic. The highest reported capacities are estimated around 2 mg/g (Yavuz et al. 2006; Park et al. 2009; Lunge et al. 2014) while plenty research works provide very low efficiencies (Shipley et al. 2010; Akin et al. 2012; Türk and Alp 2014) or are focused on unrealistic pH and concentrations values for drinking water (Tuutijärvi et al. 2009; Chowdhury and Yanful 2010; Mishra and Ramaprabhu 2010; An et al. 2011; Chen et al. 2011; Feng et al. 2012; Jin et al. 2012; Luther et al. 2012; Hokkanen et al. 2015; Balcells et al. 2016). The potential for magnetic separation also triggered some studies with other ferrite nanoparticles (Phu et al. 2009; Dey et al. 2014; Garcia et al. 2014). In one of the cases, $MgFe_2O_4$ nanoparticles showed very good results when tested in tap water (Tang et al. 2013). Nevertheless, the severe leaching of metal ions (Co, Ni, Mn, Mg) which many times are pollutants is a drawback for further implementation (Fig. 3.5).

Some other metal oxides has been recently introduced as nanoparticles in drinking water treatment technology. A separate case is TiO_2 nanoparticles since it came as the first commercial product based on nanoparticles for drinking water treatment against arsenic. Its activity is based on the photocatalytic properties and the fast kinetic it succeeds. As a disadvantage it should be noted the requirement for sun or UV light to the whole depth of the material. Indeed, when exposed to light, TiO_2 nanoparticles showed significant capacities, especially for As(III) which is most difficult to capture. In particular, aggregated TiO_2 nanoparticles achieved an efficiency of around 4 mg/g for both As(III) and As(V) in groundwater (Jing et al. 2009) with this value falling to 1.2 mg As(V)/g (Sun et al. 2007) and to 2 mg As(V)/g when combined with γ-Fe_2O_3 nanoparticles (Yu et al. 2013). The rest of the literature can only be evaluated for high residual concentration of arsenic (Pena et al. 2005; Jegadeesan et al. 2010; Özlem Kocabaş-Ataklı and Yürüm 2013). Improved efficiencies were reported for CeO_2 and ZrO_2 nanoparticles. Surprisingly, cerium oxide nanoparticles presents the best capacities among any kind of nanoparticles reaching 13.5 mg As(III)/g in distilled water (Li et al. 2012; Sun et al. 2012). Zirconia nanospheres or particles have a lower but not negligible removal ability (Hang et al. 2012; Cui et al. 2013) but when combined with CeO_2 ones they produce by far the maximum available performance of 27.1 mg As(V)/g (Xu et al. 2013). Less effort was dedicated to Al_2O_3 (Saha and Sarkar 2012), CuO (Martinson and Reddy 2009; Goswami et al. 2012) and MnO_2 (Zhao et al. 2012) without important results for drinking water treatment.

3.5.4.3.2 Antimony

Antimony is classified as a very toxic compound for water supplies as signified by its low MCL of 5 or 6 μg/L. However, compared to arsenic, not much attention has been dedicated in the understanding of its chemistry in correlation to the development of

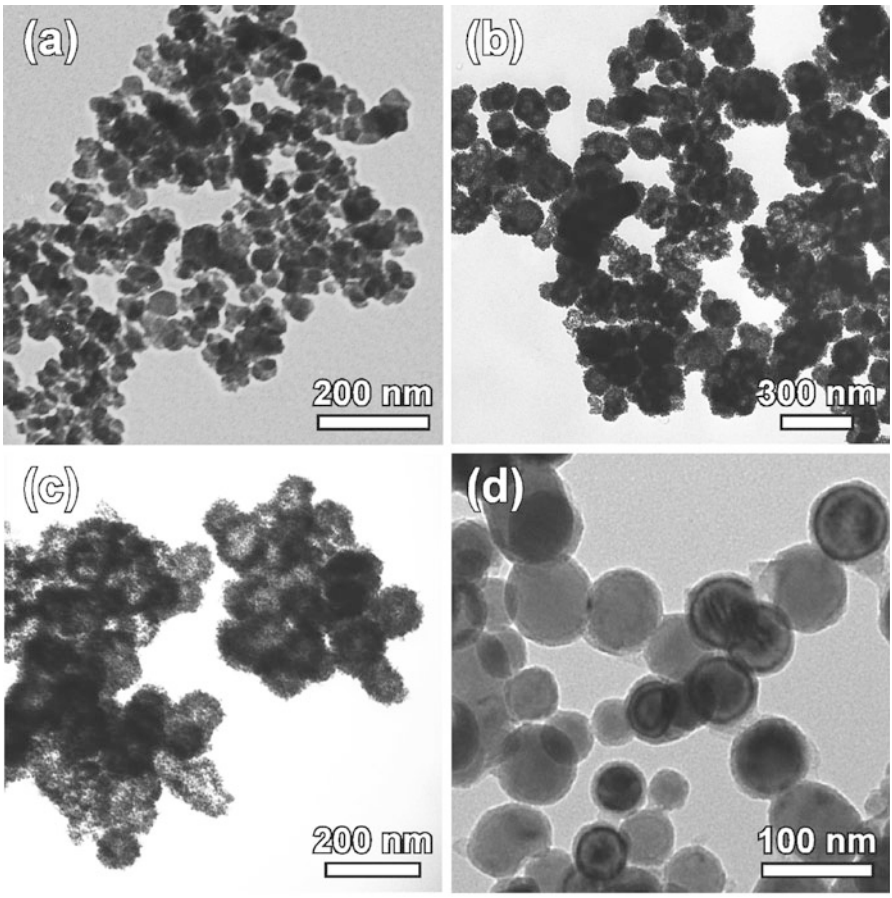

Fig. 3.5 Transmission electron microscopy images of iron-based nanoparticles successfully tested for drinking water treatment. (**a**) Fe_3O_4 nanoparticles with a mean size of 30 nm applied for Cr (VI) reduction/precipitation (Reprinted from Simeonidis et al. 2015, Copyright (2015), with permission from Elsevier). (**b**) Schwertmannite nanospheres optimized for As(V) adsorption in a column bed setup (Reprinted from Tresintsi et al. 2012, Copyright (2012), with permission from Elsevier). (**c**) Tetravalent Mn-feroxyhyte developed for the oxidation/adsorption of As(III) (Reprinted with permission from Tresintsi et al. 2013 Copyright (2013) American Chemical Society). (**d**) MgO-coated ZVI nanoparticles used for the regeneration of a saturated arsenic adsorbents. (Reproduced after modification by Simeonidis et al. 2017a with permission of The Royal Society of Chemistry)

proper treatment methods for polluted water delivered for drinking purposes. This is explained by the lower frequency of Sb detection than As, due to its limited solubility, and the absence, until recently, of regular sampling control by authorities. High concentrations of Sb are reported in water resources neighboring with hot springs, industrial and mining activities, and they are usually combined with the presence of As. Depending on the oxidative conditions of the aquatic reservoir, Sb

(III) and Sb(V) are the common species met in natural waters. The pentavalent form dominates under well-oxidized waters though the proportion of Sb(III), which is more toxic, increases in anoxic environments. Unlike the case of arsenic, adsorption of Sb(V) species is considered much more difficult than Sb(III). Such behavior is attributed to the different coordination of the dominant $Sb(OH)_6^-$ species in an octahedral geometry, compared to the tetrahedral formation of As(V) and P(V), which diminishes the tendency for complexation on solids surfaces. Trivalent Sb appears as an hydrolyzed form with neutral charge, $Sb(OH)_3$. Adsorption of both Sb (III) and Sb(V) on metal (oxyhydr)oxides proceeds with the formation of inner-sphere complexes, however, their stability is determined by the pH, competing anions (phosphates) and oxidative mechanisms which initiate secondary desorption processes. For instance, strongly bounded Sb(III) may be oxidized to Sb(V) and then dissolved back to water. In conclusion, antimony removal from water using adsorbents is a more challenging case than arsenic and at first sight the reduction of Sb (V) to Sb(III) appears as an advantageous approach.

Literature presents very few examples of antimony removal from water by inorganic nanoparticles (Table 3.4). Some of them show a potential to decrease concentration at the levels of the MCL but they refer only to Sb(III) species. More specifically, hematite-coated Fe_3O_4 nanoparticles showed a removal capacity of around 1 μg Sb(III)/g at the MCL (pH 7) (Shan et al. 2014), while FeOOH nanospheres were able to capture around 3 mg Sb(III)/g when tested in natural-like water in both batch adsorption and column experiments (Simeonidis et al. 2017b). Titanium oxide nanoparticles indicated a removal capacity of around 0.8 μg Sb(III)/g though this value was obtained under variable pH conditions between 10 and 5 while the efficiency of corresponding chitosan-coated TiO_2 nanoparticles was practically zero (Nishad et al. 2014). The rest of reported adsorbents either appeared incapable to reach MCL (Mn-feroxyhyte (Simeonidis et al. 2017b)) or were tested under extreme and not representative conditions of pH and residual concentrations (γ-MnOOH (Wang et al. 2012), ZVI (Saeidnia et al. 2016) nanoparticles). In any case, none of the systems presented any efficiency against Sb(V).

3.6 Technical and Economic Aspects

Acceptance of nanoparticles-based technologies for the removal of heavy metals during drinking water treatment does not only require the development of the proper materials by research. Qualified nanoparticles should be able to deliver their nominal efficiency under the intense conditions met in real processes while being adopted by properly designed facilities sometimes very different than the conventional ones. At the end, the competitiveness of the system will be judged by the overall cost defined not only by the nanoparticles price but also by the capital investment, the maintenance and the operational cost. Furthermore, environmental and technical limitations or even the social impact may determine the promotion of nanoparticle-assisted water purification.

A fundamental task of laboratory research is the optimization of synthesized nanoparticles in order to acquire the appropriate features with respect to the heavy metal forms which are expected to remove. As discussed, the surface configuration is the most advantageous property for using nanoparticles instead of conventional materials since any kind of interaction with water takes place there. Decreasing the particle size is in general favorable because it results to a direct increase of specific surface area. However, small dimensions introduce difficulties in the recovery of nanoparticles after their use as well as chemical instability or phase transformations which are equivalent to efficiency losses. In most cases, the surface charge intensity and polarity is a critical characteristic for the uptake of the heavy metals ionic forms. Positive-charged nanoparticles are required to attract oxy-anions and the opposite when cations are targeted. When reduction of high-valent species is the objective of treatment, nanoparticles should be prepared and stored accordingly and keep a low oxidation state on their surface in order to operate as electron donors. The tuning of such properties is usually performed during synthesis of nanoparticles especially when aqueous methods are preferred.

Optimum conditions of synthesis for a specific nanoparticulate system is the key to decrease operational cost as soon as the effective lifetime of nanoparticles can be significantly extended. However, selecting to work with nanoparticles consisting of low-cost phases, even with some deduction in removal capacity, should be always considered and balanced. For example, it is unreasonable to use Au nanoparticles for large-scale mercury uptake, in spite of their extremely high efficiency, because their cost is exclusionary. Similarly, ZiO_2, CeO_2 and TiO_2 nanoparticles can hardly compete the low production cost of their iron (oxyhydr)oxide counterparts when discussing about arsenic adsorbents.

The conditions under which nanoparticles will be applied is another important design parameter. Preliminary tests should be carried out to identify whether nominal efficiency is preserved in a water matrix with acidity, redox potential and interfering factors similar to those of a typical drinking water resource. In addition, specific competing ions should be separately studied at elevated concentrations to estimate any unexpected negative influence in the removal capacity of nanoparticles. The exact behavior of qualified nanoparticles at the initial concentration levels of the pollutant and the targeted MCL should be also considered.

Finally, the decision for an appropriate setup which implements nanoparticles contact with the polluted water is a major task. This part of water treatment is placed after suspended solids removal stage suggesting that only dissolved species appear in supplied water. As previously described, nanoparticles can be used whether aggregated, supported or dispersed. In the first two cases, traditional packed bed filters is the ideal way of application taking the advantage of the long-time technical experience of their design and operation together with the compatibility of their adoption in the water treatment line. This kind of configuration is also favorable for point-of-use or portable devices. Things become more complicated when nanoparticles are going to be dispersed in the polluted water. Better efficiency and lower energy consumption are partially counterbalanced by an increase in contact time and the volume of the facility while a separation step to collect nanoparticles at

the end of the line needs to be included. Suggestively, recovery of nanoparticles is possible by membranes as successfully realized for a concentrated slurry of TiO_2 nanoparticles (Stancl et al. 2015). Another way is to capture nanoparticles by the application of an external magnetic field. It is clear that the numerous research works with magnetic nanoparticles (ZVI, Fe_3O_4, γ-Fe_2O_3) point not only to the low cost of these phases but to the option for their magnetic recovery as well (Westerhoff et al. 2016). An example of magnetic separation of nanoparticles after their use in heavy metals removal was reported by Mayo et al. (2007) where the suspension flowed through a vertical column located in a high-gradient magnetic field generated by an electromagnet. Furthermore, a continuous-flow system consisting of a contact tank sequenced by a horizontal tube placed between permanent magnets was tested for Cr (VI) removal by Fe_3O_4 nanoparticles (Simeonidis et al. 2015). The same pattern was also applied in a continuous close-circuit setup for the secondary arsenic uptake, nanoparticles recovery, regeneration and recirculation (Fig. 3.6).

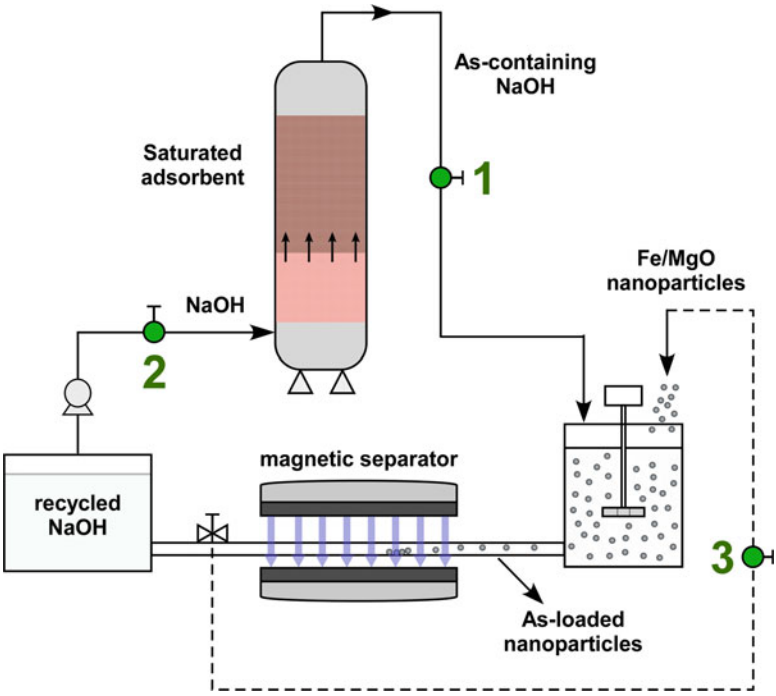

Fig. 3.6 Magnetic separation and recirculation scheme of MgO-coated ZVI nanoparticles used for the regeneration of a saturated arsenic adsorbent column filled with (Fe,Mn)OOH aggregated nanospheres. Under alkaline conditions the exchange of arsenic between the adsorbent and Fe/MgO nanoparticles is favorable in this close-circuit setup. Arsenic is adsorbed on the MgO shell by the As-rich NaOH stream and then nanoparticles are recovered in a static magnetic field. Nanoparticles are recirculated back to the contact tank until maximum capacity is achieved. (Reproduced by Simeonidis et al. 2017a with permission of John Wiley and Sons)

3.7 Environmental Issues

The qualification of any kind of adsorbent mostly depends on the efficiency of the carried uptake process. However, the strength of the adsorption is another important parameter able to determine whether a material enters real applications. Particularly, this deals with the environmental issues raised after their use when they are loaded with extremely high pollutant quantities. In the case of nanoparticles, the problem becomes more intense due to the large surface-to-volume ratio and the gradual formation of an extra layer with the captured ions. In addition, quantity requirements for nanoparticles employed for drinking water plants are expected to be in a ton-scale and therefore, a proportional volume of saturated solid wastes will be the outcome of the process. Regeneration and recycling of nanoparticles is the most favorable way to overcome the difficulty of waste handling. Unfortunately, most times regeneration is not a valid solution for technical, economical or even environmental reasons especially when the solid waste treatment turns into a highly toxic wastewater decontamination case. In general, the development of nanoparticles for drinking water purification purposes needs to be accompanied by an estimation on the risks related to the release of the loaded pollutant and the release of nanoparticles themselves to the aqueous or soil environment.

3.7.1 Leaching Behavior

Water adsorbents are usually considered as consumables being regularly replaced after reaching their effective lifetime. Their disposal in organized landfills is controlled by strict legislation demanding a laboratory study of leaching potential under specific experimental protocols. In brief, a quantity of saturated (spent) adsorbent is dispersed in an aqueous solution with defined acidity, shaken for some hours and finally, the pollutant concentration is measured and compared to the regulation limit of acceptance. The leaching solution is not always the same but varies between authorities around the world reflecting different considerations of landfill conditions and awareness for environmental protection. The E.U. follows the EN 12457-4 standard test which uses distilled water as leachant (European Standard EN 12457-4 2002) whereas in the U.S. Toxicity Characteristic Leaching Procedure (TCLP) the leachant is an acetic acid buffer solution (U.S. EPA 1986). The California State adopts the more aggressive Waste Extraction Test (WET) in which the extractant is a citric acid solution (California Office of Administrative Law 1985). The leached pollutant is expressed in mg/kg of dried solid or mg/L of leachant. Depending on the pollutant, a different threshold indicates whether the solid waste will be treated as inert, non-hazardous or dangerous.

In practice, failure to prove that saturated nanoparticles can be handled as an inert waste would have a dramatic impact in the viability of developed technology since the inertization process can multiply the overall cost to the customer. Current research on the leaching behavior of heavy metals adsorbed on inorganic nanoparticles indicates a good stability and a general success when the standard leaching tests were applied (Tresintsi et al. 2013; Simeonidis et al. 2015). However,

beyond legislation, more laboratory and field work is required in order to understand the real and long-term fate of engineered nanoparticles in a landfill. A first study on the behavior of inorganic nanoparticles suggests a complicated interaction path with the solid waste mass, the mobile aqueous phase and biological processes (Bolyard et al. 2013). It should be noted that leaching is not only a matter of the adsorbed heavy metals but it could be specifically an issue for the particle's phase itself. For this reason, the dissolution of ions from nanoparticles structure should be checked during their application in drinking water as well as during leaching tests.

3.7.2 Fate in Soil and Aquatic Systems

Growing concerns over the potential for unintended, adverse consequences of engineered nanoparticles in the environment have generated new research initiatives focused on understanding the ecological effects. In this section, we try to shed some light on the current state of knowledge regarding the likely environmental impacts of the aforementioned nanomaterials (Bernhardt et al. 2010).

Engineered nanoparticles enter the environment by the releases of solid and liquid waste streams coming from different pathways. For example, waste incineration generates atmosphere emissions that may result in nanoparticles deposition to soils and waters (Tourinho et al. 2012). The main font of soil contamination with nanoparticles is the addition of sludge from wastewater treatment units as a fertilizer to agricultural land (Sánchez et al. 2011; Pan and Xing 2012). It is estimated that sewage sludge can contribute to a significant input of nanoparticles (mostly Ag, ZnO and TiO_2) to the agricultural land every year. There, the nanoparticles are subjected to transformations after their interaction with the natural organic matter and the reactive environment (Wang et al. 2016b). Once in soil, those nanoparticles can diffuse and affect microbiota and other organisms (Pan and Xing 2012). Besides, nanoparticles can also reach aquatic systems by wind effect, rainwater runoff and/or wastewater effluents (Klaine et al. 2008), interacting with other particles and being accumulated in bottom sediments (Batley et al. 2013).

The physicochemical properties of the nanoparticles govern particle behavior in the different environment where they reside (Rivera-Gil et al. 2013). Diverse parameters such as: particle number and concentration, composition, mass, charge, surface area, size distribution, surface chemistry, stability, solubility, etc., are prone to change with the time and with their location. After environmental exposure, these changes can lead to nanoparticle aggregation/agglomeration, sorption to surfaces, surface transformation and/or dissolution to the ionic metal (Tourinho et al. 2012; Wang et al. 2016b), thus, finally determining environmental toxicity. For example, marine aquatic systems present a higher alkalinity, ionic strength, variety of colloids and types of organic matter, than freshwater systems (Klaine et al. 2008). The salinity effect on Ag nanoparticles was studied on Japanese medaka (*Oryzias latipes*) fish eggs. At high salinity conditions, an increase trend to particle aggregation and to toxicity was observed.

The interaction of the aqueous, non-toxic organic matter (humic, fulvic and tannic acid) with the metallic nanoparticles (CuO, ZnO, Ag, Cu, ZnO, Fe_3O_4, Fe_2O_3, Al_2O_3, CeO_2, SiO_2, TiO_2) is a key parameter to take into consideration in water and soils because it can change the surface properties and environmental processes (Wang et al. 2016b). The adsorption of organic matter affect colloidal stability by promoting aggregation/disaggregation, dispersion, and sedimentation, thus, influencing the fate, transport, and bioavailability of the nanoparticles in aquatic systems. For example, when metallic nanoparticles reach water systems, they are prone to agglomerate. These agglomerates tend to sediment, get in contact with benthic organisms and can induce toxicity (Batley et al. 2013). However, interaction of the organic matter can also have the opposite effect. When the agglomerates interact with the organic matter, a redispersion of the nanoparticles can occur, thus facilitating transport in the aqueous environment, decreasing bioavailability for this kind of organisms and reverting toxicity. On the other hand, resuspension may affect pelagic organisms (especially plankton) and filter feeders. In this case, toxicity can derive from direct exposure to nanomaterials or by bioaccumulation through trophic transference (Matranga and Corsi 2012). Agglomerated TiO_2, SiO_2, NCB (carbon black) and C_{60}-fullerene nanoparticles were located on the digestive glands of the mussel *Mytilus galloprovincialis* and were responsible for several physiological alterations. Similar effects on particle behavior depending on pH and the presence of organic matter, as described before, was found for soils. Soils with a high pH value and a high cation exchange capacity can enhance the sorption of Ag nanoparticles to the soil by increasing the availability of negatively charged sites and the cation exchange reactions (Anjum et al. 2013). Apart from pH and organic matter, other factors like clay content and charge of the soil also play a role in the mechanisms inducing toxicity in soils. The clay content can drive heterocoagulation processes by the interaction of Ag nanoparticles with natural colloids, changing their retention capacity in soils. The same work reported the effect of electrostatic interaction between Ag nanoparticles (determined by their coating) and the soil that influences particle's mobility. Repulsion forces tend to decrease retention whereas attractive interactions increase the retention degree on the soils (Anjum et al. 2013).

As discussed in previous sections, many metal oxides such as Fe_3O_4, CeO_2, TiO_2 and Al_2O_3 have been proposed in recent years to remove toxic metal ions and organic pollutants from water and soils. Ironically, their very same high surface area with active sites responsible for the adsorption may render them able to degrade the adsorbed toxic species, thus inducing toxicity to diverse organisms (Maynard et al. 2006). Nanoparticles can trigger diverse toxic effects on living organisms such as: generation of reactive oxygen species by nanoparticle redox activity, cell membrane interaction or damage by nanoparticles' sorption, retention of electrons produced in cell energy generation processes, or nanoparticles sorption onto proteins altering cell signaling pathways (Pan and Xing 2012). Suggestively, ZnO, CeO_2, Ag, Zn^{2+}, Ce^{3+}, Ag^{+} adsorbed to the cell membrane of the freshwater algae *Pseudokirchneriella subcapitata* cause disruption of the membrane transport mechanisms (Batley et al. 2013). Metal oxide nanoparticles such as CuO and Fe_3O_4 nanoparticles can catalyze the oxidation of organic pollutants in aqueous suspensions. Ben-Moshe et al. approached the changes in soil properties due to the presence

of these nanoparticles (Ben-Moshe et al. 2013). They found that Fe_3O_4 and CuO exhibited comparable effect on the degradation of the dissolved organic matter of the soil, however, Fe_3O_4 had a lower impact on the bacterial community composition than CuO nanoparticles. Both kinds of nanoparticles did not change the total amount of soil's materials and they showed little impact on its macroscopic properties (porosity, hydraulic conductivity, sorption capacity, etc.).

Regarding the toxicity caused in microorganisms that interact directly with the soil environment, it has been described that TiO_2 (at $\leq$2 mg/g soil) and ZnO (at $\leq$0.5 mg/g soil) nanoparticles reduce the microbial biomass and alter the bacterial composition, being ZnO more toxic (Ge et al. 2011). CeO_2 nanoparticles are also toxic for bacteria, as well as for soybean plants, algae and fish (Siddiqi and Husen 2017). The growth and development of plants has been proved to be influenced by metal oxide nanoparticles. When plants absorb metallic nanoparticles (TiO_2, ZnO, CeO_2, and Ag) from the environment, nanoparticles distribute to different tissues (leaves, steam, roots, fruits), settling around the cell membrane or inside cell organelles. These nanoparticles can trigger the activation of the oxidative stress signaling of the cell (Hossain et al. 2015). Other cell responses could take place, as alterations in the microRNAs expression that regulates main plant processes or DNA damage. As an example, radish (*Raphanus sativus*) and ryegrass (*Lolium perenne* and *Lolium rigidum*) suffered DNA damage after exposition to CuO nanoparticles. Furthermore, biotransformation processes that can lead to an enhanced toxicity or to detoxification processes can be observed (Siddiqi and Husen 2017). Plants such as maize can transform CuO nanoparticles by reducing them to Cu_2O and Cu_2S and cucumbers can reduce La_2O_3 and Yb_2O_3 to their phosphate forms if phosphate salts are present. Also cucumbers and lettuces, soybean pods and kidney beans can biotransform CeO_2 into Ce(III) and Ce(IV) species (Zhang et al. 2012; Du et al. 2016). Moreover, CeO_2 and TiO_2 nanoparticles have been pointed out as future agents that can increase the resistance to stress in plants. However, CeO_2 and ZnO have shown diverse effects on nutrient content, yield and plant biomass. In conclusion, nanoparticle concentration, growth stage and plant species are important factors to take into account regarding response to nanoparticle interaction.

Looking at freshwater systems toxicity, ZnO, TiO_2, Al_2O_3 nanoparticles and their respective bulk materials were tested in early development stage zebrafish model. It was found that immature forms of zebrafish were very sensitive to ZnO bulk/nanoparticles toxicity. They provoked tissue ulcerations at 72 h post-fertilization larvae after 5 mg/L particle exposure, a delay on embryo and larva development and a decrease on the survival and hatching rate. In contrast, at the same conditions, neither TiO_2 nor Al_2O_3 bulk/nanoparticles showed toxicity. This elucidates that variances in the chemical composition of the nanoparticles can have different impact on different species (Zhu et al. 2008). Another example of TiO_2 nanoparticle interaction, is the soil invertebrate organisms which were less affected by the core composition of the TiO_2 nanoparticles compared to Ag and ZnO nanoparticles.

The effects of metal oxide nanoparticles (TiO_2, ZrO_2, Al_2O_3, and CeO_2) has also been tested on the freshwater algae *Pseudokirchneriella subcapitata* with any effect detected on its photosynthesis efficiency. On the other hand, ZnO nanoparticles could inhibit the algae growth. In marine aquatic systems, inorganic nanoparticles

(Ag, ZnO) were described to be toxic for marine phytoplankton and diverse diatoms (*Thalassiosira pseudonana*, *Cyclotella gracilis*, *Phaeodactylum tricornutum*) due to their solubility in water and/or their release of toxic metal ions (Ag^+ or Zn^+), rather than aggregation (Matranga and Corsi 2012). However, TiO_2 was reported as non-toxic for phytoplankton at high concentrations. In contrast, TiO_2 caused oxidative stress and NO increase in marine abalone (*Hediste diversicolor*) at 1 mg/L. Cyanobacteria (*Anabaena variabilis*) were affected by TiO_2 nanoparticles because of their nitrogen fixing activity inhibition after 6 days of being exposed to 1 mg/L.

The impact of noble metal nanoparticles, which are excellent adsorbents for various contaminants due to their vast surface area and their surface tunability, has also been studied (Pradeep and Anshup 2009). Two types of polymer coated gold nanoparticles (dodecylamine-PMA coated with/without pegylation), were tested on algae *Pseudokirchneriella subcapitata* and rainbow trout gill cells (RTGill-W1) to assess their toxicity. After 72-h algae exposition, lack of interaction was observed between algal cells and nanoparticles. At high nanoparticle concentrations (46 mg/L) the light adsorbing features of gold nanoparticles decreased the algal growth. However, the same authors also exposed RTGill-W1 cells to nanoparticles, noticing their uptake after 1-h exposition (particles were accumulated in intracytoplasmic membrane enclosed vesicles) and their elimination after 24 h of depuration ($\geq$96% particles removed). Nevertheless, the toxic effects were not dramatic even at high nanoparticle concentrations (>10 mg/L). As a result, it was found that after comparing the two coatings, the amphiphilic coated gold nanoparticles were more toxic than the pegylated particles (Van Hoecke et al. 2013).

Recently, Brandl et al. have designed photo-cleavable amphiphilic deblock copolymers to decontaminate hydrophobic pollutants such as bisphenol A, 17-α-ethinyl estradiol and triclosan, present in water and soil. A decrease on the teratogenic effects of this pollutants on zebrafish embryos after nanoparticle photoactivation were reported, demonstrating not to be toxic for zebrafish immature forms (Brandl et al. 2015). In order to standarize knowledge, the toxicity impact of many inorganic nanoparticles was recently compared through a combination of tests in various microorganisms and plants. (Sánchez et al. 2011). Whereas Fe_3O_4 usually exhibits a low toxic effect, the further modification into magnetic hybrid MgO-coated Fe entities, which are proposed as arsenic water decontaminant agents, showed not to provoke acute decrease on RTgill-W1 rainbow trout cell viability even after 24-h incubation at concentrations up to 1 g/L (Simeonidis et al. 2017a).

Despite the efforts made to understand nanoparticle's fate and behavior in different environmental scenarios, more research is needed to facilitate a quantitative ecological risk assessment.

3.8 Conclusions

The application of engineered inorganic nanoparticles for the purification of drinking water is a very ambitious perspective of nanotechnology aiming to the improvement of an everyday human need and a fundamental sustainability element. The present

review attempts to bring a summary of the current knowledge on the field by considering the many different aspects that should be handled for a successful and safe implementation of nanoparticles for heavy metals removal. For the first time, to our knowledge, reported studies are evaluated under the prism of their potential to produce nanoparticles able to comply with the demands of drinking water technology and to become competitive to existing procedures. In particular, whenever applicable, given results of laboratory removal experiments are projected to the corresponding maximum contaminant level so as to provide a direct estimation of the uptake capacity for the tested nanoparticles. Importantly, the profile of an appropriate nanoparticulate phase was described for each category of examined heavy metal forms (divalent cations, high-valent ions and oxy-anionic species), according to the optimum uptake mechanism activation. Furthermore, the possible use of nanoparticles for drinking water purification is discussed as a part of a typical water treatment line in terms of cost, viability, compatibility and environmental or health implications.

Conclusively, an overview of the up-to-date research related to the removal of emerging heavy metals met in drinking water sources, indicates only a very small amount of effort directed to realistic solutions for drinking water treatment based on nanoparticles. This gap should be attributed to the absence of common experimental protocols and universal methods for the evaluation of obtained results. Trying to give an explanation on this issue, one should consider that development of nanoparticles for drinking water purification is a case of nanomaterials-water nexus. Therefore, working independently on the design of nanoparticles aiming ideal compositions and morphologies or conversely testing nanomaterials in heavy metals adsorption without providing a feedback for the optimization of their features, is not the proper strategy. Interdisciplinary projects employing experts from materials science, surface chemistry and water technology appears as the only valid way to understand uptake mechanisms, tune the properties and adapt nanoparticles to conventional or even novel water treatment schemes. Our hope is that this chapter will contribute to the establishment of new methodologies in the upcoming research inspiring the rapid implementation of nanoparticles in drinking water technology.

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Chapter 4
Nanobiosensors for Detection of Micropollutants

Bambang Kuswandi

Contents

Abstract The integration of nanotechnology in the sensor technology open ups the possibility for a wide variety of applications, such as micropollutants detection. Micropollutants are emerging as a new challenge to the scientific community, where the growing number of pollutants requires the development of innovative analytical devices that are precise, sensitive, specific, rapid, and easy-to-use to meet the increasing demand for environmental pollution control. Nanobiosensors, as a powerful alternative to conventional analytical techniques, enable the highly sensitive, real-time, and high-frequency monitoring of micropollutants without extensive sample preparation. Since nanobiosensor holds the possibility of detecting and manipulating atoms and molecules using nanodevices, which have led to the

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development of biosensors that interact with extremely small molecules that need to be analyzed, such as micropollutants.

This chapter reviews important advances in nanobiosensor structures based functionalized nanoparticles, nanotubes, and nanowires with biorecognition materials (e.g., enzymes, aptamers, DNAzymes, antibodies and whole cells) that facilitate the increasing application of nanobiosensors for detection of micropulutants. Nanomaterials such as gold nanoparticles, carbon nanotubes, magnetic nanoparticles and quantum dots have been actively studied for nanobiosensors. The use of nanoparticle-functionalized surfaces can drastically boost the specificity of the detection system, that make nanobiosensor becomes more refined and reliable. It will eventually make small devices for rapid screening of a wide variety of micropollutants with very low sensitivity and selectivity at low cost, which has become a new interdisciplinary frontier between chemical or biological detection, material science, and chemistry.

4.1 Introduction

Nowadays, nanotechnology has already found their application in various fields such as computer electronics, communication, energy, medicine, and foods etc. Nanotechnology is defined as the creation of functional materials, devices, and systems through control of matter at the 1–100 nm scale. The application of nanotechnology in sensor technology has become apparent, in particular, the use of nanomaterials, such as nanoparticles, nanotubes, nanowires, and nanofibers in nanosensor developments (Esposito et al. 2005; Ligler et al. 2003; Yih and Al-Fandi 2006). In chemical sensor and biosensor technology, nanotechnology has recently become one of the most exciting forefront fields. A wide variety of nanomaterials of different sizes, shapes, and compositions are now available. The most interest in nanomaterials is driven by their many desirable properties for sensing mechanism. Use of nanomaterials in chemical sensors and biosensors allows the use of many new signal transduction technologies in their manufacture. Because of their size, nanosensors, nanoprobes, and other nanosystems are revolutionizing the fields of chemical and biological analysis. In particular, the ability to tailor the size and structure and hence the properties of nanomaterials offers excellent prospects for designing novel sensing systems and enhancing the performance of the chemical or bioanalytical assay.

Particles that are smaller than the characteristic lengths associated with the specific phenomena often display new chemistry and physics that lead to new properties that depend on the size of those particles. When the size of the structure is decreased, surface to volume ratio increases considerably, and the surface phenomena predominate over the chemistry and physics in the bulk. The reduction in the size of the sensing part and/or the transducer in a sensor is important in order to better miniaturize the devices. The science of nanomaterials deals with new

phenomena, so that new sensor devices are being built that take advantage of these phenomena. Sensitivity can increase due to better conduction properties, the limits of detection can be lower, very small quantities of samples can be analyzed, direct detection is possible without using labels, and some reagents can be eliminated, which highly reduced the chemicals used and waste produce (Sanguansri and Augustin 2006).

In the biosensing, the transduction mechanisms are a key component. Since they are responsible for converting the responses of bio-analyte interactions in an identifiable and reproducible manner. Actually, the transduction mechanisms involve the conversion of specific biochemical reaction energy into an electrical form. Nanomaterials can be superb materials in this dimension as they have high surface area to volume ratios, which allow the surface to be used in a better, effective and more greatly functional manner. In addition, their electromechanical and optical properties are the great assets for the biosensor technology. Nanostructural materials provided by nanotechnology have revolutionized the even in the domain of molecular biology which has provided an opportunity for manipulation of atoms and molecules and monitored the biological phenomenon at the cellular level with higher precision (Vo-Dinh et al. 2001).

The terminology nanobiosensor, it has the word nano prefixed to a biosensor. In order to get to the real technology, one must understand the idea of a biosensor. As nanoscience is interdisciplinary in nature so putting the word nano as prefix often implies the use or manipulation at a scale equivalent to one-billionth of a meter. Thus, nanobiosensor is a modified version of a biosensor employing nanomaterial in such analytical device. Nanobiosensors are employed various nanomaterials and biomolecules can help to detect at very sensitive levels toxic contaminants in foods that can arise from environmental contamination during processing or handling (Jianrong et al. 2004; Yang et al. 2007). The aim of this chapter is to provide an overview of the different types of nanobiosensors (i.e. nanoparticles, nanotubes and nanowires) for environmental analysis and the mechanisms used by them, as well as their potential applications as novel nanobiosensors, which could help for detecting and monitoring of micropollutants in early stage, and thus be an important tool for solving environmental pollution issues.

4.2 Nanobiosensors

Nanobiosensors can be classified into nanosensors. Since, nanosensors can be defined as any biological, chemical, or surgical sensory points used to convey information about nanoparticles to the macroscopic world (Foster 2006). Thus, nanosensors are nanoscale devices that built with dimension of about 10 nm and masses of a few attograms (10^{-18} g). They are fabricated in order to imitate the nanomaterials found in nature including proteins, DNA, membranes and other natural biomolecules which can detect minute changes in the foods through different mechanisms (Sanguansri and Augustin 2006; German et al. 2006). Nanosensors are

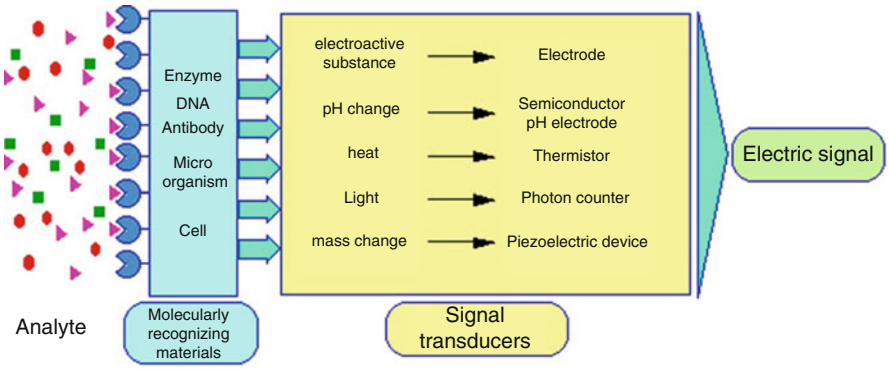

Fig. 4.1 The structure and principle of biosensors, where biosensor consists of bioreceptor (e.g. enzyme, antibody, DNA, microorganism, and cell) and transducer (e.g. electrochemical, optical, mass etc) to produce an electronic signal that is proportional to the concentration of a target analyte

employed various nanomaterials can help to detect at very sensitive levels toxic contaminants, such as in foods, that can arise from environmental contamination during processing or handling (Jianrong et al. 2004; Yang et al. 2007). There might be a possible confusion between nanosensors and nanobiosensors. Hence, it is necessary to address the relation between these two terms. Since biosensor defined as a compact analytical device/unit incorporating a biological or biologically derived sensitized element linked to a physicochemical transducer. Usually, it is aimed to produce a digital electronic signal that is proportional to the concentration of a specific analyte or group of analytes (Turner 2000) as shown in Fig. 4.1. Thus, a nanobiosensor is a biosensor on the nanoscale size, while nanosensor is wider terminology, i.e. a modified version of a physical or chemical sensor or biosensor employing nanomaterials in such analytical device. Since the nanobiosensors used in micropollutants analyses usually use an integration of biomolecule and nanomaterials, thus, in this case, the nanobiosensors could also be classified as nanosensors.

In addition, based on application, Agrawal and Prajapati (2012) classified nanosensors into four (4) classes, i.e. chemical nanosensors, deployable nanosensors, electrometers, and nanobiosensors, as shown in Fig. 4.2. Chemical nanosensor usually uses capacitive readout cantilevers and electronic in order to analyze the signal. This type of sensor is sensitive to analyze a single chemical or biological molecule. Deployable nanosensor is chemical detection system that combines a nanomaterial for sample collection and a concentration with a microelectromechanical (MEM) based chemical lab on chip (LOC) detector. This sensor can be used in homeland security, which could detect chemical in the air without risking of human life by sending it in the air. An electrometer is a nanometer scale mechanical electrometer that consists of a torsional mechanical resonator, a detection electrode, and a gate electrode, which are used to couple charge to the mechanical element. Nanobiosensor is a biosensor on the nano-scale size. One of the

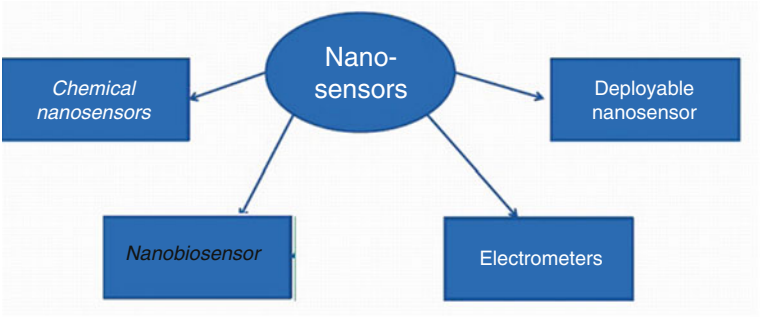

Fig. 4.2 Classification of nanosensors based on their applications that can be classified into four (4) classes, i.e. chemical nanosensors, nanobiosensors, electrometers and deployable nanosensors

most large research areas in nanosensor is biosensor. Since, some analytical features like sensitivity, specificity, rapidity of testing and other necessary attributes of biosensors are improved by using nanomaterials in their construction (Jin et al. 2003). These features of nanobiosensors provide wide scope for their applications in environmental analysis operations like inspection of raw materials, on-line process control, monitoring of storage conditions etc. Besides serving as cost effective tools the nanobiosensors could provide immense improvements in environmental monitoring.

4.2.1 Mechanism and Structure

Generally, a biosensor is defined as an analytical system that consists of a probe with biological recognition element, often called a bio-receptor, and a transducer (Fig. 4.1). The interaction of the analyte with the bio-receptor is designed to produce a measured change by the transducer, which converts the information into a measurable change, such as an electrical signal. In this case, there is an electronic component for interacting with the instrument which includes an input – output interface. The recognition element which is of biological origin binds to the analyte of interest and provides a primary signal. Bio-receptors are used because they are important elements to specificity for biosensor technologies. They allow binding the target analyte of interest to the sensor for the measurement with minimum interference from other substances in complex mixtures. A bio-receptor is a biological molecular species (e.g., an enzyme, an antibody, a protein, or a DNA) or a living biological system (e.g., cells, tissue, or whole organisms) that utilizes a biochemical mechanism for recognition (Turner 2000).

An example of this mechanism is the use of an enzyme acting specifically to convert a reactant molecule into a product. Since enzymes show a specific sensitivity to a substrate as an analyte. Furthermore, many enzymatic reactions involve

cofactors. These cofactors are other molecules or ions that assist in the reaction. During the catalysis, the cofactors may be chemically changed, and as a result, the resulting physicochemical changes can monitor or detect the enzymatic process (Kuswandi and Mascini 2005). Another example is the immune systems where antibodies interact with antigens. Here, the antigen is recognized as a foreign body. In order to against it, a specific antibody is generated by binding and operating to remove the antigen. Using this specific recognition and interaction on the molecular level, antibodies and antigens can be employed as a sensing mechanism (Sharma et al. 2010). Antibodies can be raised in vitro to detect specific molecules. Here, antibodies may serve as the basis for the biosensor detection system. DNA can also be used as a bio-recognition element. Since all of the information contained in the DNA appears encoded in a series of amino acids, and it forms the identifying backbone of that structure. Therefore, the recognition of DNA sequences is of fundamental importance to the control, reading, and detection of these molecular structures (Wang et al. 2003). Thus, the basic principle of a DNA biosensor is to detect the molecular recognition provided by the DNA probes and to transform it into the signal using a transducer. Aptamers can also be used as the bio-recognition elements in biosensor applications. Aptamers are small (i.e. 40–100 bases), synthetic oligonucleotides that can specifically recognize and bind to virtually any kind of target, including whole cells, drugs, toxins, ions, ligands, peptides, and proteins (Song et al. 2012).

The most important feature in a biosensor that can be differentiated from bio-assay is the immobilization of bio-receptor. The sensing element of a biosensor contains a bio-sensitive layer that can either contain bio-receptors or be made of bio-receptors attached to the transducer via immobilization process. Since a layer of receptor molecules that are capable of binding the analyte molecules in a selective way must be previously immobilized on the transducer surface. The immobilization of the bio-receptor molecule on the sensor surface is a key point for the final performance of the biosensor. The immobilization procedure must be stable and reproducible and must retain the stability and activity of the receptor. Nanotechnology offers the most promising strategies for immobilization of bio-receptor (Niemeyer 2001; Wang et al. 2001). It is essential to create a biosensing layer in which the sensing mechanism is immobilized. The biosensing surface may contain enzymes, antibodies, antigens, microorganisms, mammalian cells, tissues, or receptors. Nature of biosensing surface is very important, namely the prolonged use of the biosensor and an anticipated extended storage and working stability.

4.2.2 Classification

Nanobiosensors are typically classified either by bio-recognition element used for molecular recognition or by the type of transduction used for detection as shown in Fig. 4.3. Based on bio-recognition or bio-receptor used, nanobiosensor can be classified: (a) enzyme based nanobiosensors; (b) immuno nanobiosensors; and

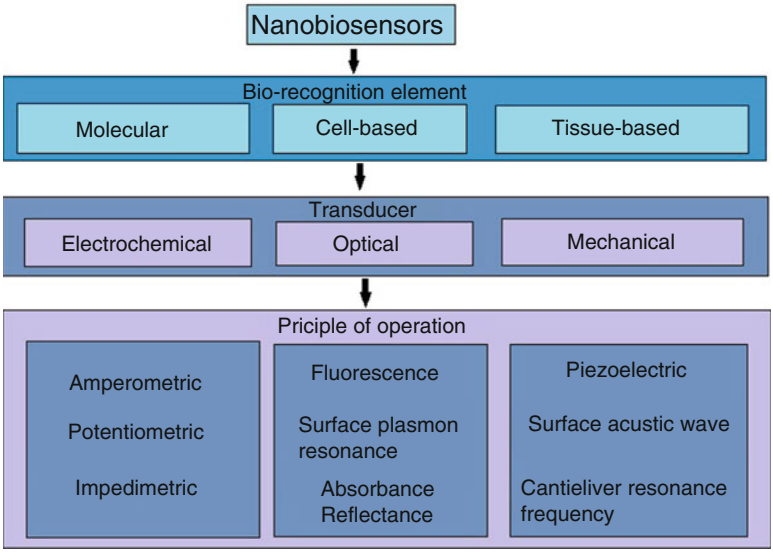

Fig. 4.3 Classification of nanobiosensors based on their bio-recognition element/bio-receptor and transducer. Based on bio-recognition used, it can be classified: (**a**) enzyme based nanobiosensors; (**b**) immuno nanobiosensors; and (**c**) DNA nanobiosensors etc. Based on structure and transduction used, it can be classified into: (**a**) optical nanobiosensor; (**b**) electrochemical nanobiosensors; and **c** mechanical nanobiosensors

(c) DNA nanobiosensors etc. Based on structure and transduction used, nanobiosensor can be classified into: (a) optical nanobiosensor; (b) electrochemical nanobiosensors; and (c) mechanical nanobiosensors. The optical nanobiosensors are including fiber optic using total internal reflection, absorbance or fluorescence (e.g. Fluorescence resonance energy transfer/FRET), chemiluminescence, bioluminescence, evanescent wave or Surface Plasmon Resonance (SPR). Electrochemical transducers are amperometric, potentiometric, impedimetric and conductometric systems. Mechanical transducers are mass sensitive piezoelectric materials which exploit the principles of change in resonant frequency of wave propagation through piezoelectric material and change in mass on analyte binding. Others are included surface acoustic wave (SAW), cantilever resonance frequency as well as thermometric devices that measure enthalpy changes during biological events. Thus, nanobiosensor brings exciting new possibilities for the development of advanced molecular recognition strategies. To achieve this goal, usually nanomaterials are employed in bio-recognition element (a) as supports for the loading of numerous indicators (e.g., biomolecules, fluorescent dyes, or Raman reporters) to amplify the recognition event through their high surface-to-volume ratio or (b) as the indicator that is generated with the aid of biochemical reactions to achieve multiple signal amplification (Fu et al. 2017).

4.2.3 Nanomaterials

Nanomaterials are defined as materials with at least one dimension smaller than 100 nm. Nanomaterials are classified into: (a) nanofilms and coatings (<100 nm in one dimension), (b) nanotubes and wire (<100 nm in two dimensions) and (c) nanoparticles (<100 nm in three dimensions) (Hochella 2002). Due to their incredibly small size, nanomaterials display unique features physically and chemically. Nanosensors are extremely small devices, with dimensions in the order of one billionth of a meter, capable of detecting and responding to physical, chemical and biological stimuli. This capability of nanosensors can be used beneficially for environmental analysis by utilizing them for detection of toxins, pathogens, industrial and environmental pollutants, heavy metals, pesticides, allergens, etc. using different mechanisms. Many researchers have reported different mechanisms to exploit the advances in nanobiosensors for environmental analyses (Chen et al. 2004; Haruyama 2003; Jain 2003; Vo-Dinh et al. 2001).

Various nanomaterials have been investigated to analyze their properties and recent applications as nanobiosensors (Jianrong et al. 2004). The research in nanobiosensor shows a constant increase in relation to the various nanomaterials with the interest to be implemented either into receptors or transducers, in order to enhance their sensitivity and multi-detection capability. These nanomaterials are nanoparticles, nanotubes, quantum dots or other biological nanomaterials. These nanomaterials can contribute to either the bio-recognition element or the transducer or both nanosensors, nanoprobes and other nanosystems have revolutionized in the fields of chemical and biological analysis in many sample matrices. Currently, a wide variety of nanoparticles with different properties, such as small size, high speeds, smaller distances for electrons to travel, lower power, and lower voltages, have found broad application in biosensor technology (Guo and Wang 2007). Several sensing platforms have been developed with nanomaterials that exploit a change in the output signal (Rosi and Mirkin 2005). Furthermore, review of the recent advances in the field of nanomaterial-based sensitive immunoassay has been reported (Fu et al. 2017). The basic modification methods of nanomaterials to produce various novel types of high sensitivity nanomaterial-based optical immunosensors categorized by different signal detection strategies: colorimetry/UV − vis spectra, fluorometry, and surface-enhanced Raman scattering were presented. Thus, nanobiosensors are categorized based on these nanomaterials (nanoparticles, nanotube and nanowires as well as biological nanomaterials) as shown in Fig. 4.4.

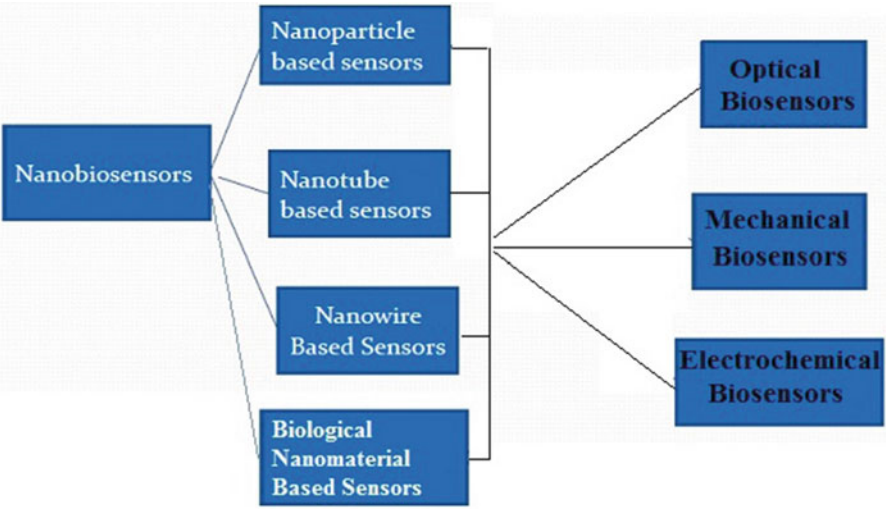

Fig. 4.4 Nanobiosensors categorized based on the nanomaterials used and related transducers, where nanobiosensors can be categorized: i.e. (i) nanoparticle based biosensors; (ii) nanotube based biosensors; (iii) nanowire based biosensors; and (iv) biological nanomaterials based biosensors

4.3 Nanomaterials for Biosensing

Nanostructured materials are interesting tools with specific physical and chemical properties because of their quantum-size effects when compared to bulk materials (Luz et al. 2013). The exploration of these different characteristics provides the possibility to improve the sensitivity of nanobiosensors. Interesting approaches have been reported on the increase in electronic properties with metallic nanostructures as components (Yanez-Sedeno and Pingarron 2005). These include the utilization of nanostructured materials with specific forms like quantum dots and nanoparticles (0D), Nanowires and carbon nanotubes (1D), and metallic platelets or graphene sheets (2D) orientations that reflect their properties. These devices offer improved sensitivities, due to their large surface-to-volume ratios, which enable the bound analyte molecules to more significantly affect the bulk electrical properties of the structure. Due to their small size, nanomaterials may be taken up by cells (Chithrani et al. 2006; Giljohann et al. 2007; Wang et al. 2010), and thus are promising candidates for in vivo sensing applications. In some cases, the inherent electrical properties of the device, such as carbon nanotubes, are particularly extraordinary and lend themselves to improved sensor sensitivity. Several sensing platforms have been developed with nanomaterials that exploit a change in the output signal (Rosi and Mirkin 2005).

One of the most important advances in the nanobiosensor technology have led to the utilization of nanomaterials, for instance metal nanoparticles (He et al. 2008), oxide nanoparticles (De Dios and Diaz Garcia 2010), magnetic nanomaterials (Haun et al. 2010), carbon materials (Rusling et al. 2009; Kim 2010), and quantum dots

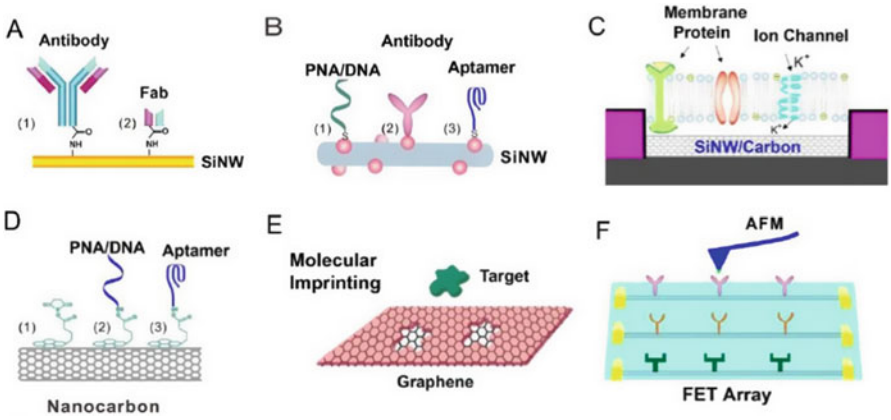

Fig. 4.5 Schematic of various functionalization scheme for nanomaterials. (**a**) antibody or antibody fragment-SiNW (Silica Nanowire) linkage; (**b**) thiol chemistry on SiNW via gold nanoparticles for PNA/DNA, antibody and aptamer; (**c**) lipid formation on SiNW/CNTs; (**d**) CNTs (Carbon nanotubes) functionalization for PNA/DNA and aptamer; (**e**) molecular imprinting on graphene; and (**f**) multiplexing functionalization via dip-pen nanolithography

(de la Escosura-Muniz et al. 2008), in order to improve the electrochemical signals of biocatalytic events that occur at the electrode/electrolyte interface. Furthermore, functional nanomaterials that bound to biological molecules (e.g. antibody, aptamer, proteins, nucleic acids) have been developed for use in nanobiosensors to detect and amplify various signals (Chithrani et al. 2006) as shown in Fig. 4.5. Furthermore, the use of nanomaterials (nanoparticles, nanotube, nanoneedle, nanowire, nanosheet, nanorod, nanobelt, and nanocomposites) for nanosensors/nanobiosensors have seen increasing growth in the last decades. Surface-modified nanoparticles, such as gold nanoparticles, silver nanoparticles, quantum dots, magnetic nanoparticles and carbon nanotubes (CNTs) can have specific target-binding properties that allow highly selective and sensitive towards micropollutants as target detection. Different types of nanoparticles demonstrate different optical, fluorescence and magnetic properties, and interactions between these properties give nanoparticles great potential for micropollutants sensing shown in Fig. 4.6 (Peng et al. 2009).

Table 4.1 shows the main types of nanomaterials being employed for further improvising upon the sensing mechanisms that are conventionally being employed in the biosensor technology. It highlights the potential advantages of several nanomaterials employed and some evidence witnessed their use so far (encoded by corresponding references). The details of different biosensors developed by the use of different materials at the nanoscale are described in the following part.

Magnetic nanoparticles made up of iron and its oxides have been used for specific and efficient detection of magnetism based events and interactions like those of magnetic resonance imaging (MRI). These particles can be coupled with fluorescent molecules or can be made to deliver specific responses by coupling with externally applied magnetic fields. Similarly, zinc and zinc oxide based nanostructures have

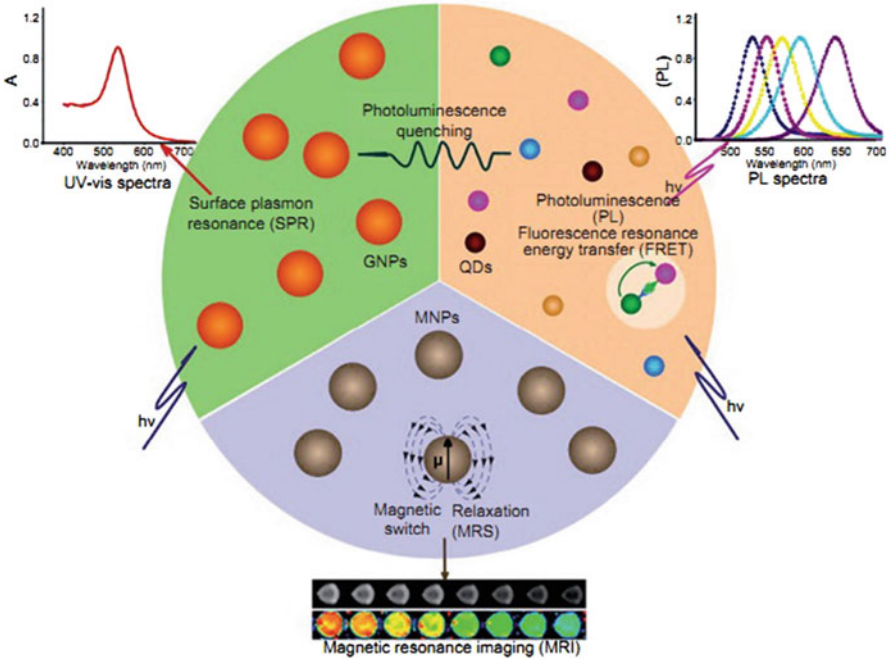

Fig. 4.6 A schematic illustration of the properties of gold Nanoparticles (GNPs), quantum dots (QDs), and magnetic nanoparticles (MNPs) for sensing applications towards micropollutants (Peng et al. 2009)

Table 4.1 Depiction the overview of nanomaterials used for nanobiosensor technology

No.	Nanomaterial type	Advatages	References
1	Carbon nanotubes	Ability to be functionalized, improved enzyme loading, higher aspect ratios, and better electrical transducer	Davis et al. (2003), Sotiropoulou et al. (2003), and Zhao et al. (2002a, b)
2	Nanoparticles	Better loading of bio-analyte, aid in immobilization, and possess good catalytic properties	Katz et al. (2004), Luo et al. (2006), Merkoci et al. (2005), and Wang et al. (2003)
3	Quantum dots	Excellent in fluorescence, quantum confinement of charge carriers, and size tunable band energy	Huang et al. (2005), Wang et al. (2002), and Zhu et al. (2003)
4	Nanowires	High versatility, good electrical and sensing properties for bio- and chemical sensing; and better charge conduction	Cui et al. (2001), MacKenzie et al. (2009), and Stern et al. (2007)
5	Nanorods	Good plasmonic materials that can couple sensing phenomenon and size tunable energy regulation, can be coupled with MEMS, and induce specific field responses	Kabashin et al. (2009) and Ramanathan et al. (2006)

been extensively used for sensing of the biochemical phenomenon in a much more precise and sensitive manner. These have been used in the optimized detection of cholesterol and many other metabolic intermediates. Continuing along the same direction, carbon nanotubes have also been used to optimize the biosensing events with reference to their ability to allow for rapid detection and much better interactions between the analyte and the bioreceptor molecule. Carbon nanotube based biosensors have been actively in use for the detection of glucose (Chen et al. 2008) and insulin (Qu et al. 2006). The text ahead mentions the advantages and outcomes of the use of different nanomaterials and their inherent benefits and the critical parameters in which they can have significant impacts and yield significantly better results.

4.3.1 Nanoparticles Based Biosensors

Metallic nanoparticles are very interesting materials with unique electronic and electrocatalytic properties depending on their size and morphology (Park 2002; El-Deab and Ohsaka 2002). Nanoparticle based biosensors are particularly attractive because they can be easily synthesized in bulk using standard chemical techniques, and do not require advanced fabrication approaches. They also offer particularly high surface areas due to their extremely small size and are typically used as suspensions in solutions (during the time when they interact with the analyte). Most biological molecules can be labeled with metal nanoparticles without compromising their biological activities (Hrapovic 2004). In particular, gold nanoparticles are much-explored materials as components for nanobiosensors, due to their capability to increase an electronic signal when a biological component is maintained in contact with its nanostructured surface (Liu et al. 2004).

Magnetic nanoparticle based biosensor also greatly improve the electron transfer across the monolayer molecules self-assembled on the surfaces of electrodes (Zang et al. 2001). This observation is especially useful in the development of electroluminescence-based nanobiosensors (Wang 2005). Besides gold nanoparticles, silver, platinum, palladium, copper, cobalt and other nanoparticles are also extensively studied in the development of nanobiosensors (Baioni et al. 2008; Hrapovic 2004; Salimi et al. 2009; Xia et al. 2011). In addition, plasmonic nanostructures such as gold nanoparticles) and silver nanoparticles are compelling candidates for the development of highly sensitive biosensors due to their unique localized surface plasmon resonances (LSPRs). The LSPR of these nanoparticles lies in the visible and infrared light range and is sensitive to the composition, size, shape, surrounding medium, and aggregation state of these nanoparticles. This plasmonic behavior provides the basis for fabrication of colorimetric sensors for environmental analyses. Furthermore, the LSPR also enhances the electromagnetic field near the nanoparticle surface, which provides the basis for surface-enhanced Raman spectroscopy (SERS) based detection. The “non-noble metal” based SERS active nanobiosensor using a self-assembled 3D hybrid nickel nanonetwork has also been

reported (Vijayakumar et al. 2017). The nanonetwork was tested for SERS detection of crystal violet (CV) and glutathione (GSH). Organic or inorganic pollutants can be detected and differentiated based upon the finger print spectra that arise when they enter SERS-active hot spots. These developments towards environmental analysis based on LSPR-based colorimetric and SERS detection have been reviews in the literature (Wei et al. 2015).

Gold nanoparticles modified DNA has been used to develop a micro cantilever-based DNA nanobiosensor (Su et al. 2003) to detect DNA even at very lower concentration through a hybridization reaction. This reaction leads to the attachment of gold nanoparticles and acts as a nucleating agent for the growth of silver particles when exposed to a photographic developing solution. The growth of silver particles increased the effective mass of the microcantilever and led to an enhanced frequency shift. This method could detect the target DNA at a concentration of 0.05 nM or lower. Micro-cavity resonators made of porous silicon have been used in nanobiosensors. These resonators possess the unique characteristics of line narrowing and luminescence enhancement. Porous silicon has been used as an optical interferometric transducer for detecting small organic molecules, such as biotin and digoxigenin, 16-nucleotide DNA oligomers, and proteins (streptavidin and antibodies) at pico- and femtomolar level concentrations (Di Francia et al. 1999).

In nanobiosensor development for melamine detection, an aptamer based gold nanoparticles as a colorimetric biosensor using label-free and labeled gold nanoparticles have also been developed (Huang et al. 2011). In the label-free gold nanoparticles procedure, gold nanoparticles are coated by the negative-charged citrate ions which could prevent gold nanoparticles from aggregation in aqueous solution, while inducing the gold nanoparticles aggregation in the presence of high concentration of salt as shown in Fig. 4.7. However, aptamers (poly-T10) could strongly adsorb on gold nanoparticles and enhance the stability of gold nanoparticles against the NaCl-induced aggregation. In the presence of melamine, aptamers will competitively bind with melamine by the stronger affinity which will decrease the salt tolerance of gold nanoparticles and will result in the subsequent aggregation of gold nanoparticles. In the label-based gold nanoparticles procedure, the ssDNA labeled gold nanoparticles is used for melamine determination, which is based on the combination of thymine with melamine. The selected ssDNA was first attached to the surface of gold nanoparticles. The DNA functionalized gold nanoparticles can assemble when the oligonucleotides hybridize, which causes the changes of colors. Melamine could induce the hybridization. When added the melamine, the functionalized gold nanoparticles are assembled upon binding of the oligonucleotide to melamine, which resulted in the red-to blue color change. Both assays are high selectivity and high sensitivity with the detection limits are of 41.7 nM and 46.5 nM, respectively. The label-based method provides a better stability, a better accuracy, and a larger response range when compared with the label-free method. The exploration of gold nanoparticles has provided new paths for enzymatic nanobiosensor development.

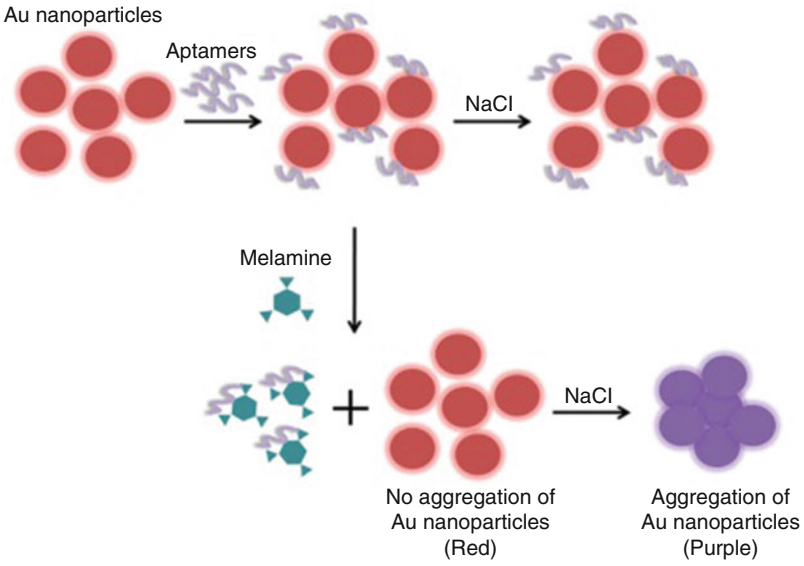

Fig. 4.7 Aptamer-based gold nanoparticles as a colorimetric sensor for the detection of melamine (Huang et al. 2011). Herein, the Aptamer was attached to the surface of gold nanoparticles. The aptamer-gold nanoparticles can assemble when the oligonucleotides hybridize, which causes the changes of colors. When added the melamine, the functionalized gold nanoparticles are assembled upon binding of the oligonucleotide to melamine, which resulted in the red-to blue color change

4.3.2 Nanotubes Based Biosensors

Carbon materials have received great attention currently with the emergence of nanoscience (Rivas et al. 2007). These include the modification of electrodes with different nanocarbons, such as carbon powder, carbon nanotubes, graphene sheets and carbon capsules (Zheng et al. 2010; Pumera 2010; Fang et al. 2008). The investigation of the electronic properties of carbon nanotubes by Iijima and coworkers (Iijima 1991) is one of the most reported approaches to explain their detection capability. Carbon nanotubes are formed by a hollow cylinder of a unique carbon sheet with a single walled carbon nanotube (SWCNT) or concentric carbon sheets of different diameters forming multiwalled carbon nanotubes (MWCNT) with sp2 bonding (Rivas et al. 2007). The particular cylindrical form of carbon nanotubes are the principal aspect that provides the quantum confinement effect in the oriented 1D nanostructured materials (Ajayan 1999). These characteristics provide the possibility to increase the chemical reactivity and electronic properties of this particular carbon material, which becomes a crucial point for biosensing devices (Pumera 2010).

Recent studies have established the fact that carbon nanotubes can enhance the electrochemical reactivity of important biomolecules (Zhao et al. 2002; Musameh et al. 2002) and can promote the electron-transfer reactions of proteins

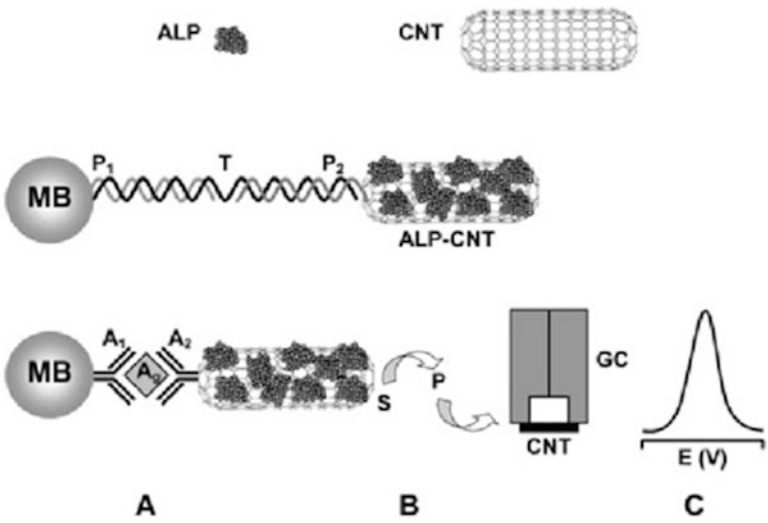

Fig. 4.8 Carbon nanotube (CNT)-derived amplification of the transduction and recognition events. (**a**) Alkaline phosphatase capture (ALP)-loaded CNT tags to the streptavidin-modified magnetic beads by the antibody or DNA recognition events; (**b**) addition of the substrate and enzymatic reaction; (**c**) electrochemical detection of the product of the enzymatic reaction at CNT-modified glassy carbon electrode (Wang 2005)

(Gooding et al., 2003; Yu et al. 2003). In addition to enhanced electrochemical reactivity, carbon nanotube-modified electrodes have been shown to be useful in accumulating important biomolecules (e.g., nucleic acids) (Wang et al. 2003), and alleviating surface fouling effects (Musameh et al. 2002). The remarkable sensitivity of carbon nanotube conductivity to the surface adsorbates permits the use of carbon nanotube as highly sensitive nano-scale sensors. These properties make carbon nanotube extremely attractive for a wide range of electrochemical biosensors ranging from amperometric enzyme electrodes to DNA hybridization biosensors. To take advantage of the remarkable properties of these unique nanomaterials in such electrochemical sensing applications, the carbon nanotubes need to be properly functionalized and immobilized. Among the many potential applications, carbon nanotubes have recently become promising functional materials for the development of advanced biosensors, such as amperometric and potentiometric biosensors.

Highly sensitive bioelectronic protocols for detecting of proteins and DNA have been described recently based on the coupling of several carbon nanotube-derived amplification processes. In these procedures, carbon nanotube played a dual amplification role in both the recognition and transduction events, namely as carriers for numerous enzyme tags and for accumulating the α-naphthol product of the enzymatic reaction (Fig. 4.8). Coverage of around 9600 enzyme molecules per a carbon nanotube such as binding event was estimated. Such carbon nanotube-derived double-step amplification pathway (of both the transduction and recognition events)

allows the detection of DNA and proteins down to 1.3 and 160 zmol, respectively, in 25–50 μL samples and indicates great promise for PCR-free DNA analysis (Wang 2005).

4.3.3 Nanowires Based Biosensors

Nanowire biosensors can be decorated with virtually any potential chemical or biological molecular recognition unit, through convenient surface properties. The nanomaterials transduce the chemical binding event on their surface into a change in the conductance of the nanowire in an extremely sensitive, real time and quantitative fashion. Boron doped silicon nanowires have been used to create highly sensitive, real-time electricity based sensors for biological and chemical species. Biotin modified silicon nanowires were used to detect streptavidin down to at least a picomolar concentration range. The small size and capability of these semiconductor nanowires for sensitive, label-free, real-time detection of a wide range of chemical and biological species could be exploited in array-based screening and in vivo diagnostics.

The conductive TiO_2 nanowire (TiO_2-NW) bundles have been fabricated and coated with antibodies that selective for *L. monocytogenes*. Then, the TiO_2-NW bundles were deposited on the surface between two gold electrodes as shown in Fig. 4.9 (Wang et al. 2009). In contaminated samples, bacteria bind to the antibodies, which cause a measurable change in impedance across the TiO_2-NW bundle. Using this technique, the nanobiosensor was able to detect as low as 4.7×10^2 CFU/mL *L. monocytogenes* in 1 h without significant interference from other food-borne pathogens. Thus, this is a significant improvement over traditional Immuno-Dot Blot analysis, which had a detection limit of 2.2×10^5 CFU/mL.

The changes in conductance or resistance across circuits manufactured from or including nanoscale components have also been used to detect members of the Bacillus (Pal et al. 2007), Salmonella (de la Rica et al. 2008), and Escherichia (So et al. 2008) bacterial genera, as well as viruses (de la Rica et al. 2008).

4.3.4 Bionanomaterials Based Biosensors

In a biosensor, the bio-receptor is combined with a suitable transducer which produces a signal after interaction with the target molecule of interest. The presence of the biological element makes the biosensor systems extremely specific and highly sensitive, giving an upper edge over the conventional methods. Over the years, a number of different natural and artificial biological elements have been used in biosensors; the most important ones are enzymes, dendrimers, thin films etc. In enzyme based biosensors, the biological element is the enzyme which reacts selectively with its substrate (Guilbault et al. 2004). Enzymes are the most used biocatalytic elements, enabling the detection of analytes in various ways. Since enzymatic

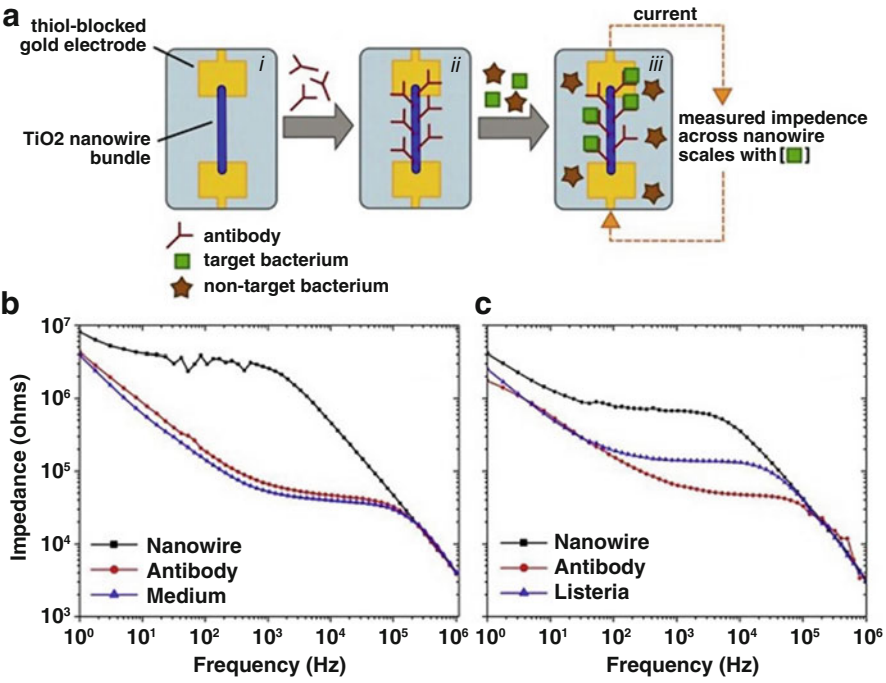

Fig. 4.9 Impedance based detection of bacteria using nanowire. (**a**) Gold electrodes protected with n-butyl thiol ligands are connected with a conductive TiO_2-nanowire bundle. Antibodies selective to the target bacterium are then bound to the nanowire bundle. When the sensor is exposed to a complex matrix containing the target organism, changes in the electrical (impedance) properties of the bundle due to bacterium-antibody binding events can be readily observed. (**b** and **c**)Sample data set illustrating the detection of *Listeria monocytogenes* at a concentration of 4.65×10^3 CFU/ml. Note that exposure to a control medium (**b**) causes no changes to the impedance across the bundle, but that exposure to the bacteria (**c**) results in easily observable impedance changes due to immuno-selective binding events (Adapted from Wang et al. 2009)

reactions are followed by the consumption or production of various species, transducers can easily detect as well as correlate these consumed or produced species to the substrates.

Dendrimers are known as organic macro-molecules with tridimensional and highly defined structure functionality (Astruc et al. 2001). The capability of these dendrimeric structures to stabilize and maintain the integrity of metallic nanoparticles was reported by Crooks (2001). The development of microelectrodes for the measurement of oxygen and hydrogen peroxide concentration is based on silicon substrate utilization through microfabrication technology. Enzymes or microorganisms are fixed on these oxygen-sensing chips by the use of photoresists. Thin nanostructured films have opened the possibility, to fabricate biosensors with a high power of detection, with intrinsic properties associated with their dimensions at the nanoscale level (Lvov et al. 1998). These interesting properties can be explained at the organizational level when a molecular arrangement is obtained at a solid

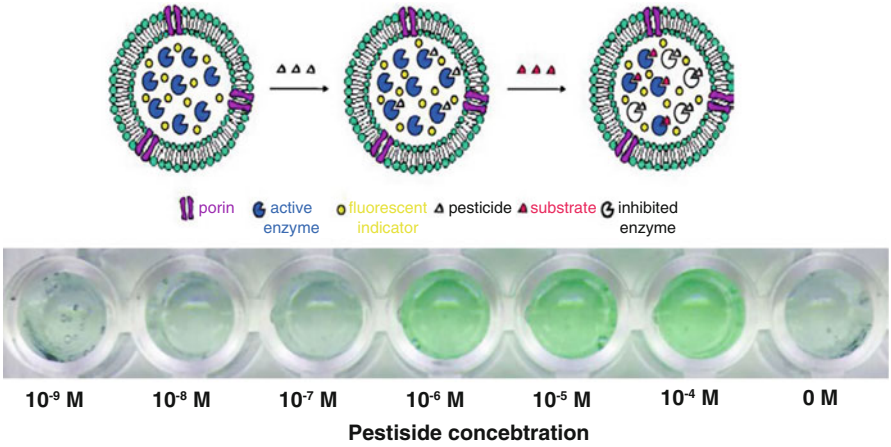

Fig. 4.10 Schematic of liposome-based nanobiosensor for pesticide detection. In the presence of pesticides, there is less enzyme to interact with the substrate. Therefore, the system becomes less acid. As a result, the pH sensitive fluorescent indicator is greenish (Vamvakaki and Chaniotakis 2007)

conductor substrate. Moreover, the possibility to improve the detection limit in biosensing devices can also be explained, by using compatible materials such as natural polymers.

Pesticide nanobiosensors have been reported based on liposome for the detection of organophosphorus pesticides as shown in Fig. 4.10 (Vamvakaki and Chaniotakis 2007). In this system, porins embedded into the lipid membrane allow for the free substrate and pesticide transport into the liposomes. Pesticide concentrations down to 10^{-10} mol L^{-1} can be monitored using this inhibition fluorescent biosensor. This work describes an approach for substrate integrating enzyme activation and corresponding current response at the substrate-bound enzyme electrode.

4.4 Micropollutants

The term "micropollutants" means organic or mineral contaminants whose toxic, persistent, bioactive and bioaccumulative properties that cannot be fully eliminated with traditional wastewater treatment methods and that are not completely biodegradable. They may have a negative effect on the environment and/or organisms (Luo et al. 2014). They are present in many products that use daily, such as drugs, cosmetics, sanitary products, insecticides, etc., at the home or in the industry. When they continuously released with wastewater effluents, can lead to long-term hazards because the contaminants bioaccumulate and can even form new mixtures in water and soils. They arrive in the natural environment mainly via municipal or industrial

wastewater, agriculture, hospital activity, transport and machinery, direct emissions and atmospheric fall-out (Richardson and Ternes 2011).

The determination of micropollutants is of paramount importance to the environment and/or organisms since the exact effects of these contaminants are not yet fully known which a cause of concern for many health authorities is. Therefore, it is necessary to invest in the development of nanosensors (chemical sensors and biosensors) for determination of these micropollutants, since they have proven to be an extremely viable alternative to traditional analytical techniques such as chromatography or spectroscopy. Considerable effort must be made to develop nanobiosensors that are inexpensive, reliable, and robust enough to operate under real conditions. Presently, nanobiosensors exhibit fascinating prospects over traditional biosensors. Nanobiosensors have marked advantages such as enhanced detection sensitivity/specificity and possess great potential for its applications for detection of micropollutants. Some of the potential applications of nanobiosensors for micropollutants detection in water and soil environment according to major families of micropollutants that can be classified into metals, metalloids, and radioactive elements; organic micropollutants; hormones (natural or synthetic); pharmaceutical products, and endocrine disruptors are some of them are given below.

4.4.1 Organic Micropollutants

Some of the organic micropollutants are pesticides, hydrocarbons, solvents, detergents, cosmetic, etc. One example is pesticides, many of the biosensor methods developed for the detection of pesticides is based on the action of the enzyme acetylcholinesterase (AChE) (Kuswandi et al. 2008; Kuswandi and Swandari 2007). Pesticides such as organophosphates and carbamates bind to a serine moiety within the active site of the enzyme, thus preventing the deacetylation of acetylcholine (Kuswandi et al. 2008; Kuswandi and Swandari 2007). The problems with this approach are that other compounds such as heavy metals and detergents also selectively inhibit the enzyme, the enzyme is unstable outside its natural environment and each pesticide has different affinities for the enzyme (Nagatani et al. 2007; Kuswandi and Mascini 2005).

In AChE based nanobiosensor, gold nanoparticles and MWCNTs were used to promote electron transfer and catalyze the electro oxidation of thiocholine in their amperometric biosensor for the detection of monocrotophos (LOD 10 nM) (Norouzi et al. 2010). Here, the flow-based system used glassy carbon electrodes that had been modified with gold nanoparticles and MWCNTs. The carbon nanotubes contained chitosan to increase the immobilization level and improve the stability of AChE. Similarly, polyaniline (PANI) was used as a mediator in the amperometric biosensor (Somerset et al. 2007, 2009). In this work, the nanobiosensor was constructed to harvest its dual role as immobilization matrix for AChE and use its electrocatalytic activity towards thiocholine (TCh) for amperometric biosensing. The biosensor mechanism for the Au/MBT/PANI/AChE/PVAc biosensor is shown in Fig. 4.11.

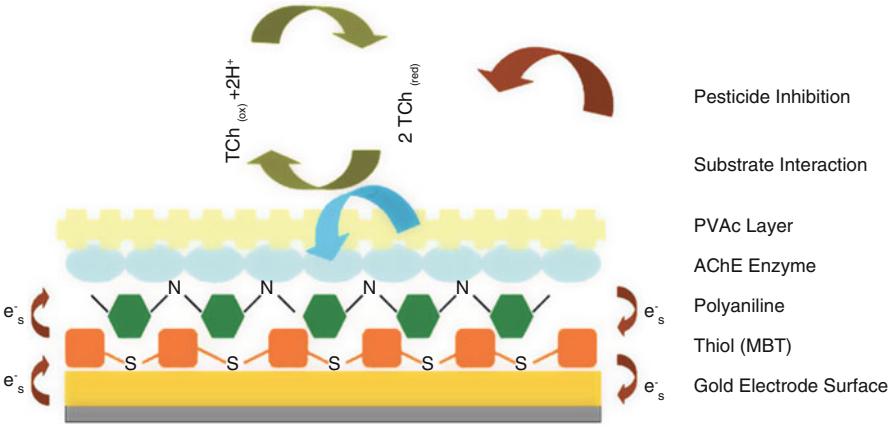

Fig. 4.11 The schematic representation of the Au/MBT/PANI/AChE/PVAc biosensor reaction occurring at the gold SAM modified electrode (Sommerset et al. 2009). Herein, the acetylthiocholine (ATCh) is catalyzed by AChE to produce thiocholine and acetic acid. Thiocholine is electro active and is oxidized in the reaction, which in turn, the conducting polyaniline reacts with thiocholine and accepts an electron from mercaptobenzothiazole as it is oxidized through interaction with the gold electrode surface

It further shows that as acetylthiocholine (ATCh) is catalyzed by AChE, it forms thiocholine and acetic acid. Thiocholine is electro active and is oxidized in the reaction. In return, the conducting polyaniline reacts with thiocholine and also accepts an electron from mercaptobenzothiazole as it is oxidized through interaction with the gold electrode.

Other pesticides, such as 2,4-Dinitrophenol (DNP) that also used as an antiseptic has also been detected using nanobiosensors. A colorimetric nanobiosensor has been developed based on the chromogenic effect of latex microspheres hybridization with Gold nanoparticles (Ko et al. 2010). In this nanobiosensor, a toxin analog, DNP–bovine serum albumin was attached to gold nanoparticles which allowed the hybridization of DNP with an anti-DNP antibody on latex microspheres resulting in the formation of pinkish-red color. A model toxin, DNP–glycine was detected and quantified via a competition that occurs between the analog-conjugated-gold nanoparticles and the toxin molecules for the binding pocket in the anti-DNP antibody. When the gold nanoparticles were displaced from host latex microspheres in the presence of the toxin molecules, a visible color change occurred from pinkish-red to white.

Dichlorodiphenyltrichloroethane (DDT) chemically known as 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane is one of the most widely used organochlorine pesticides in the world, has also been detected using nanobiosensors. An immune-nanobiosensor based on gold nanoparticles in dipstick format using competitive immune assay was developed to detect DDT at the nanogram level (Lisa et al. 2009). Herein, the immuno-dipstick, gold nanoparticles with specifically defined sizes were synthesized and conjugated to anti-DDT antibodies, which served as the detecting

reagent. DDA (1,1,1-trichloro-2,2-bis(chlorophenyl)acetic acid) -BSA conjugate, used as the antigen, was immobilized on nitro cellulose (membrane strips). Gold nanoparticle conjugated anti-DDT antibodies were treated with free DDT to form an immunocomplex, which then with the DDA-BSA conjugate. Depending on the concentration of free DDT in the sample the binding of gold nanoparticles conjugated anti-DDT antibodies to the immobilized DDA-BSA varied and was detected by the development of red color (due to the gold nanoparticles) and the intensity of color development was inversely proportional to the DDT concentration with maximum intensity at zero DDT concentration. Another approach was based on a surface plasmon resonance (SPR) that used molecularly imprinted nanoparticles (plastic antibodies) to enhance the pesticide detection (Yilmaz et al. 2017). Molecular imprinting based affinity sensor is prepared by the attachment of atrazine (chosen as a model pesticide) imprinted nanoparticles onto the gold surface of SPR chip. The imprinted nanoparticles showed more sensitivity to atrazine than the non-imprinted ones. In order to show the selectivity of the atrazine-imprinted nanoparticles, competitive adsorption of atrazine, simazine, and amitrole was studied. The results showed that the imprinted nanosensor has high selectivity and sensitivity for atrazine. Recently, a good review on enzymatic nanobiosensors has been summarized focussing on the detection of pesticides and food-borne contaminants (Verma 2017) that display ultrasensitivity and quick detection time in real-time analysis, where detection limits are at the nanomolar to picomolar level for contaminants analyzed by enzymatic nanobiosensors.

Besides pesticides, other organic micropollutants, such as polycyclic aromatic hydrocarbons (PAHs) are also detected using nanosensors. The nanosensors for PAHs have been developed using single walled carbon nanotubes (SWCNT) (Carrilo-Carrion et al. 2009); Gold nanoparticles (Mailu et al. 2010), graphene oxide (Shen et al. 2012), etc. SWCNT-doped cadmium selenium quantum dots fluorescence has been used for detection of pyrene, benzo(a)pyrene, benzo(a)anthracene and perylene determinations (Cerrilo-Carion et al. 2009). The optical nanosensor exhibited high sensitivity to pyrene and a wide linear range, low detection limit at <1 nM, rapid response time and good recovery values were achieved. Another fluorescence nanosensor was by Duong et al. (2011) was based on cadmium selenium/zinc sulfide quantum dots functionalized with sol-gel for the detection of anthracene, phenanthrene, and pyrene in mineral water. The trace level of PAHs could enhance the fluorescence intensity of the CdSe/ZnS quantum dot-entrapped membranes and achieved a low detection limit at 5 nM.

4.4.2 Pharmaceutical Products

Pharmaceutical products can be any type of drugs that can toxic, persistent and have a negative effect on the organisms or environment, such as antidepressants, hypolipidemics, analgesics, antibiotics, bronchodilators, chemotherapy products. On of example is ampicillin, which belongs to the penam class of Beta-lactam

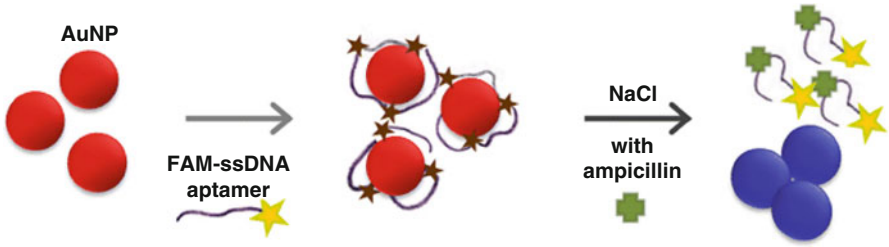

Fig. 4.12 The dual fluorescence-colorimetric method for the ampicillin detection employing the AMP17 ssDNA aptamer. The 5′-fluorescein amidite-modified aptamer (FAM-AMP17 aptamer) is quenched by adsorption onto the surface of the Gold nanoparticles. If ampicillin and salt (NaCl) are added to the solution, fluorescence is recovered and the Gold nanoparticles aggregate. However, if the AuNP solution treated with the only salt shows no obvious changes (Song et al. 2012)

antibiotics, has been used extensively in medicine and agriculture to treat bacterial infections (*Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Escherichia coli*, *Salmonella*, and *Shigella*) and to increase animal growth.

An apta-nanosensor for the detection of ampicillin using a gold nanoparticle based on dual fluorescence–colorimetric detection has been developed (Song et al. 2012). In this aptasensor, the selected aptamers were confirmed to have high sensitivity and specificity to ampicillin. AMP17 ssDNA (5′-GCGGGCGGTTGTATAGCGG-3′) aptamers were used for adsorption onto the surface of the gold nanoparticle. Because of the specific interaction between the ampicillin and the aptamer, the presence of ampicillin caused the aptamer to release the gold nanoparticle and as a result, the liberated gold nanoparticles were aggregated in the presence of salt causing a color change from red to purple (Fig. 4.12). Since it was shown that the higher the concentration of ampicillin in the sample, the more free gold nanoparticles were present in solution, making this method an interesting alternative for the detection of ampicillin.

The work based on voltammetric nanosensor was constructed for the detection of Amoxicillin using gold nanoparticles with ethylenediamine (en) as a cross linker (gold nanoparticles/en-MWCNTs nanocomposites. The combination of good electron transfer property of MWCNTs and the catalytic property of Gold nanoparticles are responsible for the enhancement of electrocatalytic performance of the screen printed electrode (SPE) (Muhammad et al. 2016). The result obtained in the analysis of Amoxicillin in spiked bovine milk samples demonstrated the applicability of this sensor for analysis of Amoxicillin as micropollutants in real samples.

4.4.3 Metals and Metalloids

Recently, various nanomaterials have been utilized in conjunction with biosensor to enhance its sensitivity to the specific metal detection, such as heavy metals. The nanomaterials that have used including MWCNTs (Guo et al. 2011; Bagheri et al.

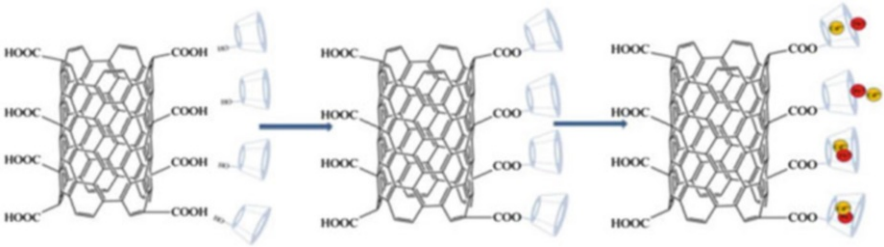

Fig. 4.13 Schematic of the synthesis procedure of CMWCNTs-β-CD-Nafion composite and the interaction between CMWCNTs-β-CD-Nafion composite and the heavy metal ions (Adapted from Guo et al. 2011)

2013), Gold nanoparticles (Zhou et al. 2014; Wan et al. 2015; Chen et al. 2015), silver nanoparticles (Zhou et al. 2011; Ravindran et al. 2012), silica mesoporous/nanospheres (Cheng et al. 2015) and graphene oxide (Zhu et al. 2015; Promphet et al. 2015). Therefore, in the following description, the nanosensors for heavy metal ions are also discussed along with nanobiosensors.

MWCNT modified with 2-amino thiophenol has been used to detect Pb(II) ion in water samples using potentiometric sensor (Guo et al. 2011). The amino thiophenol functionalized MWCNT sensor exhibited excellent analytical performance attributed to the strong covalent bond between an amino group of amino thiophenol and the carbonyl group of MWCNTs to form the solid framework for Pb(II) binding. In a separate study, Bagheri et al. (2013) have also made use of the MWCNT functionalized with triphenylphosphine for an electrochemical sensor for the detection of Pb(II), Hg(II) and Cd(II) ions, where the phosphorus group of triphenylphosphine monolayer on the MWCNT-modified carbon screen-printed electrode (CSPE) binds to the heavy metal ions. It was successfully used for trace metals determination with low detection limit at sub-pM level. Very recently, a bismuth film/carboxylic acid functionalized MWCNT-β-cyclodextrin-Nafion nanocomposite modified glassy carbon electrode (Bi/CMWCNTs-β-CD-Nafion/GCE) was developed for the sensitive detection of Cd(II) and Pb(II) as shown in Fig. 4.13 (Zhao et al. 2016). Due to unique properties and synergistic effects of CMWCNTs, β-CD, Nafion, and Bi film, the developed electrode exhibited some advantages over traditional glassy carbon electrodes, such as large surface area, good sensitivity and stability, reusability and electronic conductivity. The proposed nanosensor has been applied to detect trace Cd(II) and Pb(II) in soil samples with satisfactory recovery results, which holds great promise for its wide applications including for micropollutants detection.

Gold nanoparticles have been widely reported for Hg(II) metal ion detection in water via simple nanosensor technique based on colorimetry (Ding et al. 2012; Zhou et al. 2014; Li et al. 2014; Chen et al. 2015) with the level of determination from nM to sub-nM level, which was much lower than the World Health Organization (WHO) limit for Hg(II) in drinking water (Ding et al. 2012; Zhou et al. 2014; Li et al. 2014; Chen et al. 2015). The nanosensor response was attributed to the change of color of

the gold nanoparticles solution, very often from ruby red to royal purple resulting from the aggregation of gold nanoparticles when no Hg(II) was present. In the presence of the Hg(II), the color of Gold nanoparticles solution could be reverted. Electrochemical nanosensors based on gold nanoparticles are also possible (Wan et al. 2015; Gong et al. 2010) for the determination of Pb(II) and Cu(II) metal ions using gold nanoparticles modified screen-printed electrode. They yielded good limit of detection for Pb(II) and Cu(II) metal ions at ppb level. Another electrochemical nanosensor from a monolayer of gold nanoparticles on the chitosan-functionalized graphene oxide-glassy carbon electrode was successfully designed by Gong et al. (2010) for rapid and specific detection of Hg(II) using square wave anodic stripping voltammetry with a lower detection limit of <1 ppb. In addition to the used of functional groups as recognition elements, urine has also been used for Hg(II) ions sensing. The uric acid and creatinine in urine can synergistically bind to gold nanoparticles as well as selectively adsorb Hg(II) ions. Herein, the low-cost sensor fabrication, a low detection limit of 50 nM was achieved in this case (Du et al. 2013). It has been shown that Zn(II) and Cu(II) can also be detected using agglomeration, resulting in suspension color change of 20 nm chitosan-capped gold nanoparticles (Sugunan et al. 2005). Chitosan is a well-known chelating agent for heavy metals and the presence of Zn(II) and Cu(II) can cause colloidal instability and loose aggregation (agglomeration) of gold nanoparticles. This phenomenon causes a rapid color change that is directly related to the heavy metal concentration. Pb (II) ions with a tunable detection limit of 100 nM to 200 μM has been detected following an aggregation-dissociation protocol (Liu and Lu 2003) using the DNAzyme-directed assembly of gold nanoparticles cleaves in the presence of Pb (II) and results in a blue to red color change (Fig. 4.14).

Apart from gold nanoparticles, silver nanoparticles have also been exploited for optical nanosensor construction for Pb(II), Cr(VI) and Hg(II) metal ions analysis in water (Kumar and Anthony 2014; Zhou et al. 2011; Ravindran et al. 2012; Farhadi et al. 2012). For instance, Zhou et al. (2011) have employed 4-mercaptobenzoic acid (4-MBA) functionalized silver nanoparticles as a receptor in a colorimetric

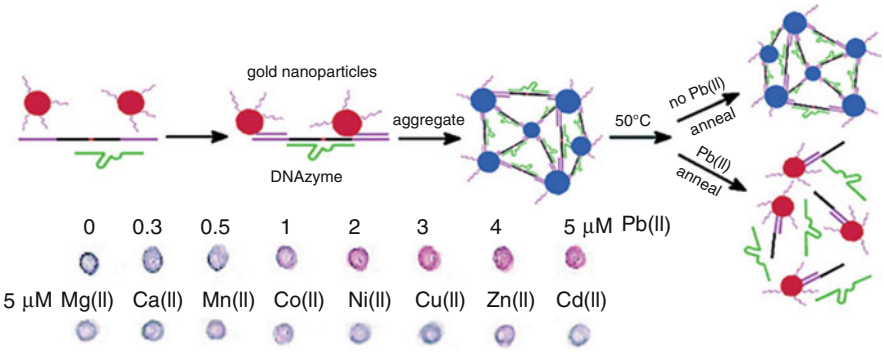

Fig. 4.14 DNAzyme-directed assembly formation and cleavage of gold nanoparticles in a Pb^{+} colorimetric nanosensor (Adapted from Liu and Lu 2003)

nanosensor for the detection Cu(II) ion. The presence of Cu(II) ion would induce the aggregation of 4-MBA modified Silver nanoparticles and this resulted in a color change from bright yellow to purple and a detection limit of down to 25 nM was attained. Another optical nanosensor based on citrate ion coated silver nanoparticles for Cr(VI) metal ion was reported (Ravindran et al. 2012) with a low detection limit at nM level. The detection of heavy metals using graphene oxide modified carbon/gold screen-printed electrode for the determination of Pb(II) and Cu(II) has recently been reported (Zhu et al. 2015; Promphet et al. 2015; Wei et al. 2012). The nanosensor is a simple and rapid method and demonstrated a wide linear response range and a low detection limit at <10 nM level. An integrated heavy metal sensing platform designed from tin oxide (SnO_2) modified with graphene-glassy carbon electrode (Wei et al. 2012) and graphene oxide functionalized polyaniline-polystyrene nanoporous material have also achieved a wide linear range and a low detection limit at ppb level.

4.4.4 Endocrine Disruptors

A wide and varied range of substances is thought to cause endocrine disruption. Chemicals that are known endocrine disrupting compounds include diethylstilbestrol, dioxin and dioxin-like compounds, polychlorinated biphenyls (PCBs), DDT, and some other pesticides. Dioxins and dioxin-like compounds are polychlorodibenzo-*p*-dioxins (PCDDs) and polychlorodibenzofurans (PCDFs). They are very toxic environmental pollutants and carcinogens, because of their high stability and resistant to degradation. A sensor for rapid and sensitive detection of dioxins have been reported using oligopeptide-cysteine-quartz crystal microbalance (QCM) (Mascini et al. 2004, 2005). Herein, the synthesized polypeptide was functionalized with two terminal cysteine residues and structured including (A) [N] Asn-Phe-Gln-Gly-Ile[C], (B) [N]Asn-Phe-Gln-Gly-Gln[C] and (C) [N]Asn-Phe-Gln-Gly-Phe[C]. The monolayer of the polypeptide on the cysteine functionalized QCM could directly allow electrostatic interactions between the amino acids and the dioxins. A low detection limit at 1 ppb level was achieved. Another method for dioxins determination reported very often involving immunosensors such as employing monoclonal antibodies-modified bovine serum albumin on QCM (Park et al. 2006), antibody functionalized polypeptide-gold thin layer using surface plasmon resonance (SPR) (Soh et al. 2003) and SPR utilizing bovine serum albumin conjugated with CM5 sensor chip (Tsutsumi et al. 2008). In the last work, the resulting immunosensor has been applied for the determination of dioxin with good reproducibility (RSD < 6.0% n = 4) and a low detection limit at <1 ppb level.

Other endocrine disruptors are polychlorinated biphenyls (PCBs), they are commonly used in industrial applications such as condensers, transformers, and capacitors. They are hazardous synthetic substances and suspected to have a harmful influence on the endogenous hormone, which could promote cell malignancies. Conventional methods for the determination of PCBs were often reported using

gas chromatography-mass spectrometers and high-performance liquid chromatography (Concejero et al. 2001). However, nanosensor/nanobiosensor could be an alternative method for simple detection of PCBs. For instance, nanosensors for rapid and direct detection of polychlorinated biphenyls (PCBs) employed immunoassay with fluorescence transduction (Endo et al. 2005), electrochemical method (Laschi et al. 2003), and piezoelectric techniques (Pribyl et al. 2006) and surface plasmon resonance (SPR) method (Tsutsumi et al. 2008).

Hong et al. (2008) have employed an SPR nanobiosensor based on gold film modified with cytochrome c for the detection of PCBs. The changing conformation of the immobilized cytochrome was followed by detection with SPR spectroscopy. The nanobiosensor exhibited a high sensitivity with a low detection limit at <1 ppb level. *Pseudomonas fluorescence* bacteria was also used to construct PCBs biosensor via a spectrofluorimetric technique. This highly sensitive optical biosensor contained encapsulated bacteria in alginate beads (Liu et al. 2007, 2010). The biosensor was successfully used to detect PCBs in samples with a low detection limit at <1 ppb level. Endo et al. (2005) used monoclonal antibody grafted on polystyrene beads to determine PCBs with a micro-flow immunosensor chip. The reaction was based on antigen–antibody binding where the antigen was conjugated to horseradish peroxidase. In the presence of hydrogen peroxide and a fluorogenic substrate, fluorescence can be generated. A rapid response time and low detection limit of <1 ppt level were achieved.

In contrast to the aforementioned techniques, flexible substrates such as paper-based SERS (surface-enhanced Raman scattering) substrates are easier to make, low-cost, and can be applied to curvy surfaces (Lee et al. 2010). A paper-based SERS swab was fabricated by simply dipping a filter paper in gold nanorods suspension. The gold nanorods were adsorbed efficiently onto the surface of filter paper due to the electrostatic attraction between the negatively charged cellulose and the positively charged CTAB-coated gold nanorods. The biggest advantage of this SERS substrate is easy to use for the collection of trace samples from a solid surface. By swabbing a glass surface contaminated with a 140 pg 1,4-benzene-dithiol (1,4-BDT) residue, the chemicals were readily adsorbed on the paper surface and their Raman spectrum was easily obtained (Lee et al. 2010). Similarly, a star-shaped μPAD whose fingers were coated with polyelectrolyte was fabricated (Abbas et al. 2013). This μPAD showed the capability to separate chemicals based upon their charge and to concentrate the chemicals into the small volume of the tips (Fig. 4.15). For example, positively charged Rhodamine 6G (R6G) readily moved to the fingertip coated with positively charged poly(allylamine hydrochloride), while it was retained at the entrance of the finger coated with negatively charged poly (sodium4-styrene sulfonate). This μPAD exhibited a preconcentration factor of 10^9 for R6G and thus a super low detection limit of 100 nM was detected (Abbas et al. 2013).

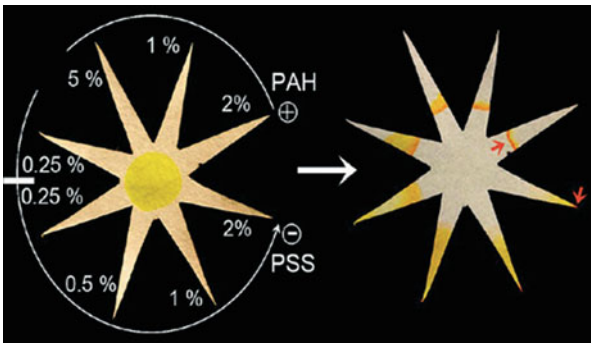

Fig. 4.15 A star-shaped paper with eight fingers was coated by polyelectrolyte, which could separate and pre-concentrate chemicals efficiently (Adapted from Abbas et al. 2013)

4.5 Conclusion

Recently, biosensor technology has been revolutionized by the integration with nanotechnology to develop nanobiosensors in very small size. Since, nanosensors employed various nanomaterials enable the use of chemical or biological components to react or bind with a target molecule and transduce this event into detectable signals for rapid detection of micropollutants that can be classified into the major families, i.e. metals, metalloids and radioactive elements; organic micropollutants; hormones (natural or synthetic); pharmaceutical products, and endocrine disruptors. They can play a vital role in assessing these micro pollutants, which will help to take rapid respond in preventive actions if required. Nanobiosensor development focuses on developing novel and innovative technologies that have the ability to make significant contributions in our daily life. These technologies take the form of nano-engineered, biologically active surfaces, or liquid-solid interfaces, and the tools necessary to characterize them.

The emergence of nanotechnology has opened up new horizons for the development of nanosensors and nanoprobes with submicron-sized dimensions, which are suitable for intracellular measurements. The attention is being focused on the study of various nano aspects, such as the quantum size, mini size effect, surface and the macro-quantum tunnel phenomenon, that is unique to nanomaterials, and is actually their most attractive aspect. Novel nanomaterials and new nanostructures need to be exploited to be used as nanobiosensors. Preferably, nanobiosensors could be integrated within tiny biochips as lab on chip with on-board electronics, sample handling and analysis. This will greatly enhance their functionality, by providing devices that are small, portable, easy to use, low cost, disposable, and highly versatile analytical tools. Even though a wide range of nanobiosensors have been developed in the last two decades, the futuristic goal of low-cost, high throughput, multiplexed lab-on-a-chip devices is yet to be truly realized in our daily life. Therefore, well-structured interdisciplinary research programs that involve, bioscience scientist, chemist, engineers and physicians have to be conducted, to reveal more refined, reliable and affordable nanobiosensors in the near future.

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Chapter 5
Nanotechnology Prospects and Constraints in Agriculture

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Contents

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Abstract Particles at nanoscale has lead revolutionary developments in all major sectors like medicine, pharmaceuticals, drug delivery, electronics and including agriculture and food due to expression of different properties like optical, mechanical, magnetic and other physical properties than their bulk counterparts. The technology deals with study of nanoscale particles and their behavior is called nanotechnology. With increase in demand for feeding the growing population has leading to adopt newer, stable and ecofriendly technologies for sustainable agriculture. Among the advanced technologies, nanotechnology has finding the applications in agricultural and allied sectors. Application of nanotechnology in agriculture has great potential and enhances the quality of life. Increasing applications of nanotechnology in agriculture and allied areas is due to enhanced quality of produce, food quality and safety. Issues leads to utilize nanotechnology in agriculture are climate change, urbanization, sustainable use of natural resources and environmental issues like runoff and accumulation of pesticides and fertilizers. Nanotechnological applications agriculture ranges from nanopesticides, nanofertilizers, controlled delivery devices, water management, soil management, aquaculture, poultry, veterinary, detecting of pathogens, precise agriculture etc. Nanotechnology plays a pivotal role in agriculture from field to plate stage. Different types of nanoparticles which varies in size, shape and chemical nature are utilized at different stages and phases of agriculture, water management, soil management and post-harvest. Like every technology, nanotechnological approaches has its own pros and cons. Emphasis is going on to make nanotechnology safer to humans and environment by increasing its potential and utilizing greener nanomaterials and nanotechnology. This chapter provides a detailed overview potential of nanotechnology in the field of agriculture as different types of nanopesticides, nanoformulations, nanofertilizers, nanosensors, entry and uptake of nanomaterials of utilized nanoparticles in plants, involvement in plant functioning, risks associated with nanotechnology and greener options to overcome the risks. Uptake, translocation and mechanism of action of nanomaterials has been discussed along with its potential. Conventional nanomaterials has finding its potential in almost every phase of agriculture but due to smaller in size its entry into plant, environment and humans is very easy which have risks associated with it and synthesis of nanoparticles involves generation of huge hazardous waste. In order to reduce these risks and toxicological effects in nanotechnology, adoption of greener methods for synthesis of existing nanoparticles, green nanomaterials usage is research trend in present. In this context, present article has given reference of need of green nanotechnology and some of the key points involved in it which aims for nutritional security in agriculture along with safer and sustainable environment.

5.1 Introduction

World population is increasing at an alarming rate and is expected to reach nine billion by the end of year 2050. Agriculture is the cultivation of animals, plants and fungi for food, fiber, biofuel, medicinal plants and other products used to sustain and enhance human life. In order to feed the increasing population by utilizing the available natural resources like land, water and reduction of current yield losses caused by pests are major challenges in agriculture. Freedom from hunger is not only a basic human right: it is essential for the full enjoyment of other rights, such as health, education and work, and everything that flows from these (FAO 1960). This results the main emphasis of agricultural development all over the world was the increasing productivity per unit area of land used for crop production to feed the ever-increasing population. This was substantially accomplished through over exploitation of natural resources and excessive use of fertilizers and pesticides plays a major role. This has placed major pressures on our environment resulted in climate change and global warming due to run-off and accumulation of agrochemicals which results in threatening environmental sustainability and food safety and security (Bhattacharyya et al. 2010).

Highlighting present research trends like its impact on food safety and security and what the future holds, within the sciences the nanosciences has helped to foster the emergence of nanotechnology in agriculture for crop management in a better way (Filipponi and Sutherland, 2007). Nanotechnology is one of the most fascinating and rapidly advancing sciences and possess potential to revolutionize many disciplines of science, technology, medicine and agriculture. Conversion of macromaterials in to nanosize particles (1–100 nm) gives birth to new characteristics and the material behaves differently (Bhattacharyya et al. 2011).

In twenty-first century, Nanotechnology is regarded as one of the key technologies and plays a pivotal role. It enhances the management and conservation of inputs, resources and improves current agricultural practices in crops, animal production and fisheries (Sekhon 2014). In global food production, nanotechnological applications has potential to increase quality of food and waste reduction for "sustainable intensification" of agricultural production (Pérez-de-Luque and Hermosín 2013). Thus, food production and agriculture are among the most important fields of nanotechnology application. Along with other emerging technologies such as biotechnology including genetics, plant breeding, disease control, fertilizer technology, precision agriculture, and other allied fields, in developing countries, nanotechnology has got important application for enhancing agricultural productivity and sustainable production (Sastry et al. 2010; Jha et al. 2011) (Fig. 5.1 and Table 5.1). The emergence of nanotechnological applications in agriculture is mainly due to wide use of pesticides and fertilizers which causes environmental pollution, loss of biodiversity and increase resistance of agricultural pests and pathogens due to existing conventional agrochemicals. For alleviation of these problems nanopesticides – which are pesticides that contain nano-scale chemical toxins and nanoformulations can be used which represents an efficient means for targeted

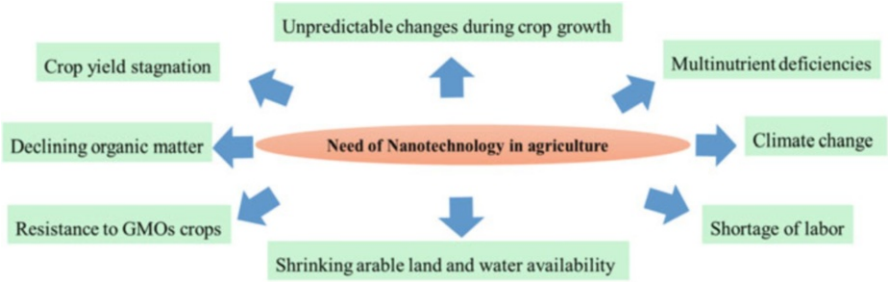

Fig. 5.1 Highlighting some of the promising roles and benefits of nanotechnology in agriculture at different phases and stages

Table 5.1 Different types of nanotechnological interventions and its multifarious applications in different fields of agriculture along with reported references

Nanoparticle	Main application	References
Nanopesticides	Crop protection	Jayaseelan et al. (2012) and Krishnaraj et al. (2012)
Nanosensors	Plant disease diagnosis	Chartuprayoon et al. (2010) and Kang et al. (2010)
Nanoformulations	Delivery systems	Guan et al. (2010), Liu et al. (2006), and Pepperman et al. (1991)
Nanocoatings	Post-harvest technology	Liu et al. (2008a, b)
Nanobiosensors	Identification of quality of agricultural produce	Lopez et al. (2009) and Van Dyk and Pletschke (2011)
Nanoremediation	Soil management	De Windt et al. (2005) and Mohamed and Khairou (2011)
Nanofilters/ nanoadsorbents	Water management	Reverchon and Adami (2006) and Hajeh et al. (2013)

distribution of fertilizers/pesticides in a controlled fashion with high site specificity, thus reducing collateral damage (Kuzma and VerHage 2006). Nanotechnology can be used for combating the plant diseases either by controlled delivery of functional molecules and also as a diagnostic tool for disease detection by using nanosensors (Boom 2011) (Fig 5.1 and Table 5.1).

5.2 Nanopesticides and Nanoscale Carriers (Nanoformulations)

Production losses due to pests and diseases remains 20–40% irrespective of pesticide application. Conventional pesticides needs repeated and larger dose of applications to control these pests and diseases which leads to toxicity to beneficial organisms, leaching losses, environmental hazards etc. Nanotechnology has addressed these

negative consequence of conventional pesticide and control of pests and diseases with emergence of nanopesticide (El-bendary and El-Helaly 2013). Nanopesticides will reduce the rate of application because the quantity of product actually being effective is at least 10–15 times smaller than that applied with classical formulations, hence a much smaller than the normal amount could be required to have much better and prolonged management. Nano-based pesticides are promising in this respect as they address both issues. Nano-chemical pesticides – or nanopesticides means which are pesticides that contain nanoscale chemical toxins. Characteristics of this new pesticide are: (i) increased toxicity, stability or diminished solubility in water as compared to bulk molecules of the same chemical toxins and (ii) controlled release of pesticides.

The use of active ingredients is one of the most cost-effective and versatile means of controlling insect pests. A nanotechnological approach consists of nanoscale carriers (nanoformulations) which can be utilized for the efficient delivery of active ingredients like fertilizers, pesticides, herbicides, plant growth regulators, etc. (Goswami et al. 2010). These carriers helps in bringing down the pest population below the economic threshold limit with lesser dosages of pesticide in controlled delivery for longer period. Different carrier types are involved in the efficient delivery, better storage and controlled release include: encapsulation and entrapment, polymers and dendrimers, surface ionic and weak bond attachments among others. These carriers helps in improving stability against environmental degradation, increase insecticidal activity and reduces the rate of application, chemical runoff which finally alleviates environmental problems. These carriers acts as a shell or protective coating which consists of active ingredients and they can anchor the plant roots to the surrounding soil structure and organic matter. These carriers will results in decrease of uptake of active ingredients, thereby reducing the amount of inputs to be used and also the waste which prevents in accumulation of residues in soil. Some nanoscale carriers are stimuli responsive which are triggered by environmental conditions like temperature, light, humidity etc. and releases active ingredients up on time.

There is lot of scope of nanotechnology in agriculture. Among the world different countries are using nano based approaches for different purposes. Some case studies are presented here in this context. Nanosilica has found exceptional nanopesticide having several applications. Nano bio-mineralized SiO_2 is used as protectant against plant fungal diseases (Wang et al. 2001). Nanostructured alumina has proved as potential insecticide in agriculture (Stadler et al. 2010). In agriculture, the use of active ingredients like pesticides are encapsulated in nanoscale carriers to improve delivery systems more efficiently and to reduce undesirable impacts on environment. Nanocapsules or nanoliposomes are being used in the development and formulation of agrochemicals (Perez de Luque and Rubiales 2009). Nanoemulsions are using as carrier for efficient pesticide formulation delivery (Liu et al. 2008a, b). Porous hollow silica nanoparticles (PHSNs) are found as promising carriers for controlled delivery systems of water soluble pesticides in agriculture (Chen and Yada 2011). Some of the inorganic, organic nanoparticles and nanoscale carriers has been discussed below:

5.2.1 Nanosilver

Silver is now an accepted agrochemical replacement. It eliminates unwanted micro-organisms in planter soils and hydroponics systems. It is being used as foliar spray to stop fungi, moulds, rot and several other plant diseases. Moreover, silver is an excellent plant-growth stimulator. There are literally thousands of other essential uses for this odorless, nearly tasteless and colorless, totally benign, powerful, non-toxic disinfectant and healing agent. They were highly stable and very well dispersive in aqueous solution. It eliminates unwanted microorganisms in planter soils and hydroponics systems. It is being used as foliar spray to stop fungi, moulds, rot and several other plant diseases.

Nanosilver has more efficacy and activity compared to silver as such due to smaller nanoparticle size. Nanosilver is the most studied and utilized nanoparticle for bio-system. It has long been known to have strong inhibitory and bactericidal effects as well as a broad spectrum of antimicrobial activities. Silver nanoparticles, which have high surface area and high fraction of surface atoms, have high antimicrobial effect as compared to the bulk silver. Nanosilver colloid is a well dispersed and stabilized silver nanoparticle solution and is more adhesive on bacteria and fungus, hence are better fungicide. This popularity of nano silver has caused concern about regulating and classifying the nanosilver as pesticide (Anderson 2009).

5.2.2 Nanosulfur

Sulfur has a wide range of applications in different agriculture area. Sulfur can be used as fungicide against many plant diseases such as the apple scab disease in the cold conditions, also Sulfur used in the culture of grapes, vegetables, strawberry and many cultivated plants. However, sulfur can be considered as a high efficiency pesticide that used in agriculture where it has good effect against a wide range of powdery mildew diseases as well as black spot. Sulfur nanoparticles have many advantages over micro-sulfur for their peculiar quantum size properties and high surface areas. Nanosulfur proved to be efficacious as a fungitoxic agent over the commercially available elemental sulfur (Duran and Seabra 2012). Sulfur has broad spectrum of antimicrobial activity, acts against antibiotic resistance. Mechanism of action of sulfur is reaction with organic acids and forms pentanoic acids or multifunctional organic acids having anti-microbial properties. Sulfur is an essential macronutrient important to plant after carbon, hydrogen and oxygen. It is very effective, non-toxic, cheaper and easily available than other metal nanoparticles. Sulfur exists in several allotropic forms almost in the range of 30. Cyclo-octa sulfur is one of the allotrope of sulfur is the active principle involved in mechanism of action of anti-microbial nature. Elemental sulfur and sulfur nanoparticles almost mechanism action, chemical properties and its involvement in plant nutrition,

physiological activities are similar. But solubility of elemental sulfur is very poor which is resolved in sulfur nanoparticles.

5.2.3 Titanium Dioxide Nanoparticles

Titanium dioxide nanoparticles occurs naturally. Titanium dioxide is an oxide and photo catalyst of the tough and resistant metal named titanium. Titanium dioxide is white colour and loses its odour and colour when it is reduced to nanoparticle. Titanium dioxide used mostly in manufacture of pigments. Titanium dioxide nanoparticles has several applications in variety of fields like cosmetics, sunscreens, food preparation, and drug delivery systems. Mechanism of action of titanium dioxide against to pathogens are when exposed to light generates radical which are reactive oxygen species and these free radicals attack cell walls of bacteria. Due to its photocatalyst nature of titanium dioxide has also led to self-cleaning products as well as enhancing sterilization and deodorizing processes. Medical applications of titanium dioxide nanoparticles has demanding in recent years. Application of these nanoparticles in agriculture has started these years due to its anti-bacterial properties and photocatalytic nature. Being a good photo catalyst titanium dioxide mostly utilized in pesticide degradation purpose. This activity resulted in the usage of titanium dioxide as pesticide due to its formation of non-toxic compounds and has great potential in disinfection activity. Titanium dioxide nanoparticles showing enhanced antibacterial property and reduction of resistance of bacterial species (Owolade et al. 2008). In plants it stimulates some metabolic activities results in increase of biomass and improves photosynthesis activity and efficiency and enhance nitrogen fixation.

5.2.4 Silica Nanoparticles

Structural composition of silica is one atom of silicon is attached to two oxygen atoms in a tetrahedral manner. This orientation has leads two types of structures one is amorphous and other one is crystalline nature. Nanosilica with amorphous structure has high potential as a pesticide and also considered safety for humans by World health organization (WHO). Nanosilica using as nanopesticide against pests in storage grains, household and pathogens. Due to its surface properties nanosilica is using as a fillers in composites making. Silica nanoparticles enhances resistance in plants due to disease caused by pathogens and also involves in the physiological activity and growth of plants (Brecht et al. 2004; Carver et al. 1998). Aquatic and terrestrial plants accumulate Silicon and its oxides at higher amounts in their tissues. Due accumulation in their tissues like stem, leaves and roots which enhances inner resistance to pathogen and pests and reduce toxicities. Conventional silica

application may not be readily available and not be effective for biocontrol action as the adherence on plants is transient.

Silicon and its oxides after application to soil, helps in reduction of leaching of phosphorus, potassium, mobility of iron, aluminum and manganese, soil erosion; improves stability of soils by increasing water holding capacity, microbial activity, soil texture, cation exchange capacity etc. In plants silica is involved in physiological functions like organic compound synthesis, transpiration, antioxidant synthesis etc. (Yuvakkumar et al. 2011).

5.2.5 *Copper Nanoparticle*

Copper acts as fungicide in large variety of plants by producing reactive hydroxyl ions which disrupts biomolecules in fungus. Copper nanoparticles has shown increased fungicidal activity with minimum quantity (Borkow and Gabbay 2005). With minimum quantity of copper it is able to decrease microorganism to 99.9%. It has strong anti-bacterial activity mostly effects gram negative strains. Cooper oxide has potential antibacterial activity against Bacillus, Pseudomonas, Staphylococcus etc. Mechanism of action of Copper nanoparticles is due to release of ions and its tendency to change from different oxidation states has led to its antimicrobial activity. These properties has more influenced in nanoparticles due to its smaller size and high surface at volume ratio results in more interaction of copper ions to more closely with the microbial membranes.

Copper metals able to produce the hydroxyl radicals which binds with DNA molecules and reacts with it which leads to disorder in helical structure and damage the nucleic acids and proteins. Denaturing of proteins automatically makes enzymes ineffective. When protein at cell surface denatures inactivates materials across membrane of the cell, affects membrane integrity and lipids. Copper ions disrupts biochemical processes. The denaturing effect of copper ions on protein and enzymes gives its antimicrobial characteristics. Complete mechanism of action of copper ions needs to be further studied. Besides its antimicrobial characters copper ions as a role of nutrition and involves in plant physiological and biochemical mechanisms.

5.2.6 *Alumina Nanoparticles*

Alumina is a hexagonal closely packed molecule with octahedral sites in lattice. Alumina nanoparticles exhibits a wide range of antibacterial activity and also thermodynamically stable over a wide thermal range. Alumina nanoparticles disrupts cell wall mechanism leading to infecting of bacterial cells. Alumina disrupts bacterial cell wall due to reaction of released metal ions and its interaction on surface wall due to its charge. Few studies revealed more mutagenic and disrupting of alumina nanoparticles compared to normal alumina on bacteria, algal species

(Balasubramanyam et al. 2010). It also exhibits anti-algal activity with same mechanism which results in decrease of chlorophyll content.

5.2.7 Clay Based Nanomaterials

Certain clay based nanomaterials are being used as carriers for active ingredients like metal nanoparticles, micronized metals/metal oxides, pesticides etc. for its control release and efficient use. ***Nano porous Zeolite*** This is one of kind of nanoscale carriers for entrapment of agrochemicals and releases the active ingredients in slow release manner over time. Slow release is due to presence of larger surface area. Aluminum zeolites are also used because they are highly porous and allow the retention of the soil. These zeolites help the dry soil also to retain all the moisture content and help to grab nutrients from the soil (Manzer and Mohamed 2014). ***Clay nanotubes*** Clay nanotubes (Halloysite) have been developed as carriers of pesticides for low cost, extended release and better contact with plants, and they will reduce the amount of pesticides by 70–80%, hence reducing the cost of pesticide and also the impact on water streams (Carretero and Pozo 2009; Grasielli et al. 2012).

5.2.8 Polymeric Nanomaterials

Other than above mentioned metal nanoparticles and clay based nanoparticles there is emerging revolution around nanoscience based polymer chemistry in form of different carriers for delivery systems and as showing its potential of inhibition of some diseases. Some of them are nanomicelles, nanogels/nanohydrogels, nanoemulsions, nanoencapsulation, nanoliposomes, nanocomposites, nanospheres, polymeric nanoparticles etc. These nanomaterials has better adaptability against environmental stresses and few biotic stresses of plants. These materials exhibits better physic-chemical properties compared to conventional polymers (normal sized) like bioavailability of drug to targeted site, controlled and sustained release of active ingredients, dispersion ability etc. (Moraru et al. 2003).

5.2.8.1 Nanospheres

In polymeric matrix homogenous distribution of active ingredient takes place.

5.2.8.2 Nanocapsules

Unlike nanospheres, in nanocapsules active ingredients distribution will be concentrated at the center of the lined polymer matrix.

5.2.8.3 Nanogels

Polymer matrix formed by cross linking technique having hydrophilic three dimensional structure able to absorb large volumes of water.

5.2.8.4 Nanomicelles

Matrix is formed by both hydrophilic and hydrophobic moieties by suspending in aqueous solutions.

5.2.8.5 Nanoliposome

It is bilayer lipid vesicle, where active ingredient is encapsulated in between matrix.

5.3 Nanofertilizers

Fertilizers are solid, liquid or gaseous substances which contain one or more plant nutrients applied to soil or plant for improving soil fertility, improve the crop development and yield quality. Now a days fertilizers plays a major role in providing nutrition to plants. Due to decreasing soil fertility fertilizers needs to apply repeatedly. Existing fertilizers undergoes several losses like volatilization, leaching off, degradation losses. In order to avoid these losses fertilizers now entrapping in nanoscale carriers for its controlled and efficient utilization throughout of the crop time (Gogos et al. 2012). Nanofertilizers are applied in slow and efficient way all the required nutrients is taken up by the plant and restores the required and efficient energy in it for which the yield increases drastically. When fertilizers are in the form of encapsulated this can be achieved. Coating of fertilizer particles on nanomaterials due to higher surface tension holds the material more strongly than the conventional fertilizers and helps in controlled release. Delivery of macro and micronutrients to the plants in controlled and sustained release is an important advantage of agriculture which can be achieved through nanotechnology.

Nanofertilizer enabled technologies improves solubility and dispersion of insoluble nutrients in soil, reduce soil absorption and fixation, increase bioavailability, increase fertilizer efficiency, uptake ratio of nutrients present in soil and save fertilizer usage, release pattern of water soluble nutrients will be controlled without any losses of leaching, percolation and vaporization, extend the duration of availability of nutrients and also reduce loss rate due to leaking and leaching over conventional fertilizers (Cui et al. 2010).

Plant availability of nutrients present in nanomaterials depends on several soil properties, especially soil pH, soil organic matter, nature and type of soil. Certain

studies has been done in different crops to assess the nutrition of plants and physiological observations due nanofertilizers compared to conventional fertilizers. Significant increase in yields have been observed due to foliar application of nanoparticles as fertilizer (Tarafdar et al. 2012). Certain other nanofertilizers like silver, calcium, cesium dioxide, copper and its oxides, iron and its oxide, magnesium, manganese, molybdenum, phosphorus, zinc and oxide in crops like pearl millet, peanut, cucumber, lettuce, maize, barley, soybean, pea, cowpea, mung bean, rice, chickpea, cluster bean etc. in different concentration ranges has resulted in improvement of seed germination, seedling growth, chlorophyll content, yield, root elongation, plant growth, uptake of nutrients etc. has been observed (Parveen et al. 2016; Liu et al. 2004; Zhao et al. 2014; Taha et al. 2016; Adhikari et al. 2016; Delfani et al. 2014; Pradhan et al. 2013; Yuvaraj and Subramanian 2015; Taran et al. 2014; Liu and Lal 2014; Zheng et al. 2005; Lin and Xing 2007; Burman et al. 2013).

5.4 Uptake and Mechanism of Nanomaterials

Nanomaterials like nanopesticides, nanoformulations and nanofertilizers are broadly of two types one is metal nanoparticulate in nature and the other one is encapsulated in organic polymer or zeolite where active ingredient released with time. The nanomaterial which are of different of nature should enter into through the plant to show its mechanism. To understand the uptake and entry into the plant through various plant tissues like roots below the soil and above ground tissues like cuticles, trichomes, stomata, stigma, and hydathodes. Cell wall of plant acts as a barrier for the entry of nanoparticles or any external elements. Generally the pore diameter of cell wall ranging from 5 to 20 nm. The nanoparticles size of lesser than pore size will enter in to the plant and finally reaches to plant cell organelles by crossing plasma membrane. Sometimes even larger nanoparticles than pore size will enter during enlargement of pores which takes place when nanoparticles interact with plant, endocytosis which forms a cavity around nanoparticles, through channels cross the membrane by interaction with proteins or ions. Some of the nanomaterials like insoluble particulate in nature enters by direct uptake, translocation (mesoporous silica, carbon nanotubes etc.). The uptake, translocation and biotransformation of different nanomaterials is shown in Fig. 5.2 (Rico et al. 2011). Nanoparticles after reaching cell organelles interact with cytoplasm and interferes in metabolic activities of the plant.

Nanomaterials which are using as nanopesticides and nanoformulations shows its pesticide activity by phagocytosis, cell wall disruption, oxidative stress, metal reduction potential, the metal donor atom selectivity etc. Mechanisms involved by nanomaterials is shown in Fig. 5.3. The phagocytosis of nanoparticles depends on physicochemical parameters like type, size, shape, surface structure, surface charge, concentration and chemical nature which gives toxic effects. But principal factors of nanoparticles which influence pesticidal activity is shape, size and concentration. Depending upon size of nanoparticles there will be interaction with pathogens.

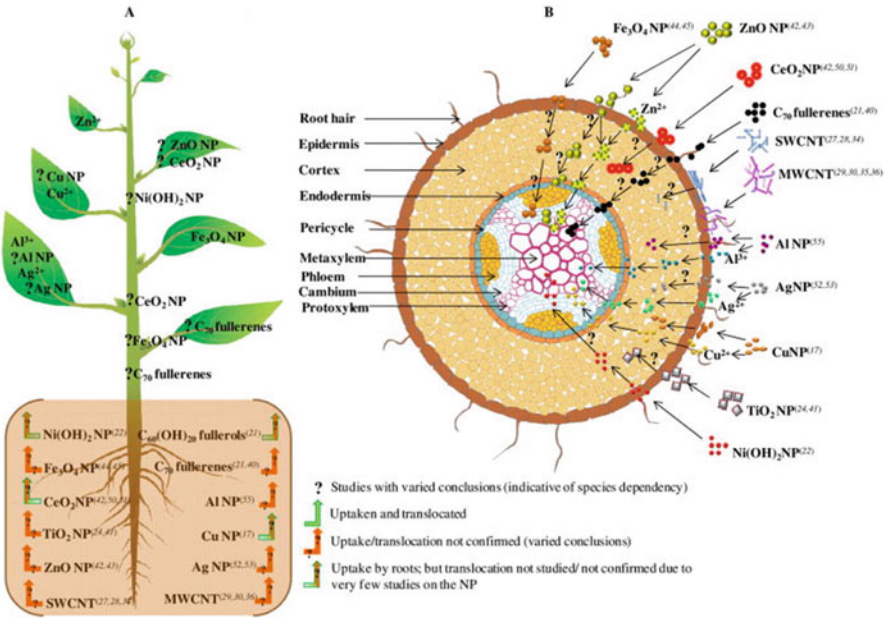

Fig. 5.2 Uptake, translocation and biotransformation pathway of various nanoparticles in a plant system. (**a**) Plant showing the selective uptake and translocation of nanoparticles. (**b**) Transverse cross section of the root absorption zone showing the differential nanoparticle interaction on exposure. The superscripts depict the reference cited in the original article (Reproduced with permission from Rico et al. (2011) from American Chemical Society)

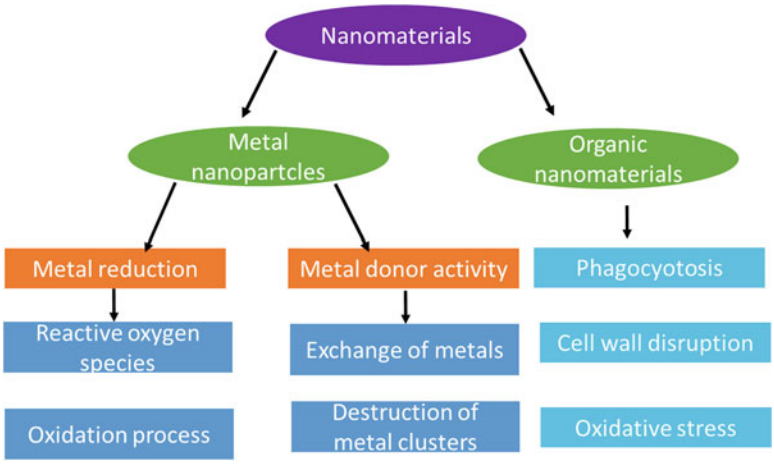

Fig. 5.3 Different types of nanomaterials based on its chemical nature and its respective mechanism of action on different insect-pests and pathogens

Lower concentration of nanoparticles stimulates pathogenic activity without effecting much to pathogen and even higher doses causes risks associated with human and environment. So, optimum concentration is required for its mechanism of action. Shape relates to its active facets of nanoparticles which allows interaction with pathogens. Higher number of active facets results in higher pesticidal or antimicrobial activity. Most of the mechanism of nanoparticles due to generation of reactive oxygen species which leads to above said symptoms like oxidative stress, inflammation, disruption of cell wall, genetic damage and finally leads to cell death. The benefit of using nanopesticides, nanoformulations over conventional ones is due to reduced amount, targeted action and hence more susceptibility.

5.5 Role of Nanoparticles in Functioning Plants

Nanoscience is evolved as an emerging and advanced technology in almost every field ranging from electronics, pharmaceuticals, drug delivery systems, food industry and agriculture. The evolutionary trend in agriculture is mostly due to its direct positive effects by utilizing smaller quantities of the nanomaterials compared to conventional types. Other than its direct effects in plants as nanopesticide, nanoformulations for control and targeted delivery of active ingredient, some these nanomaterials is playing its unique role in functioning, development and metabolism of plants as artificial organs (Giraldo et al. 2014; Cossins 2014). The functioning of plants by nanomaterials is done after its uptake by plants. Nanomaterials after application had been adsorbed by the plant surfaces and entry into plant by different paths mostly through plant natural openings. However, the uptake path and rate of nanomaterials depends on the concentration, size, surface and chemical nature of nanomaterials. The type of metabolism involve by a particular nanomaterial varies from plant to plant. A few studies have been conducted on nanoparticles are beneficiary to plant (Table 5.2).

5.6 Nanosensors

Major losses in crop yields and quality is due to pests and diseases. Management of any diseases prior to complete loss of crop depends on detection of stage of disease infection. Some of diseases like viral ones which are infected by vectors causes unavoidable losses to the crops. Application of pesticide at that will not be of much use. Detection of these kind of diseases at correct stage by nanotechnological approach like nanosensor is more advanced technique and a milestone to agriculture (Elibol et al. 2003). Nano based sensors for diagnosis of diseases helpful as precautionary measure for application of pesticides without causing heavy infections by pathogens. Nanosensors for disease diagnosis include multiplexed diagnostics kits, in order to detect the exact strain of pathogen and the stage of application of some

Table 5.2 Various types of nanomaterials and its functioning as artificial plant organs to involve in metabolism of plants along with reported references

Nanomaterial	Involved in plant metabolism	References
Carbon nanotubes	Germination and seedling growth, root elongation	Morla et al. (2011) and Miralles et al. (2012)
Aluminum oxide	Root length	Lee et al. (2010)
Titanium dioxide	Chlorophyll content, root length, plant growth, germination, Hill reaction, non-cyclic photophosphorylation, protect chloroplasts from aging, net photosynthetic rate, conductance to H_2O, and transpiration rate, regulation of photosystem II	Lee et al. (2010), Feizi et al. (2013), Song et al. (2012), Mahmoodzadeh et al. (2013), Hong et al. (2005), and Qi et al. (2013)
Sulfur	Dry weight	Patra et al. (2013)
Silicon dioxide	Growth parameters	Yuvakkumar et al. (2011) and Suriyaprabha et al. (2012)
Silver nanoparticles	Germination and seedling growth, root length, dry weight of root and shoot Antagonize inhibition by 2,4-dichlorophenoxyacetic acid (2,4-D) on plant growth	Savithramma et al. (2012), Salama (2012), and Karuppanapandian et al. (2011)
Zinc oxide	Micronutrients (copper, manganese and zinc), shoot dry weight, biomass, germination, stem, root growth and yield, dry weight	Zhao et al. (2014), Burman et al. (2013), Dhoke et al. (2013), Prasad et al. (2012), and Patra et al. (2013)
Graphene oxide	Germination	Anjum et al. (2014)

therapeutic to stop the disease. Detection and utilization of biomarkers, that accurately indicate disease stages, is also an emerging area of research in bio-nanotechnology. Nanosensors for disease detection based on the principle of quantitative measurement of differential oxygen consumption in the respiration (relative activity) of "good microbes" and "bad microbes" in the soil (Arshak et al. 2007). Nanosensors for detecting is indeed attached to other advanced analytical technologies like surface plasmon resonance, mass spectrometry, chromatography, or electrophoresis chips, can support the development of viable sensor components (Scognamiglio et al. 2014; Mousavi and Rezaei 2011).

Applications of nanosensors other than disease diagnosis includes recognition of biological molecules such as sugars, proteins, contaminants, pesticides and their metabolites. Nanosensors are also utilized for Controlled Environmental Agriculture (CEA) for determination of the crop growth and soil health conditions. Nanosensors at CEA plays pivotal role by having ability in determination of best time of harvest of the crop, health of crop and food security like microbial or chemical contamination of the crop. Nanoscale devices have capability to detect nutrient deficiency long before symptoms is possible. Nanosensors are used for in situ detection, as miniaturized portable devices, and as remote sensors, for the real-time monitoring of large

areas in the field. Global positioning system (GPS) is linked with nanotechnology for real time monitoring for automation of management of crop and detection of deficiency etc. These biosensors have huge impact on Precision Farming methods. Some of the nanosensors has designed sensors which can give environmental changes ones they are incorporated in equipment (Patel 2002). In this context nanosensors are helping farmers by giving precise control and maintaining farm with timely requirement to crop. Nanosensors mostly referred in smart agriculture to aid in decision-making during crop monitoring, analysis of nutrients and pesticides in soil and water use efficiency.

Through nanofabricated technologies and characterization tools now-a-days it is possible to study the physical, chemical and biological interactions between plants and pathogens. This aids in management strategy of disease by understanding complete mechanism of disease infestation. Advanced integration of micro-fabricated xylem vessels with nanosized features are used to understand the above mechanism (Cursino et al. 2008).

Nanosensors are developed to detect contaminants in water bodies, food products and other raw food materials. Electronic nose (E-nose) is presently in use for detection of different odours by using gas sensors composed of nanoparticles and enzymes are using for detection of biomolecules. Some of the different types of nanosensors as follows:

5.6.1 Carbon Nano Tube

A carbon nanotube is made of carbon and tube-shaped material having a diameter measuring on the nanometer scale. Carbon molecules are held by Vander Waals force which makes it responsible for having many applications like filtration, monitoring environment and energy storing environment etc. (Baughman et al. 2002). Among its applications in different fields, carbon nanotubes having lots of scope in agriculture also, for detecting uptake of nutrients from soil and other contaminants. Carbon nanotubes is an open or closed end tubular structures made up of concentric layers grapheme sheets and categorized into single wall carbon nanotube and multi-walled carbon nanotubes based on the number of grapheme sheets rolled to made. Diameter range of single walled and multi walled carbon nanotubes are in the range of 0.8–2 nm and 5–20 nm respectively. Length of each carbon nanotube varies as per the application purpose mostly starts from 100 nm to several centimeters. Multi walled carbon nanotubes plays pivotal role compared to single walled nanotubes. The applications of carbon nanotubes are mostly in medicine, as sensors, electronics, delivery systems due to its tubular structure, functional properties, chirality of carbon compounds and its association with materials. Mostly its higher efficiency allowing to utilize in remediation pollutants, degradation of pesticides and sensing of pollutants and contaminants. And as a delivery systems for nutrients, pesticides had also been explored.

5.6.2 Nanoaptamers

Aptamers are single stranded nucleic acid of size less than 25 kDa which is of natural or synthetic origin and works on the principle of target specific binding which fits to the target with strict bonding in three dimensionally. Nanoaptamers has higher efficiency compared to normal ones. These kind of sensors helpful in detection of plant diseases, crop resistances and yield production more effectively. For detection of herbicide and pesticide (Atrazine and Malachite green) respectively, an efficient aptamer sensor was devised to monitor the toxicity level in food which is kept for consuming with the luminescent assay technique. Wide variety of nanomaterials are used in nanoaptamers like nanoparticles and nanoclusters, semiconductor nanoparticles, carbon nanoparticles, magnetic nanoparticles etc. along with different transducing systems. Principle of nanoaptamers depends on specific properties, surface charge, size and nature of nanomaterials used in it. Broadly aptamers are classified into two types one is optical and other is electrochemical. Aptamers are target specific and selective towards its target. Nanoaptamers are three dimensional in nature and named as synthetic antibodies due to their selective nature (Sharma et al. 2015). Aptamers selectivity allows detection of wide variety of targets or analytes like pathogens, chemical molecules, heavy metals, biomolecules, toxins etc.

5.6.3 Smart Dust Technology

These are the nanosensors which are tiny wireless devices consisting electromechanical sensors. This is a technology used for meteorological observations, environmental hazards, energy usage, and to monitor environmental hazards. Mainly it works on three principles, sensing, processing and computing through environmental changes. It monitors and tracks irrespective of sensor location, size etc. through wireless transducers, radios, sensors. Sensors are of electrochemical in nature, micron sized and undetectable due to its small size. Some of the drawbacks of this technology is impact on environment and toxicity.

In agriculture, smart dust technology is used in precision agriculture where it tracks and monitors temperature, humidity, rainfall and harsh weather conditions. Irrigation use efficiency will be increased due to usage of this technology as it detects soil moisture and humidity around rhizosphere and saturation levels of soil like field capacity, wilting point etc., based on these data irrigation volume, duration can be controlled. Birds and predators can also be tracked and allows to necessary precautionary measures. Advantages of this technology in agriculture is very less power consumptive, cheaper, self-organizing material, easy to handle like mobile handset, lesser maintenance due to environmental conditions (Shyam et al. 2012).

5.6.4 Nanowire Sensors

It is sensitive to outside signals consisting of two molecules (1) Single stranded DNA serves as detector and (2) carbon nanotube serves as transmitter, which acts a hybrid between these two. The analyte can be detected independently based on the surface properties. Boron doped silicon nanowires are highly sensitive and efficiency is high is now being used (Cui et al. 2001). Mechanism of nanowire sensors is a field effect which is transduced due to field-effect transistors. It is used in generation and measurement of electrophysiological signal. Surface properties of nanowires such as surface to volume ratio plays a major role and benefits in several ways due to its efficiency in sensitivity, selectivity and stability. Nanowire sensors are made up of metal oxides or metals or silicon or polymers have been reported. Nanowires of 10 nm size has an ability to detect analytes at a level of ppb. Nanowire sensors are one dimensional structures easy to synthesize by simpler methods and cheaper. These are promising sensors with effective and specific receptors and finds more application in powerful detection for biological platforms. Positive attributes includes real-time electrical signal transduction, ultra-high sensitive, simplicity, low cost and rapid detection which makes suitable for disease diagnosis and drug discovery. Although highly sensitive, its signal intensity is very low and can be easily contaminated by a background noises. Modification of surface chemistry and reduction of time of immobilization and complexity of receptor binding receptors will improve analytical intensity and robustness of nanowire sensors.

5.6.5 Nanoshell Sensors

Nanoshells containing nanoparticles which are spherical in nature. It consists of core made up of silica which is in dielectric in nature and shell made up of gold. The shell is thin in thickness which almost forms layer around silican core. Gold nanoshells properties is similar to colloidal gold. Unlike colloidal gold which shows optical absorption but gold shells shows both the properties of optical absorption and optical resonance due to relative size of core and shell thickness. Gold nanoshells are coated and used as sensor for detecting analytes and rapidly used in immunoassays testing of biological media. Gold nanoshells are specific which combination of promising features is in single particle. Sample preparation is not required. Due to its resonance and scattering at specific wavelengths in both visible and infrared regions, this phenomena of gold nanoshells are used in imaging. Analytes are sensed by gold nanoshells due to interaction with receptor binding sites and detection by infrared spectrophotometer detects the aggregation of antibody and nanoshell in the presence of analyte. Nanoshells attach to the analytes and form immunoassay like lock and key arrangement. Sensing is ten billion times higher compared different nanosensors (Jain 2005). In general a particular nanoshell gives its peak at a particular spectrum region and a fixed wavelength but due to presence of analyte the change in

wavelength is observed. The change is due to interaction of nanoshell with analyte and indicates type of analyte nature.

5.7 Other Application of Nanotechnology in Agriculture and Its Allied Sciences

Agriculture requires lot of water for its production. Increase in population and polluting the existing water by industrialization are the main causes for water scarcity. To improve water usage, conservation techniques in agricultural productions are following like drip irrigation, sprinkler, precision agriculture, soil conditioners etc. For converting polluted water into agriculturally utilizable water several nanotechnological based purifications are following. Some are carbon nanotubes, nanoporous ceramics, magnetic nanoparticles etc. (Theron et al. 2008).

Prior to purification detection of pollutants is a major task because some of the contaminants present in parts per billion (ppb). Even at that minute levels continuous accumulation in crops and finally entering into food chain leads to residual and toxicity problem. For detecting and sensing the contaminants at ppb level nanotechnological applications like nanosensors plays a major role from over a last decade. Nanoremediation is one of the advanced technology for decontamination of solid waste present in water bodies (U.S. EPA 2014). Now a days nanoremediation is finding scope in decontamination of excess pesticides, toxic waste and obsolete waste during manufacturing at industrial level (Crane and Scott 2012).

Desalination is a phenomena of purification of saline water to obtain fresh water through removal of minerals and salts by using chemical, mechanical and electrical mediated membrane means, thermal process. Desalination is cost involving process. Through intervention of nanotechnology has provided cost effective and ecofriendly opportunities for desalination. Nanotechnology processes for desalination are nanofiltration and membrane technology. Nanocomposite based thin film technology has combined application of both organic and inorganic materials which benefits such as good permeability, packing density and high efficiency. In this technology mostly titanium dioxide and zeolite nanoparticles are being used by many (Theron et al. 2008; Tang et al. 2013).

Reverse osmosis is method widely using for removal of salts and minerals in general. Due to nanofiltration in reverse osmosis efficiency is increased and whereas nanofilter operates at very less pressure (70 and 140 psi) due to its larger membrane pore size (0.05–0.005 m) compared to reverse osmosis (Cloete et al. 2010). It is used for removal of cations, organic pollutants, biological contaminants, natural organic matter, minute quantities of U (VI), arsenic and nitrates from groundwater and surface water (Sharma et al. 2010).

Through adsorption phenomena toxic and carcinogenic metals are removed from water. Adsorption is a surface process where molecules/metals (adsorbate) are attached or adsorbed on surface of adsorbent. Several factors are responsible for

this surface phenomena like temperature, pH, particle size, time of exposure, chemical nature etc. nanoadsorbents are proving its potential due to small size, high reactivity, larger surface area, no of active sites etc. which leads to good adsorption. Mercury is being a neurotoxic and cariogenic substances which causes minimata disease by entering into food chain is worldwide problem. Removal of mercury in contaminated water using nanoadsorbents like alumina, alumina in combination with gold nanoparticles etc. has attempted (Hajeh et al. 2013). Other than mercury the removal of other substances like arsenic and cadmium by iron oxide nanoparticles.

Nanophotocatalysis has emerged as a green technology for the complete mineralization of hazardous organic chemicals present in waste water converting finally into carbon dioxide and simple mineral acids which are effected by various factors such as pH, oxidizing agents, catalyst loading, doping content and the influence of calcinations temperature. Nanophotocatalyst is stable, inexpensive, easily available and highly photoactive, non-toxic when compared to conventional photocatalysts. Nanopolymers and nanocomposites are reported for the photocatalytic degradation of organic contaminants present in wastewater (Sharma and Sharma 2012).

Water is being infected by several pathogens like viruses, bacteria which responsible for diseases. Disinfecting water is a huge task. Disinfectants which are commonly being used for treating drinking water are chlorine, ozone, chloramines and chlorine dioxide. Nanomaterials are currently being used for water disinfection. Silver NPs are effective against viruses and bacteria (Egger et al. 2009). Zerovalent silver are found effective in inactivation of HIV-1 virions (Petrik et al. 2014). Biogenic silver has been found to be very effective against *Enterobacter aerogenes*-infecting bacteriophage and is used for disinfection in drinking water supply (Quang et al. 2013).

Success, marketing and profit of agriculture produce depends mostly on post-harvest management techniques. Mishandling of agricultural produce after harvesting, at any stage from removal of field heat to post harvest storage everything leads to less shelf life of produce and occurrence of pests and pathogens. Among different post-harvest managements nanotechnology has finding application in post-harvest management now a days. Nanowax or nanolatex coating plays a major role in post-harvest management of fresh fruits and vegetables by keeping the produce fresh, improving shelf life storage, controls the water loss through respiration and protection from microbial and mold invasions which finally enhances the perceptual qualities and competitiveness in growing market demand (Khot et al. 2012).

Agriculture is nothing but farming. Farming not only includes cultivation of plants or crops but also poultry, cattle, fishery etc. Agriculture is a complex farming system. Applications of nanotechnology in agriculture includes poultry, cattle and even in aquaculture also. Nanotechnological implications in livestock mostly as a carrier for improving efficient drug delivery and reducing dosage of antibiotics or drugs required at certain stages (Barik et al. 2008). To enhance feed intake and absorption in livestock nano based carriers are utilizing. For diagnosis of pathogens in livestock at correct stage and recommendations of medicine etc. In aquaculture,

water plays a major role. In detection of toxins nanosensor based identification is an improved method even at ppb levels (Dhillon et al. 2012).

5.8 Constraints of Nanotechnology

Nanotechnology is now a days an emerging scientific field in almost all areas. Its potential well defined over a decade and ago. Despite of its potential it has causes some unintended adverse effects on human and environment while during synthesis and handling (Bouwmeester et al. 2009). Nanoparticles effects human beings by entering into food chain and drinking water supplies (Bandyopadhyay et al. 2013). At the time of inhalation size of the particles creates problem by entering into lungs (Jinquan et al. 2004). Some of the particles like carbon nanotubes, asbestos nanoparticles has showed severe impact on lung diseases (Buzea et al. 2007). These ill effects are due to lack of complete understanding on fate and behavior of nanoparticles in humans and environment after application. Stability and degradation of inorganic nanoparticles sometimes becomes a question mark due to its environmental and residual concerns (Bonne et al. 2000). Numerous commissions and union like European Union, Royal commission on environmental pollution are formed in different countries for risk assessments of nanotechnological approaches (COT 2005). Detection of risks associated with nanomaterials are extremely limited (Dhawan et al. 2009). Nanotechnological risk assessment is a challenging task, as large no.of nanoparticles being synthesized for different purposes and their impact on environment and human is very difficult to track (Nel et al. 2006).

Other than toxicity effects in humans and on environment, nanoparticles are showing phytotoxicity effects after applying to plants. Reports showed nanoparticles showed positive or no consequential effects and some other reported nanoparticles exhibited phytotoxicity. Mechanisms behind nanophytotoxicity are unclear depends on several factors like chemical nature, surface area of nanoparticles. Application of nanoparticles and uptake through the root openings changed the roots composition which affects the uptake of nutrients into plant roots. Phytotoxicity caused by nanoparticles occurs are of two types. They are (1) chemical toxicity due to release of toxic natured ions and (2) size and surface of particles which causes stress in plants. Nanoparticles after uptake by plants, accumulate in the plants by phenomena of chelation and aggregations which leads to change of surface activity of plant parts towards other nutrients and also shows its inhibition on surrounding plant activities. Phytotoxicity in plants is also of two types (1) cytotoxicity: disruption of cell activities like photosynthesis, chlorophyll, respiration rate, enzyme synthesis, pollen development etc. and (2) Genotoxicity: inhibiting activities like mitosis, meiosis, nucleic acid composition etc. Because of these two kinds off toxicity visible symptoms will be seen (Rico et al. 2011 and Peralta-Videa et al. 2011). A good understanding of the mechanisms of the nanoparticle phytotoxicity is important for the targeted application and concentration of nanoparticles. Some of phytotoxicity effects of nanoparticles is tabulated in Table 5.3.

Table 5.3 Some of the nanoparticles and its symptoms of phytotoxicity effects on different plants

Nanoparticles	Crop	Particle size (nm)	Phytotoxicity	References
Zinc oxide	*Glycine max*, *Zea mays*, *Oryza sativa*, *Brassica pekinensis*, *Pisum sativum*	<50	Decrease in root growth (length and weight), loss of root cell viability	Hossain et al. (2016), Xiang et al. (2015), and Huang et al. (2014)
Copper oxide	*Zea mays*, *Oryza sativa*	40–80	Inhibited root elongation and reduced shoot length	Yang et al. (2015)
Ferric oxide	*Oryza sativa*	7–13	Root phytohormone inhibition	Gui et al. (2015)
Silver	*Oryza sativa*	50	Breakage in cell wall and vacuole	Mazumdar and Ahmed (2011), Schaller et al. (2003)

5.9 Green Nanotechnology

In order to reduce the global efforts in risk assessment and due to ever increasing demand of nanotechnology, researchers should choose for green nanotechnology (Tomey et al. 2007). Green nanotechnology refers to usage of nanotechnological process to enhance environmental sustainability directly or indirectly by reducing negative effects. Green product design, and green methods for synthesis and manufacturing, should be adopted in both laboratory and industrial which results in achievement of better effects and eco-friendly sustainable environment. Green nanotechnology involves usage of aqueous based synthesis instead of use of harmful and carcinogenic solvents for synthesis to achieve the goals in an energy efficient manner (Carma 2012). Utilization of metal based synthesis should be avoided and instead use of microbe mediated synthesis (Narayanan and Sakthivel 2010). Synthesis of nanoparticles with a wide variety of naturally derived and biodegradable materials like plant based cellulose, chitosan is a novel concept. In plants there are several biomolecules and secondary metabolites which are known to reduce metal compounds (Iravani 2011; Sanchez-Mendieta and Vilchis-Nestor 2012). Single-step green synthesis or reduction of metallic ions by plants extracts is an eco-friendly technique (Gan 2012).

Researchers has found safer plant based cellulose nanofibres an alternative approach to carbon nanotubes which damages to lung tissue (Qi and Hegmann 2008; Petersen et al. 2011). Biological molecules present in plants involves in several plant mechanisms. Cellulose is one of the natural abundant material which widely occurs in almost all biomasses. Cellulose is nothing but a group of β 1-glucose groups linked together covalently by acetyl oxygen bonding. The pattern of cellulose consisting of 10,000–15,000 glucose units together and arranged as tight linked crystalline region and intermittent amorphous fibrillar region with hydrogen bonding (Samir et al. 2005). The amorphous microfibirillar regions ranges from 5 to

50 nm and easily subjected to hydrolysis unlike crystalline region. During hydrolysis amorphous domains broken into smaller particles called as cellulose nanocrystals. Cellulose nanocrystals is a border term which also includes microcrystalline cellulose, nanowhiskers, nanofibers, nanofibrills etc. (Habibi et al. 2010).

Cellulose nanocrystals, have gain considerable attention as nano-reinforcement for polymer matrices. Derived from the most abundant polymeric resource in nature and with inherent biodegradability, nanocellulose is interesting nanofiller for the development of nanocomposites for agricultural applications (Brinchia et al. 2013). Well dispersed cellulose nanocrystals are able to enhance several properties of polymers, i.e. surface wettability, controlled release of active compound. Nanocomposites reinforced with cellulose nanocrystals extracted from different natural sources are of gaining importance. Cellulose nanocrystals are rigid rod-like crystals with diameter in the range of 10–20 nm and lengths of a few hundred nanometers. The application of cellulose nanocrystals as reinforcement in polymer matrixes has attracted considerable attention since it offers a unique combination of high physical properties and environmental welfare. Cellulose nanocrystals based nanocomposites generally exhibit significant improvements in thermal, mechanical and barrier properties compared to the neat polymer or conventional composites. Chemical functionalization of cellulose nanocrystals improves its dispensability inorganic solvents and this greatly expands its potential applications. Moreover, cellulose nanocrystals are finding extensive applications in high strength delivery system (Azizi et al. 2005). The conventional approach of synthesis of hydrophilic composites comprises use of inorganic fillers or unprocessed agri-waste. Use of nanocellulose as filler provides an opportunity to generate smart delivery systems with high loading, mechanical strength and superior hydrophilic character. It is anticipated that nanotechnology innovations in renewable resources like cellulose nanocrystals for future sustainability in agriculture.

5.10 Conclusions

In agricultural sector, applications of nanotechnology is one the growing field. Due to increase in pests and diseases, climate change, urbanization are the causes for utilizing the nanotechnological based implications has brought revolution in agriculture and allied sectors from stage of field farming practices to marketing, trading and storage stage. Development and application of nanomaterials in agriculture has led to high productivity, food safety and security for increasing population demand. Potential of nanotechnology in detection of foreign bodies such as pathogen infections, contaminants detection and quantification, management of water quality, in livestock and aquaculture has brought scope to farmers with profit and efficient management systems. With lots of applications, there are unforeseen risks also associated in the form of toxicity to human and other environmental concerns. Understanding the risks associated and toxicological nature of nanomaterial during synthesis, handling and involving in different mechanisms is challenging job for researchers. In order to reduce to toxicity of nanomaterials during synthesis,

characterization and application in agriculture, adopting greener routes is a best option. Protocols of development and efficient utilization of greener nanotechnology its adoption is one the research area in future. Awareness related to interaction of nanomaterials to other biomolecules and understanding of mechanism of action is also one the challenging area in nanotechnology.

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Chapter 6
Surface Modification of Advanced and Polymer Nanocomposites

Maliha Rahman, Farhan Zahin, Md Abid Shahriar Rahman Saadi, Ahmed Sharif, and Md Enamul Hoque

Contents

Abstract The continuous progression in the development of clay-polymer nanocomposites (CPN) is due to their ever growing utilization in several end use applications. Nanoclays are habitually in agglomerated micro particles due to the humidity of the surrounding air as it is strongly hydrophilic with high ability to absorb water from the atmosphere. The properties of clay-polymer nanocomposites critically depend on the distribution of clay particles in the polymer matrix and the adhesion between the two. The compatibility between the matrix and the

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reinforcement is mandatory to achieve desired properties. With this concern, this chapter discusses various techniques used for the modification of clay nanoparticles. Different modifiers like organic salts, inorganic acids, silane, supercritical-CO_2 have been reported to modify clay surface and increase the inter layer spacing of clay which promotes hydrophobicity and intercalation of polymer chains into the galleries during nanocomposite preparation. In addition, modifiers also help disaggregation and exfoliation of nanoclays into polymer matrices which are the prerequisites of exploiting the beneficial reinforcement effect of nanoclay. These modifications have brought better mechanical properties and higher biodegradability to the clay-polymer nanocomposites. A brief outline on various types of polymers and clays used in nanocomposites and various application fields of clay-polymer nanocomposites are also illuminated in this chapter.

6.1 Introduction

A nanocomposite is a multiphase solid material where one of the phases has one, two or three dimensions of less than 100 nm, or structure having nano-scale repeat distance between the different phases that make up the material. In polymer nanocomposites, the filler has at least one dimension in the nanometer scale and its nanoscale dispersion within the polymer matrix leads to the tremendous interfacial contacts between the polymer and inorganic filler which causes to the superior properties than those of bulk polymer phase. When the dimensions of filler particles are decreased to the nanoscale, their properties change also significantly. It is called the nano-effect (Olad 2011; Paul and Robeson 2008; Shivendu et al. 2016; Nandita et al. 2016a). Clay-polymer nanocomposites are a typical example of nanotechnology. Polymer-clay nanocomposites are formed through the union of two different materials with organic and mineral pedigree (Singh 2016). By tailoring the clay structure in polymers on the nanometer scale, novel material properties have been found. They offer tremendous improvement in a wide range of physical and engineering properties for polymers with low filler loading. This technology can now be applied commercially and has received great attention in recent years. The first commercial application of these materials was the use of clay/nylon-6 nanocomposites as timing belt covers for Toyota cars, in collaboration with Ube in 1991 (Gao 2004; Kotal and Bhowmick 2015; Indibay 2016).

This field has been studied heavily in the past decade due to various advantages of natural particulate reinforcements over conventional reinforcements e.g. low cost, comparable specific tensile properties, non-abrasive to the equipment, high creep resistance, high toughness, reduced energy consumption, non-irritation to the skin, less health risk, renewability, recyclability and bio-degradability. These hybrid

materials are suitably applicable for aerospace, construction, sport, automotive industries, flame retardant or fire safety applications, gas barrier materials, food or liquid packaging industries, biomedical applications, energy applications, home-furnishing applications etc.

Clays are naturally found as platelets, stacked from a few to as many as one thousand sheets. Single sheet of montmorillonite clay can have an in plane Young's modulus ranging between 178 and 265 GPa. These excellent properties of nanofillers make them suitable candidates for reinforcing polymer matrix (Bhattacharya 2016). However, one of the main problems that arise when adding clays to polymers is the dispersion of the particles and adhesion of clay and polymer matrices. A totally exfoliated structure (i.e., the silicate layers are completely and uniformly dispersed in a continuous polymeric matrix) is necessary to maximize the mechanical properties, but the tendency of the particles to agglomerate is difficult to overcome. This is because most of the polymers are hydrophobic while clays or silicates are hydrophilic, so it is necessary to make a prior treatment to the clay so as to make it more compatible. One of the most reliable methods for increasing compatibility consists is converting the hydrophilic silicates into organophilic ones (Camargo et al. 2009). By doing this, the excellent mechanical properties of the individual clay layers can function effectively, while the number of reinforcing components also increases dramatically because each clay particle contains hundreds or thousands of layers. As a consequence, a wide range of engineering properties can be significantly improved with a low level of filler loading, typically less than 5 wt%. At such a low loading level, polymers such as nylon-6 show an increase in Young's modulus of 103%, in tensile strength of 49%, and in heat distortion temperature of 146%. Other improved physical and engineering properties include fire retardancy, barrier resistance, and ion conductivity.

Figure 6.1 shows traditional clay-polymer microcomposite and advanced clay-polymer nanocomposite. In the later one, modified clay particle gives better reinforcing properties by exfoliation and intercalation with polymeric chains.

6.2 Clay as Reinforcement

Clay minerals are essentially hydrous aluminosilicates with very fine particle size. These small crystalline particles are consists of silica- oxygen tetrahedral sheets and aluminium or magnesium octahedral sheet, where an aluminium or magnesium ion is octahedrally coordinated to six oxygens or hydroxyls. The interlaminar distance of the d001 plane of the clay is relatively small, and the interlayer environment is hydrophilic. According to the difference of charges on clays, there are two broad classes of clay minerals. One is cationic clays which have negatively charged alumino-silicate layers because of isomorphous substitution of silicon ion by aluminium ion in the tetrahedral layers or similar substitution of aluminium ion by magnesium ion. Thus, cations like sodium, potassium and calcium may be attracted to the mineral surface to neutralize the layer charge. The other is anionic clays which

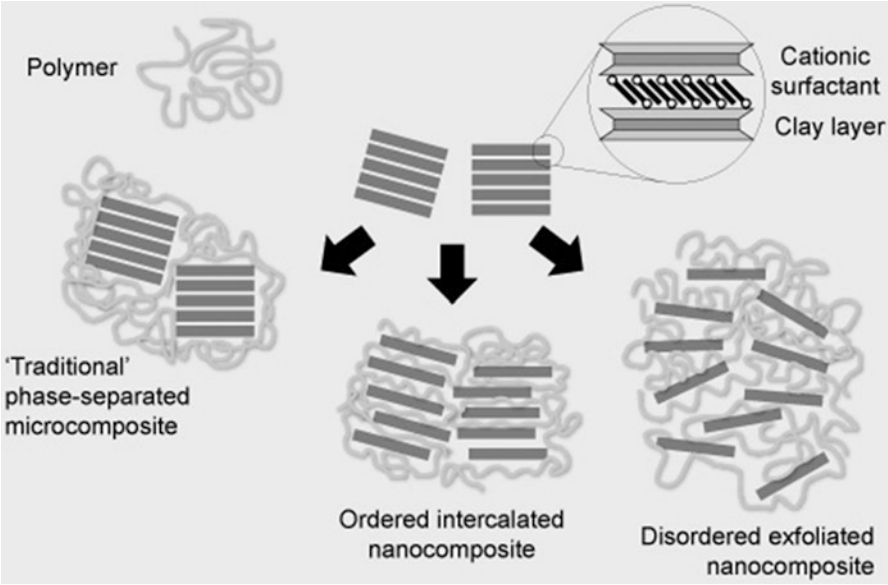

Fig. 6.1 Intercalation and exfoliation of silicate layers of clay particles in polymer matrix due to clay surface modification Indibay (2016)

are rarer in nature and have positively charged brucite-type metal hydroxide layers with anions and water molecules balanced which are located interstitially. Cationic clays are mainly prepared starting from the minerals, whereas anionic clays are usually synthesized. Again when one octahedral sheet is linked to one tetrahedral sheet, it is called 1:1 layer silicate, such as kaolin subgroup and serpentine subgroup. The structure created from two tetrahedral sheets sandwiching an octahedral sheet is called 2:1 layer silicate, such as smectite subgroup and vermiculite subgroup. At present, the clay minerals of the 2:1 layer type smectite group are widely used in various branches of industry due to their high cation exchange capacity, swelling ability and high surface area, which are critical to be used as reinforcement.

Clay-polymer nanocomposites, this class of material uses smectite-type clays, such as hectorite, montmorillonite, and synthetic mica, as fillers to enhance the properties of polymers. Among smectite clays, Montmorillonite (MMT) is the most widely used clay nanofiller, sandwiched between two silicate layers of an octahedral sheet of alumina (Fig. 6.2). The nanometer-scale sheets of aluminosilicates have dimensions of 1–5 nm thickness and 100–500 nm in diameter. These dimensions lead to platelets of high aspect ratio, more than 50. Thus when blended with polymer, it enables stress transfer from the polymer to the mineral. The stiffness of the clay minerals results in increased mechanical properties of the blend (Bhattacharya 2016).

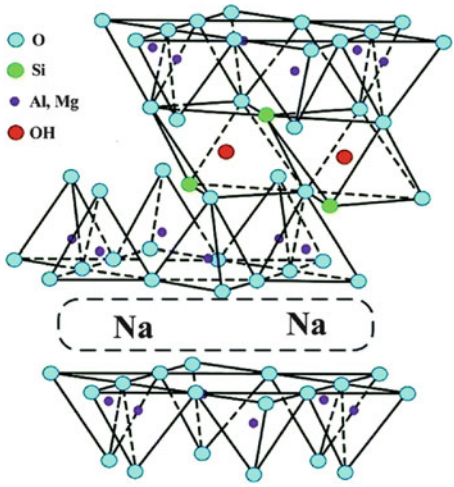

Fig. 6.2 Scheme of the Sodium-Montmorillonite clay structure (Chen et al. 2015)

6.3 Compatible Matrices

A good number of thermoset and thermoplastics have been paired with clay nanoparticles in hopes of creating a superior material. At present, development has been widened into almost every engineering polymer including thermoplastics like polypropylene, polyethylene, polystyrene, polyvinylchloride, acrylonitrile butadiene styrene, polymethylmethacrylate, polyacrylonitrile, polycarbonate, polyethylene oxide, polyimide, polylactide, polycaprolactone, poly p-phenylene vinylene, poly pyrrole; thermosets like PET, epoxy resin, phenolic resin, polyurethane, polyvinyl pyridine and elastomers like ethylene-vinyl acetate copolymer, rubber and their derivatives.

6.4 Modification of Clay

The final aim of fabricating clay-polymer nanocomposites is to separate and disperse the individual clay plates in a polymer matrix (Gao 2004). The applied approach depends on the compatibility of the clay and polymer to be used. This regulates if pretreatment of the clays and polymers is essential before intercalation. If the surface of the silicate layers in the clays is suitable with the polymer, direct intercalation amongst the two can occur without the need for pretreatment. This is the case with water-soluble polymers such as PEO and PVP (these polymers and the surface of silicate layers are all hydrophilic). The van der Waals forces between the silicate layers result in easy absorption of hydrophilic molecules and the capacity to expand perpendicular to the layers. This results in the separation of individual clay layers in these polymers. However, most polymers are hydrophobic and are not compatible with hydrophilic clays. In this case, pretreatment of either the clays or the polymers

is essential. The most widespread methods for clay modification are the use of amino acids, organic alkylammonium salts, tetra organic phosphonium salts, alkylimidazolium, alkylpyridinum and silane compound to alter the clay surface from hydrophilic to organophilic (Mittal 2011). The clays modified in this way are branded as organoclays. Although the organic pre-treatment adds to the cost of the clay, the clays are nonetheless relatively cheap feedstocks with minimal limitation on supply (Xi 2006; Adeosun et al. 2012).

There are mainly two ways of clay modification e.g. physical modification and chemical modification. In physical modification method, only adsorption of modifying agents takes place on clay surface. No alteration in the clay structure takes place and however, it helps slight enhancement in the properties of resulting polymer composites. This improvement in the properties may be due to the fact that only weak physical forces of attraction exist between clay and the modifying agents (Babu 2017). But in the case of chemical modification method, polymers with functional groups or organo silane compounds are usually tethered on to surface of the clay. In addition to this, modification is carried out by ion exchange process with the help of cationic or anionic functional groups. Hence, chemical modification helps in achieving stronger interaction among clay particles and modifying agents. This interaction in turn leads to the improvement in dispersion ability of clay particles in the polymer matrices. The nano-sized thickness of individual layers present in the clay particles, high aspect ratio and large surface area exhibited by clay materials when dispersed in the polymer matrices lead to the improved thermal, barrier, optical as well as mechanical characteristics of clay-polymer nanocomposites. The schematic illustration for the modification of clay particles is shown in Fig. 6.3.

6.4.1 Clay Modification by Organic Surfactants

Clay surface can be modified by organic modifier through a cation exchange process by replacing sodium and calcium cations present in the inter layer space or clay galleries by alkylphosphonium or alkylammonium (onium) cations, also called surfactants. In addition to the surface modification and increasing the hydrophobicity of clay layers, the insertion of alkylammonium or alkylphosphonium cations into the galleries causes to some degree of increasing in the inter layer spacing which promotes the following intercalation of polymer chains into the galleries during nanocomposite preparation. Also the alkylphosphonium or alkylammonium cations can provide functional groups which interact with polymer chains or initiate the polymerization and therefore increase the interfacial interactions (Lin and Juang 2004). The lamellar interlayer expansion is generally proportional to molecular lengths of the intercalating agents. Cation exchange reaction starts at the edges of clay particle and then spreads toward the centre in a highly regular fashion. Kinetic

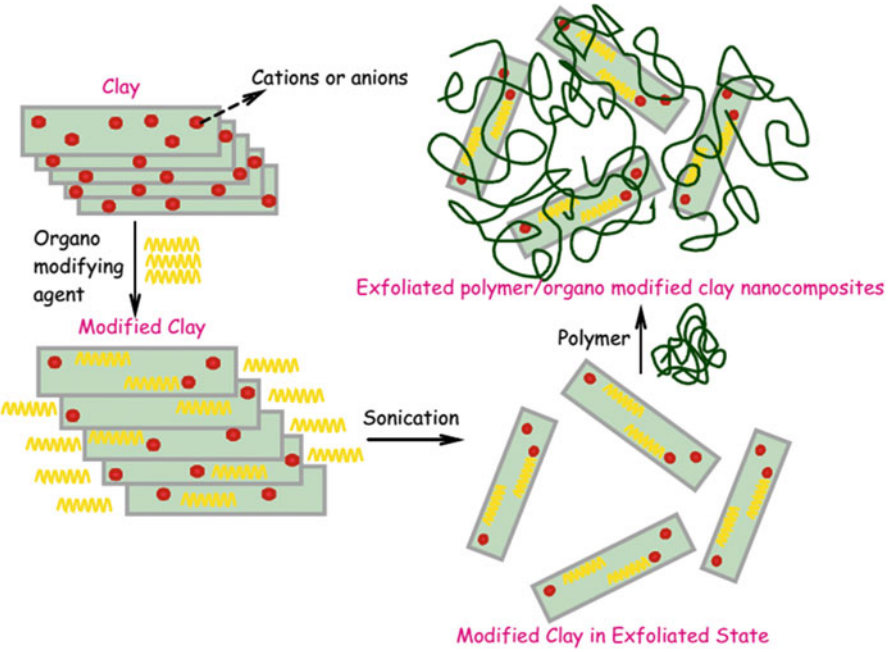

Fig. 6.3 Schematic representation for the preparation of exfoliated polymer-organomodified clay nanocomposites. Organo modifiers are attached to clay surface which assists exfoliation of clay particles (Babu 2017)

studies have shown that when the temperature increases the reaction rate will be increased (Lin and Juang 2004). Also the clay minerals' chemical and structural characteristics have profound influences on the rate of ion exchange reactions. At the same time, reaction rates are influenced by the valence and size of the exchanging inorganic cations. When highly charged silicates are saturated with larger and less hydrated monovalent cations such as K^+, Rb^+, $NH4^+$, Cs^+, the attraction between layers is the greatest. When the layers are saturated with Na^+, Li^+, Ca^{2+}, Mg^{2+} which have larger hydration energies, then the attraction between the layers will be overcome and the basal spacing will be increased. There are a number of organic compounds that can be used as surfactants like alkylimidazolium, alkylpyridinum salts, poly(oxyalkylene)-polyamine salts. However, the modification principle of these salts is the same. Figure 6.4 schematically shows the organically modification of clay layers using alkylammonium cations via the ion exchange process (Olad 2011).

However, the anionic clays such as Al-Mg layered-double-hydroxides (LDH) are different from cationic clays like montmorillonite (MMT), not only in opposite charges of ionic characteristics but also in charge density. The strong interlayer electrostatic interaction among individual Mg-Al oxide platelets leads to a tight

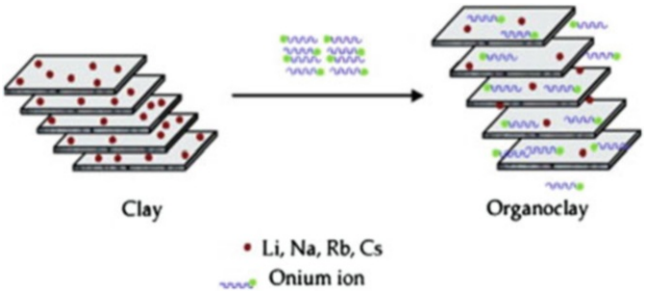

Fig. 6.4 Scheme of the modification of clay layers by organic onium cations causing wide inter layer spacing (Olad 2011)

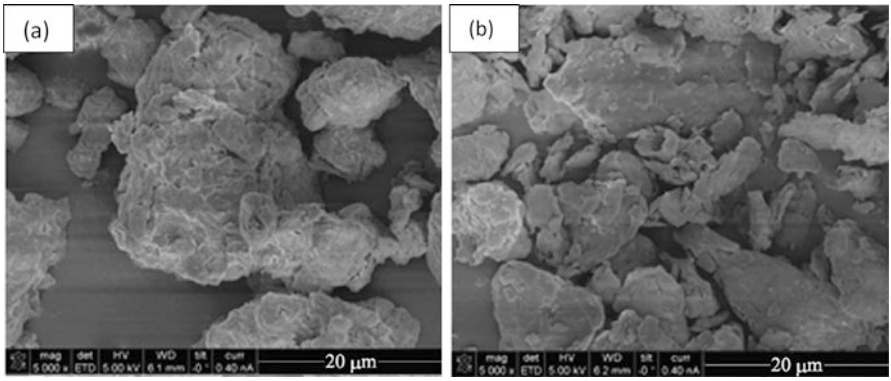

Fig. 6.5 SEM micrographs for (**a**) unmodified sodium montmorillonite, showing large aggregation of particles, (**b**) sodium monmorillonite modified with octadecyl trimethyl ammonium chloride, showing disaggregation of large particles (Liu and Xiao 2012)

stacking of the lamellae and difficulty for organic incorporation. Alkyl carboxylates and sulfonates are common species as the intercalating agents, but which could widen the interlayer spacing only up to 30 Å. In addition to the limitation on interlayer widening, the rate of ion exchange reaction is considerably slower than the MMT intercalation. In comparing with the alkyl carboxylic acids, the amidoacids are suitable for interacting with the anionic LDH clay. For example, poly (oxyalkylene)-polyamine salts-derived amidoacids of high molecular weight could render LDH wide basal spacing of 92 Å (Lin and Juang 2004; Liao et al. 2010; Chiu et al. 2012).

Figure 6.5 shows the change of the morphology of Na^+-MMT clay before and after modification with octadecyl trimethyl ammonium chloride (OTAC). Before modification the Na^+-MMT is adhesive and aggregated to form a compact structure. After modification the large particles are split into small ones because of the ion exchange reaction with OTAC and the compact structure got looser.

6.4.1.1 Exfoliation of Clays

Besides the wide expansion of basal plane of layered silicates through intercalation, random silicate platelets can be obtained by using amphiphilic copolymers, such as hydrophobic backboned polyamidoacids, Mannich condensates and other polyamines. The subsequent formation of amine-HCl salts is required for such exfoliation agents. Their structures generally consisting of multiple amines enable to form stable emulsion in water with clays and exchange their counter Na+ ions with Na+ containing clays. As a result, the layered stack of multiple silicate sheets in the primary clay structure are exfoliated and randomized into individual clay platelets. The process involves the exfoliation of the layered clay through ionic exchange reaction and further NaOH treatment to phase separate and recover the organic amines (Lewandowska et al. 2014; Lin et al. 2006, 2010).

6.4.1.2 Arrangement of Organic Cations in the Clay

The arrangement of organic cations in organo-clays depends on the size of organic cation, such as the length of alkyl chain and layer charge of the clay minerals. Generally the organic cations only form monolayers. But also the organic cations may form bilayers, pseudotrimolecular layers or paraffin complexes. Different arrangements of organic cations affect the basal spacing of organic clays. For example, in the case of hexadecyltrimethylammonium, the C-16 alkyl chain may form from monolayers to paraffin complexes which correspond basal spacing of d001 are 13.7A, 17.7A, 21.7A and >22A. Different interlamellar arrangements of alkylammonium ions are as follows:

Monolayers: When the packing density of the chains is low, the chains are assumed an arrangement with the C-C-C plane parallel to the layers, i.e. the chains will lie parallel to the silicate layers. The characteristics basal spacing is 13.6 Å. This spacing is often observed for short alkylammonium ions ($n < 8$). The values of 1.61 nm and 1.79 nm for the organo-MMT (OMMT) are consistent with monolayer arrangement of organic cations in the interlayer space when octadecyl trimethyl ammonium chloride is used as surfactant.

Bilayer: chains are parallel to the silicate layer. Typical basal spacing is about 17.6 Å. The basal spacing of 1.88 nm for the OMMT is in agreement with a bilayer arrangement of organic ions in the interlayer space when octadecyl trimethyl ammonium chloride is used as surfactant.

Pseudotrimolecular layers: The polar end groups of the alkylammonium ions remain attached to the layers. Forming kinks, the unpolar chain ends are shifted one above the other and the interlayer separation is determined by the thickness of three alkyl chains. The basal spacing is about 22 Å.

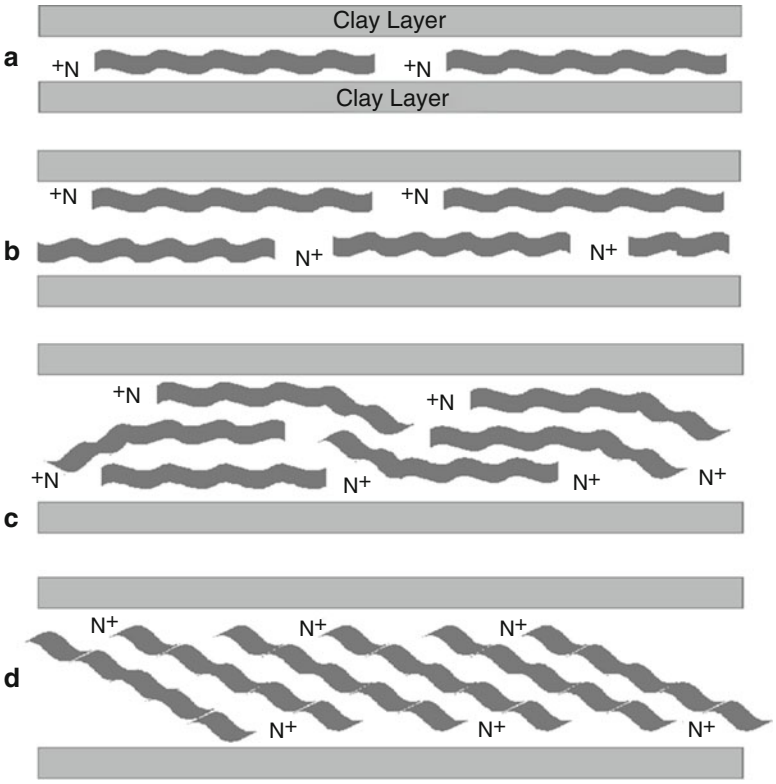

Fig. 6.6 Arrangements of alkylammonium ions into clay layers**,** (**a**) Monolayer (basal spacing is about 1.37 nm), (**b**) Bilayers (basal spacing is about 1.77 nm), (**c**) Pseudotrimolecular layer (basal spacing is about 2.17 nm), (**d**) Paraffin complex (basal spacing is >2.2 nm) (Xi 2006**)**

Paraffin-type layers: The ammonium groups remain attached to the silicate layer, the chains in all-trans conformation point away from the surface. As the orientation of the methyl end group is different for even or odd, the basal spacings increase stepwise (alternating spacings). The basal spacings of 2.40–3.09 nm for the OMMT was reported, corresponds to a pseudo trilayer to paraffin- type monolayer arrangement of intercalated organic cations when octadecyl trimethyl ammonium chloride is used as surfactant (Xi 2006; Liu and Xiao 2012). These four types of arrangements are shown in Fig. 6.6.

6.4.1.3 Methods of Organoclay Preparation

There are several methods of treating natural clays with organic surfactants and preparing organoclays depending on the choice of surfactants and the clay being modified.

6.4.1.3.1 Wet Method

Singla et al. (2012) have showed two procedures for modification of montmorillonite clay, depending upon the solubility of salts in aqueous phase. For the salts which were soluble in aqueous phase, the following procedure was used. Five grams of Na-MMT were dispersed in 500 mL of distilled water for 24 h at rooms temperature, using a magnetic stirrer. Using an aqueous solution of salt, the amount of surfactant added was equivalent to the cation exchange capacity (CEC) of clay. The cation exchange reaction occurs rapidly. The resulting organoclay suspension was mixed further for 12 h. The suspended organoclay was filtered under vacuum. The resulting organoclay was dispersed into 50 mL of fresh distilled water and mixed further for 4 h. No chloride traces were detected by addition of silver nitrate, after two washing. The resulting organoclay was dried at 60 °C for 24 h under vacuum. Finally the resulting material was ground, in order to obtain a fine powder.

Once more to produce organoclays with water insoluble salts, different procedure was as followed. Five grams of sodium MMT were dispersed into 500 mL of distilled water at room temperature, using a magnetic stirrer. After 24 h, mixing was stopped and 200 ml of diethyl ether solution of salt, was slowly poured into the clay dispersion. The resulting system contained a clear upper organic phase and a turbid bottom mineral phase. After 12 h of moderate mixing, the mineral phase became transparent and the organic phases became turbid. Then the system was warmed up to evaporate the diethyl ether (60 °C), using a Rota-evaporator. After solvent evaporation, the organic phase became a sticky solid precipitate. The precipitated organoclay was filtered and dispersed in hot water (80 °C) for 4 h. The washing was repeated three times, until no chloride traces were detected with silver nitrate after the third washing. The resulting organoclay paste was manually mixed with 40 ml of petroleum ether using a spatula. After free petroleum ether evaporation, using Rota-evaporator, the organoclay was dried at 80 °C for 24 h under vacuum. Then it was ground, using a Pestle Mortar (Singla et al. 2012).

6.4.1.3.2 Dry Method

Dry method provides an economical method of making organophilic clays by avoiding the addition of any significant amount of water to the clay. Dry and finely ground clay at equilibrium moisture is sprayed with a solution of the activator substance, and the sprayed clay is then subjected to dry compaction two or three times, and is then reground to provide an organophilic clay. This method therefore avoids the added cost of later removing the water, or other solvent. The resulting organophilic clay has properties comparable to such clays made by the wet method described above, but it is less expensive to make, since the drying step of the prior method is completely avoided. The mechanical working accomplished by compacting is sufficient. Clays which may be treated according to the dry method include smectite clays such as nontronites, montmorillonites, saponites and hectorites, Black Hills Bentonite, calcium bentonites, Wyoming bentonite, sodium

bentonites, and synthetically prepared clays including synthetic montmorillonite, saponite, beidellite and stevensite. Wyoming bentonite is presently preferred (Alther and Ferndale 1983).

6.4.2 Clay Modification by Supercritical-CO_2 (sc-CO_2)

A recent approach to prepare polymer nanocomposites using Supercritical carbon dioxide (sc-CO_2) in the melt intercalation process was reported by Lesser et al. They used a modified hopper in the feed section of the extruder to allow polymer and clay to interact with sc-CO_2 before processing. It was found that the presence of sc-CO_2 promotes significant increase in the basal spacing of the clay, and thereby may enhance the ease of the polymer intercalation into the galleries of the clay. Alternatively, Manke et al. developed a process that allows clay particles to be pre-treated with sc-CO_2 in a pressurized vessel and then rapidly depressurized into another vessel at atmospheric pressure to force the clay platelets apart. The result was exfoliated nanoclay particles as observed by X-ray diffraction. Nguyen and Baird (2007) have developed a process to help exfoliate and disperse the nanoclay into PP matrix which involves the use of a pressurized CO_2 chamber to assist in the exfoliation and delivery of the clay into a stream of polymer melt in the extruder. It allows only the clay to be in direct contact with sc-CO_2, as opposed to both clay and that the mixture of exfoliated clay and sc-CO_2 is fed into the extruder in a one-step process instead of a two-step like Manke's process.

Transmission electron microscopy (TEM) micrographs of various nanocomposites prepared using different processing techniques are presented in Fig. 6.7. Figure 6.7a shows TEM micrographs for nanocomposites prepared by conventional singles crew melt compounding. 4% clay and Polypropylene were dry blended in a Kitchen Aid type mixer and then the mixture was fed to an extruder

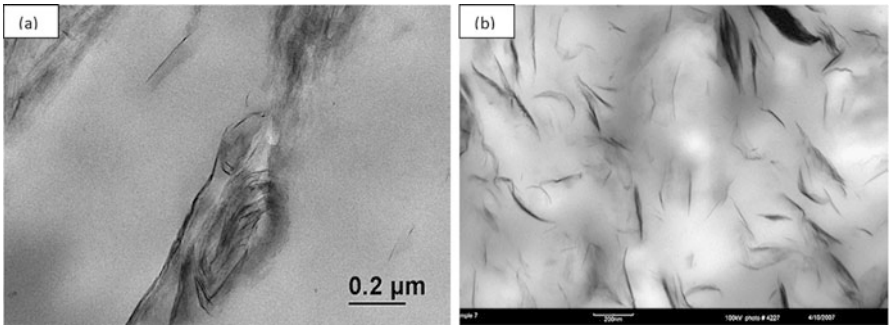

Fig. 6.7 TEM micrographs (with magnification 34,000×) for clay-polymer nanocomposites prepared by (**a**) conventional single screw melt compounding, (**b**) treating clays with supercritical CO_2 in a pressure vessel and injecting into molten polymer. The later one shows better clay particles dispersion into polymer matrix (Nguyen and Baird 2007)

and re-pelletized. The 4 wt% nanocomposite prepared via this method represents an immiscible system with very large aggregates or tactoids in the order of several tens of silicate layers. Figure 6.7b shows TEM micrographs for nanocomposites where the clays were allowed to be in direct contact with sc-CO_2 in the pressurized chamber, at 3000 psi and 80 °C for a period of time (12–24 h) and then the pressure was rapidly released. The mixture of the nanoparticles and sc-CO_2 was then injected into the molten polymer stream in a single-screw extruder. The best nanodispersion can be seen in the nanocomposites prepared using the later method for concentration as high as 6.6 wt% clay (Nguyen and Baird 2007).

6.4.3 Modification of Clay by Inorganic Acid

Acid activation has been extensively studied as a chemical treatment method for the enhancement of the catalytic properties and surface of fibrous clays (sepiolite and palygorskite), amorphized (calcined/grounded) kaolin and smectitic clays (saponite and montmorillonite). The method involves leaching of the clays with inorganic acids, triggering disaggregation of clay particles, removal of mineral impurities, and dissolution of the external layers, thus changing the chemical composition and the structure of the clays. Solubility of the clay minerals in acids is of vital importance because it reveals certain characteristics of the clay minerals (Dai and Huang 1999). The acid treatment is advantageous in terms of enlarged surface area, porosity and number of acid centers with respect to the parent clays. The acid treated clays are composed of a combination of non-attached clay layers and a hydrous, amorphous, and partially protonated silica phase.

Figure 6.8 represents a XRD spectra of kaolinite clay treated with different concentrations of sulphuric acid (1M, 3M, 5M and 10M). The untreated clay has sharp peaks, whereas, the treated clays have decreased peak height for lower concentration of acid (1M and 3M). When the concentration of acid is further increased, the peaks disappear (5M and 10M) (Panda et al. 2010). This suggests, the acid treatment has segregated the clay plates into a disordered structure of different orientation, an amorphous state.

6.4.3.1 Treatment Procedure

The chemical activation can be carried out by adding 50 g of the clay to 500 ml of sulphuric acid solution of different concentrations and refluxing at 110 °C under the atmospheric pressure for 4 h. The resulting clay suspension should then be rapidly quenched by adding 500 mL ice cold water. After that, the content is then filtered, repeatedly washed with distilled water to remove any unspent acid, dried in an oven, calcined at 500 °C for 1 h and ground in a mortar pastel to powder form (Carrado and Komadel 2009).

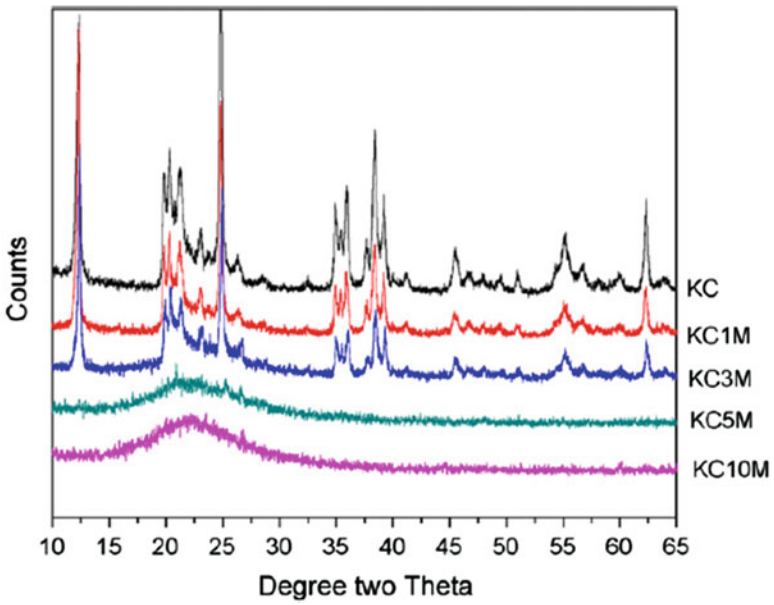

Fig. 6.8 XRD of pure and acid treated kaolinite clay. Decreased peak sharpness in acid treated clay suggests segregated clay plates (Panda et al. 2010)

6.4.4 Silane Treatment

The silylation (which is the reaction of an organo-chloro or organo-alkoxy-silane with a compound containing a reactive group) of surface silanol groups is rarely used as the sole surface-modification technique because only a small fraction of hydroxyl groups is available at clay platelet edges (Carrado and Komadel 2009). The rest are buried inside atomic planes of the layered structure and therefore inaccessible. One of the main advantages of silylation is that the treated clay mineral has a lower organic content. Silylation has been employed to graft functional groups to improve exfoliation and material properties of the nanocomposites. Silane modified clay are best suited for application in thermoset and elastomer matrices i.e. epoxy and rubber.

The surface of clay fines i.e. kaolinite can be changed from hydrophilic to hydrophobic and/or oleophilic by organo-functional molecules, with surface hydroxyl groups, Lewis and Bronsted sites etc. For example, organic groups are grafted on the clay surface with diazomethane and acetyl chloride:

$$\equiv \mathrm{Si{-}OH} + \mathrm{CH_2N_2} \rightarrow \equiv \mathrm{Si{-}OCH_3} + \mathrm{N_2}$$

$$\equiv \mathrm{Si{-}OH} + \mathrm{CH_2N_2} \rightarrow \equiv \mathrm{Si{-}OCH_3} + \mathrm{N_2}$$

$$\equiv \mathrm{Si{-}OH} + \mathrm{CH_3COCl} \rightarrow \equiv \mathrm{Si{-}O{-}\overset{\overset{\mathrm{O}}{\|}}{C}{-}CH_3} + \mathrm{HCl}$$

Where Si–OH represents a surface hydroxyl in the clay structure. Other examples are chlorination of clay and reactions with Grignard reagents and organometallic compounds:

$$\equiv \text{Si–OH} + \text{SOCl}_2 \rightarrow \equiv \text{Si–Cl} + \text{SO}_2 + \text{HCl}$$
$$\equiv \text{Si–Cl} + \text{C}_6\text{H}_5\text{MgBr} \rightarrow \equiv \text{Si–C}_6\text{H}_5 + \text{MgBrCl}$$
$$\equiv \text{Si–Cl} + \text{CH}_3\text{Li} \rightarrow \equiv \text{Si–CH}_3 + \text{LiCl}$$

A series of organic derivatives of kaolinite e.g., the ether and ester derivative of kaolinite etc. can be prepared with chlorinated kaolinite as a precursor. The usual organic derivative of clay fines, a filler of surface modified clays, is commonly obtained by using coupling agents, for example, surface modification of clay fines by silane coupling agents:

$$\text{X}_3\text{SiR} + 3\text{H}_2\text{O} \longrightarrow \text{RSi(OH)}_3 + 3\text{HX}$$
$$\text{Clay}|\text{-OH} + \text{RSi(OH)}_3 \longrightarrow \text{Clay}|\text{-O-}\overset{|}{\underset{|}{\text{Si}}}\text{-R} + \text{H}_2\text{O}$$

where X_3SiR is the silane coupling agent, X denotes an alkoxyl group such as $–OC_2H_5$, $–OCH_3$ etc., R represents a group which can be combined with polymers, such as $–CH_2NH_2$, $–C_2H_3O$. After surface modification, the organic groups are attached to the clay minerals, and the surface properties are altered (Dai and Huang 1999).

The morphological effects of clay surface treatment using a silane coupling agent on dispersion and intercalation of clay/polymer nanocomposites can be investigated by TEM. Figure 6.9 shows clay dispersion and polymer intercalation for both

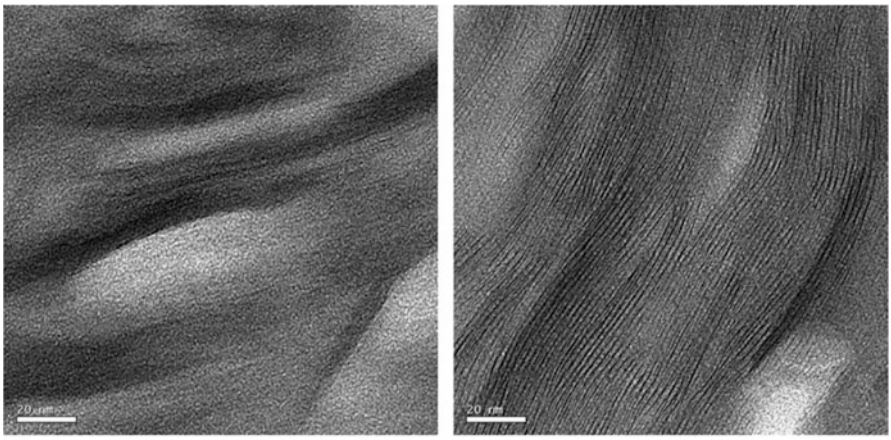

Fig. 6.9 TEM of (**a**) untreated and (**b**) silane surface-treated clay-epoxy nanocomposites. The later one shows uniform distribution of clays where the untreated clays show agglomeration (Ha et al. 2010)

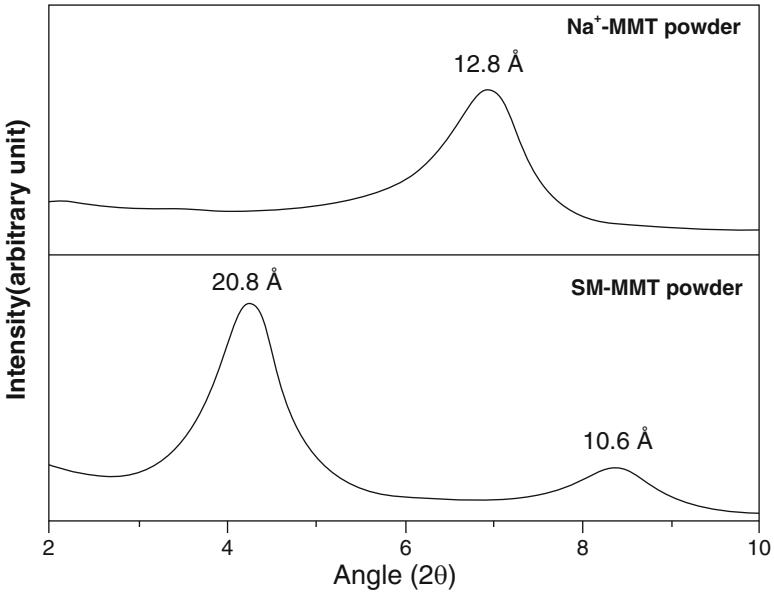

Fig. 6.10 XRD analysis of unmodified Na-bentonite and silane modified bentonite clay. Unmodified clay shows sharp peak at $2\theta = 7.0°$, calculated d-spacing is ~1.28 nm. Silane modified clay shows sharp peak at $2\theta = 4.2°$, calculated d-spacing is ~2.08 nm (Ha et al. 2007)

nanocomposites. Dispersion of layers is poor for untreated samples case and clay agglomeration was observed in various spots (Fig. 6.9a). Only parts of the layers show intercalated polymer. On the other hand, a more uniform distribution of clay is observed in silane-treated samples (Fig. 6.9b). The distances between layers are constant and increase relative to untreated samples due to better intercalation of polymer into the clay layers (Ha et al. 2010).

Figure 6.10 shows X-ray diffraction patterns of the unmodified Na-montmorillonite powder (Na^+-MMT) and the surface-modified clay powder with 3-amonopropyltriethoxysilane (SM-MMT), which shows the d-spacing. As shown in the figure, for an unmodified clay, a sharp peak occurred at around $2\theta = 7.0°$, in which the d-spacing was calculated to be ~1.28 nm. The surface-modified clay with 3-amonopropyltriethoxysilane, however, shifts the peak to the lower 2θ value at around 4.2°, which corresponds to a d-spacing value of ~2.08 nm. Therefore, the d-spacing of modified clay is larger by about 0.8 nm than that of the unmodified clay (Ha et al. 2007).

6.4.4.1 Silane Treatment Procedure

Silane treatment of clay can be carried out by dispersing one gram of untreated clay in 100 ml of distilled water (solvent) at 25 °C using a mechanical stirrer. One gram of

Table 6.1 Improvement in mechanical properties of nanocomposite by organic modification of clay (Lewandowska et al. 2014)

Sample	Tensile strength (MPa)	Young's modulus (GPa)	Tensile strain at break %
Chitosan	54.9 ± 2.5	1.4 ± 0.3	$3. \pm 0.3$
Chitosan+unmodified montmorillonite	81.0 ± 2.4	$2. \pm 0.6$	3.2 ± 0.5
Chitosan+ montmorillonite modified with octadecylamine	123 ± 3.4	2.7 ± 0.7	3.0 ± 1.3

Table 6.2 Improvement in composite properties by clay-supercritical CO_2 interaction (Nguyen and Baird 2007)

Sample description	d-spacing, d001 (A°)	Young's modulus (GPa)	Yield's strength (MPa)
Made by conventional way (4 wt% clay)	30.87	1.611	13.68
Made by clay-sc-CO_2 interaction in pressure vessel (4 wt% clay)	35.31	1.848	16.10

a silane coupling agent e.g. 3-aminotriethoxysilane dissolved in 100 ml of solvent is added to the clay dispersion under constant stirring for a period of 30 min. The suspension is then filtered and dried for 48 h at 60 °C under vacuum (Ha et al. 2010).

6.5 Effect of Clay Modification on Composite Properties

Improvement in clay-polymer compatibility brought by clay modification renders improved mechanical properties of nanocomposites. Lewandowska et al. (2014) have studied chitosan composites with various clays. They have found that addition of nanoclay after its surface modification improved the mechanical and thermal properties of the composite much more than montmorillonite without modification [d] (Tables 6.1 and 6.2).

Nguyen and Baird (2007) have shown that interaction between clay and sc-CO_2 causes higher inter layer separation and brings improved mechanical properties.

Again, reinforcing nanoclay into polymer matrix increases its biodegradability. Modification of nanoclays further increases biodegradation of pristine clay-polymer nanocomposites. Stloukal et al. (2015) have found that the addition of nanoclay enhanced the biodegradation of PLA nanocomposites under composting conditions, when compared with pure PLA, particularly by shortening the lag phase at the beginning of the process (Table 6.3). Whereas the lag phase of pure PLA was observed within 27 days, the onset of CO_2 evolution for PLA with native montmorillonite was detected after just 20 days, and from 13 to 16 days for PLA with organo-modified montmorillonite. Similarly, the hydrolysis rate constants determined was higher for PLA with organo-modified MMT (Stloukal et al. 2015) (Fig. 6.11).

Table 6.3 Specification of different combination of samples for biodegradability test (Stloukal et al. 2015)

Sample	Montmorillonite	Organic modifier
PLA	_	_
PLA-Na	Cloisite Na+	None
PLA-A10	Nanofil 116	None
PLA-A20	Cloisite 10A	Dimethyl, benzyl, hydrogenated tallow, quaternary ammonium salt
PLA-B30	Cloisite 20A	Dimethyl, dihydrogenated tallow, quaternary ammonium

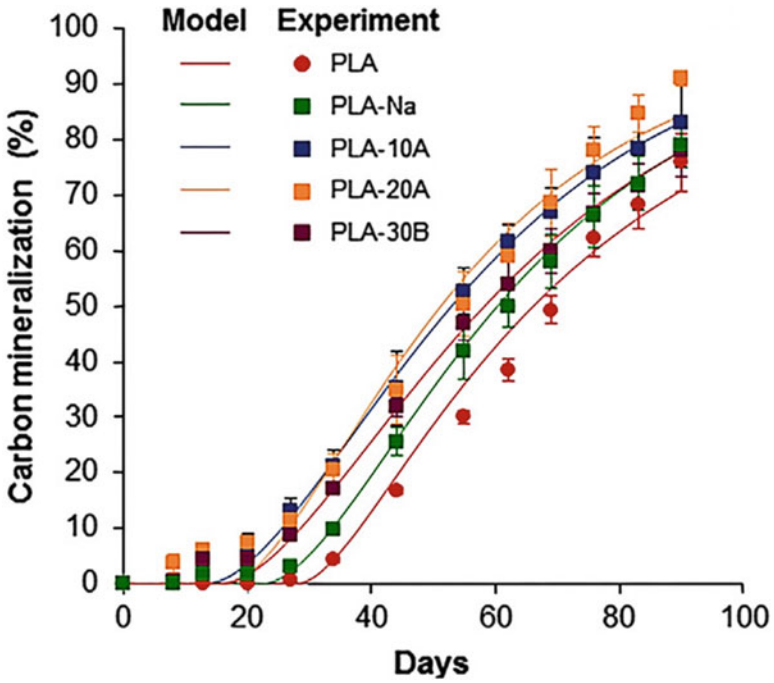

Fig. 6.11 Biodegradation under the compost environment of pure PLA and PLA-clay nanocomposite films. Clay modification shows increased biodegradation with onset of CO_2 evolution for PLA within 27 days, for PLA-Na after 20 days and for PLA-20A within 13–16 days (Stloukal et al. 2015)

6.6 Applications

Many companies have taken a strong interest and invested in developing clay-polymer nanocomposites because of their distinctly improved performance in mechanical, thermal, barrier, optical, electrical, and other physical and chemical characteristics (Morgan 2007; Galimberti et al. 2013; Shunmugasamy et al. 2015;

Arao 2015; Anadão 2012; Cogen et al. 2013; Nandita et al. 2016b; Shivendu et al. 2017). Thus, growing number of commercial products has become available. Approximately 80% of the clay-polymer nanocomposites are used in the automotive, aeronautical and packaging industry. The main fields of clay-polymer application are discussed here.

6.6.1 In Automobile Industry

CPN have been a major attraction in the automotive world for many years. The driving forces for using CPN in the automotive field are increased comfort, lighter weight of the vehicle, with fuel saving and reduction in CO_2 emission, better drivability and greater safety. The most common use of polymer-clay nanocomposites has been in mechanical reinforcement of thermoplastics, especially polyamide-6 and polypropylene. The aforementioned polyamide-6 clay nanocomposite produced by Ube/Toyota was used to replace a metal component near the engine block that yielded some weight savings. The clay in this application has improved the heat distortion temperature of the material, allowing it to be used in this higher temperature application. GM/Blackhawk has also announced polypropylene-clay nanocomposites for automotive applications, and the clay brought an increase in flexural and tensile modulus while maintaining impact performance. The most important parts in a car equipment where CPN are used are engines and power train, suspension and breaking systems, exhaust systems and catalytic converters, frames and body parts, paints and coatings, lubrication, tyres, and electric and electronic (Morgan 2007; Galimberti et al. 2013; Shunmugasamy et al. 2015).

6.6.2 As Flame Retardant

The use of polymer-clay nanocomposites for flame retardant applications is becoming more common, especially as it is realized that the clay nanocomposite can replace part of the flame retardant package while maintaining fire safety ratings at a lower flame retardant loading. This results in a better balance of properties for the nanocomposite material compared to the non-nanocomposite flame retardant product, and in some cases, better cost for the flame retardant resin, especially if the organoclay is cheaper than the flame retardant it is replacing. Organoclay can replace traditional flame retardant on more than a 1:1 by weight basis, meaning 1 gram of organoclay can replace more than 1 gram of traditional flame retardant, resulting in weight saving. The synergistic enhancements of clay nanocomposites for fire safety applications has led to two commercial products: a Wire & Cable jacket material (organoclay + aluminum hydroxide) produced by Kabelwerk Eupen AG, and a series of polypropylene + organoclay + flame retardant systems (Maxxam™ FR)

produced by PolyOne. CPN can also be combined with Phosphorus and Intumescents to replace halogenated flame returdants (Arao 2015). The possible use of CPN in wires and cables is based on the improved barrier properties and flame resistance and retardance.

6.6.3 As Gas Barrier

Another major application of clay nanocomposites is for gas-barrier materials. Clay nanoparticles create a complex network in the polymer matrix, such that various gases either diffuse very slowly or not at all through polymer chains and pinholes in thin films or thicker polymer parts. In the packaging industry, the superior oxygen and carbon dioxide barrier properties of the nylon nanocomposites have been used to produce PET multilayer bottles and films for food and beverage packaging (Anadão 2012). Mitsubishi and Nanocor produce high-barrier CPN with the trade name Imperm® N based on polyamide. In a three-layer PET bottle, a 100-fold reduction of oxygen transmission rate is possible compared to virgin PET. The stiffness of CPN is doubled while maintaining gloss and clarity of the copolyamide film. Permeation of gasoline, methanol, and organic solvents is limited. Films and thermoformed containers (for potato chips, ketchup, cheeses) are also prepared. PET bottles with this Imperm nanocomposite are commercially used in Europe for beer and other alcoholic beverages (Morgan 2007; Cogen et al. 2013).

6.6.4 In Sporting Goods

First commercial application of CPN in sporting goods is tennis ball, the Double CoreTM Tennis Ball commercialized by Wilson Sporting Goods in 2001. This type of CPN is based on elastomers (Galimberti et al. 2013). The same technology used for tennis balls, based on a micrometre layer of a CPN of vermiculite in butyl rubber, was tested in inflated balls for other sports, such as soccer, basketball, American football, rugby, and volleyball, though commercial products are not yet available in the market.

6.6.5 Biomedical Application

CPN fills several necessary premises for application in medical materials such as biocompatibility, biodegradability and mechanical properties. For this reason and for being finely modulated by adding different clay contents, they can be applied in

tissue engineering – the hydrogel form, in bone replace- ment and repair, in dental applications and in medicine control release (Anadão 2012). With CPN based on polyurathene designed for biomedical applications such as blood sacs in ventricular-assist devices and total artificial hearts, water vapour permeation was reduced by more than 50% at an organoclay volume fraction of only 0.02 (Galimberti et al. 2013).

6.7 Future Prospects

Polymer clay nanocomposites are already used in many applications to enhance existing properties of a particular material, and further research and development efforts should focus on development of true multi-functional materials. Certainly, clay nanocomposites will continue to be used for enhanced mechanical, flammability, and gas barrier properties, but fundamental limits in clay chemistry limits them from being used easily in applications requiring electrical and thermal conductivity or optical applications. Hence, combinations of organoclays with other nanofillers to obtain a true multi-functional material will likely arise in the future. Combining an organoclay with carbon nanotubes or quantum dots, can yield a very interesting nanocomposite with enhanced mechanical, flammability, thermal, and electrical properties, allowing it to be a replacement for many different materials in a complex part. Again, the clay can enhance the properties of some existing mechanically fragile system while keeping other properties intact. Some early initial research has been done on combining more than one type of nanofiller in a polymer matrix. These materials have likely been in use for quite some time already, but as the chemist and materials scientist become better at designing the system through fundamentals, new products and applications utilizing this technology will grow in number and capability.

However, in spite of these efforts and some achievements in commercial development of clay-polymer nanocomposites, their design, manufacturing and applications are often experimental, and large-scale manufacturing is still in its infancy. The reasons are mostly because of the inadequate theoretical knowledge on such nanostructure materials, such as a basic standard for the selection of surfactants and the modification of clays for the purposes of targeted polymer matrix, the mechanisms of superior reinforcement observed as compared with their micro-counterparts, and the formation of processing-structure property relationship for such nanocomposites. Therefore, further development of clay-polymer nanocomposite materials depends largely on our understanding of the above fundamentals in relation to their formation, processing, property prediction and design.

6.8 Summary

The perception of clay-polymer nanocomposites is an innovative approach for design of new materials with specialized properties. The different modification techniques used for the preparation of polymer compatible clay materials showed impact on the dispersion of clay fillers in the polymer matrices. The desired properties for the clay- polymer nanocomposites are mainly dependent on the type of modifying agents used for modification of clay materials. In this study, we tried to explore the working principle of different surface modification techniques and their subsequent effect on the properties of composite. We can conclude that both salt treatment and silane treatment help the clay particles to exfoliate in polymer matrix. Development of new clay-polymer nanocomposites with added functional properties will create further scope for expansion of materials technology.

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Chapter 7
Photovoltaics and Nanotechnology as Alternative Energy

Mallika Dasari, Rajesh P. Balaraman, and Punit Kohli

Contents

Abstract The combustion of conventional energy sources such as fossil fuels is linked to global climate change. The extraction, transportation, and supply of fuels based on fossil are also associated to local and regional geo-political and economic instability, and concerns over socio-economic sustainability in various parts of the world. Therefore, there is a strong push to enhance use of renewable energy without impacting economic growth. Further, it is becoming increasingly more important to utilize and incorporate renewable energy to meet ever increase world power consumption. The use of photovoltaics as a renewable solar energy has gained greater attention since 1990s. According to International Energy Agency (IEA), solar photovoltaics are expected to become the world largest producer of energy by contributing >15% to the global demand by 2050. Although more extensive reviews are available in the literature, in this mini-review we discuss various available

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alternative energy sources, and provide history, development, and characterization of photovoltaic devices (including first-, second- and third-generation photovoltaic devices with different chalcogenide materials). Emphasis is given to recent developments in the area of photovoltaic devices including Forster resonance energy transfer (FRET) and perovskite-based photovoltaics. The wide applications of photovoltaics in residential (>200 GW), construction (BIPV module), and space industry have also been reviewed in this article.

7.1 Significance of Alternative Energy Sources

This article starts with an insight into basic understanding on renewable energy sources. First, the article will discuss the significance of alternative energy sources and their contribution to world energy consumption and production. Further, the history and developments through the first-, second-, and third-generation photovoltaic cells are discussed. This is followed by discussion on FRET-based and perovskites-based photovoltaic devices. The application of photovoltaics in different sectors including residential and space are also discussed. The article concludes with the description on photovoltaic device physics, and characterization of photovoltaic devices.

Energy production through fossil fuels accounts for 68% of the world's energy demand (Turner 1999; Dresselhaus and Thomas 2001). The combustion of fossil-fuel provides energy that literally "run" the world. Fossil-fuel are primary referred to coal, natural gas, petroleum, and any other carbon-based fuel that were formed through anaerobic decomposition of buried organisms and plants millions of years ago. However, there is a penalty for "human comfort" sought through fuel combustion – (1) There is strong, and perhaps irrefutable scientific hard data, linking by-products of fossil-fuel combustion reaction and gases (particularly methane) released during fuel production (or extraction) to global climate change. (2) Burning fossil fuels cause air, soil, and water pollution by releasing various combustion byproducts into the atmosphere (Hoffert et al. 2002). (3) Fossil fuel reserves are finite and irreplaceable; they will be devoid in the future (Menyah and Wolde-Rufael 2010). (4) There is a strong disconnect in the kinetics of fossil-fuel synthesis (which takes millions of years) to its rate of extraction and combustion fossil-fuel which is many orders faster than its synthesis. This means that this is "one-way" reaction process of depletion of the fossil fuel. (5) Earth's population is expected to increase ten billion by 2050.(Cohen 2003) Increase in population along with high-quality of life will no doubt require many orders of higher energy demand than is needed today. For these reasons, it is absolutely necessary to find alternative energy sources to fossil fuels that can provide energy for a growing population. Actions must be taken now to find and attain more sustainable and beneficial energy alternatives for our future generations.

7.1.1 Alternative Energy

"Alternative energy" refers to energy production through sources other than combustion of fossil fuels. Alternative energy (sometimes also referred to as renewable energy) may allow reducing various combustion byproducts including CO_2, CO, Hg, etc. during energy production, transmission, and usages. Fossil-based fuel combustion traps both heat and greenhouse gases (CO_2, SO_2, N_2O, CH_4, CO, etc.) collectively. These energy sources and related advanced technologies may assist in reducing or stabilizing the rapid build-up of green-house gases in the atmosphere by providing cleaner alternates of energy (Jenkinson et al. 1991). The trapped greenhouse gases and heat within the atmosphere are implicated by increase in earth's temperature (Cox et al. 2000). Evidence of this is confirmed by increase in the earth's temperature by ~0.8 °C in a relative very short time period of one century (Solomon et al. 2009). Further, the studies have predicted that a continuous increase in greenhouse gases in the atmosphere will elevate the surface temperature between 1.1 °C and 6.4 °C by the end of twenty-first century, causing irreversible damage to earth as we know now (Shindell et al. 1999; Root et al. 2003). An increase in surface and atmosphere temperature can lead to many serious and catastrophic risks and disastrous such as melting of the glaciers and ice caps (a major source of trapped freshwater), raising sea levels, and may cause frequent droughts, intense storms, and floods that will affect human health, food production and agriculture, wildlife, and emergence of new diseases (Patz et al. 2005; Adams et al. 1988). Conventional energy sources have been displayed in a pie chart in Fig. 7.1 (Goldemberg 2007;

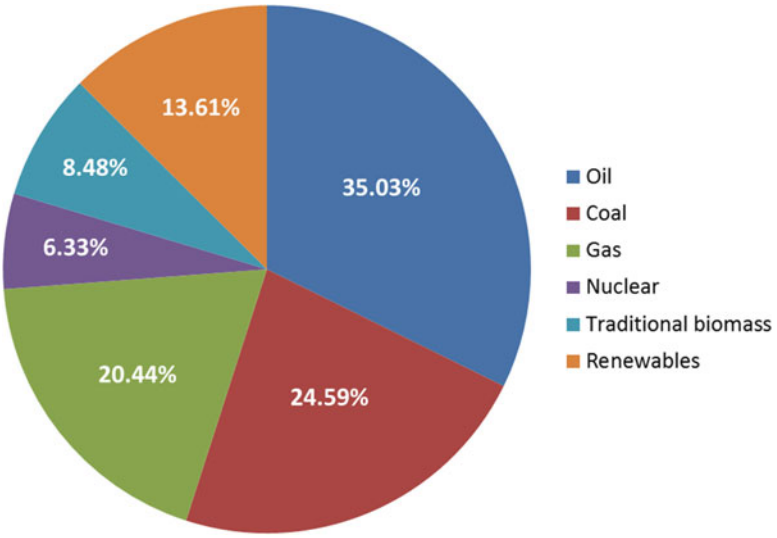

Fig. 7.1 The pie graph shows the distribution of energy produced by different sources (Goldemberg 2007; Chow et al. 2003)

Chow et al. 2003). The chart depicts that <15% of the total energy is produced by renewable energy sources. Major renewable energy sources are discussed in the following paragraphs.

7.1.2 Currently Available Alternative Energy Sources

Several alternative energy sources are currently being used in fulfilling the world's demand on power consumption in a safe, easy, and efficient manner. Alternative energy sources such as solar, wind, hydroelectric, biomass, geothermal and tidal energy have been widely implemented in developed, developing, and under-developed countries. This also contribute to indirectly boosting the local economy through advances in the science, technology, and manufacturing (Jacobson and Delucchi 2011).

7.1.2.1 Wind Energy

Wind energy contributes to 0.32% of the total renewable energy production (Voivontas et al. 1998) and is produced in areas where the wind speed is consistently high all year along (Lie and Cartwright 2006). The turbines in wind power systems utilize wind to regulate blade rotation speed to produce electricity (Xie et al. 2013) with the aid of an electrical generator (Gipe 2004). The installation of a wind turbine generator is relatively easy occupying relatively small amount of space allowing power production in agricultural land. A significant concern of wind-based power energy production is suitable geographical areas with consistent appropriate wind speed available for consistently production of electricity. Another concern is unpleasant (frequency ~few Hz to ~100 Hz) generated by turbines generating electricity (Møller and Pedersen 2011).

7.1.2.2 Hydropower

Another alternative way to harness nature's energy is through potential energy stored in water. The energy harvested by use of a water dam is referred as hydroelectric energy (Varun et al. 2009). As the water flows from the reservoirs, the potential energy stored in the water converts into kinetic energy with the rotation of turbines which generates electricity (Yeh 1985). Hydroelectric energy accounts for only 0.41% of the total renewable energy production used today (Goldemberg 2007). The hydroelectric energy production is clean and does not pollute the environment (Yüksel 2010) but a major concern comes from its large capital expenses, and damage to natural and human habitants (Dursun and Gokcol 2011).

7.1.2.3 Biomass Energy or Bioenergy

Bioenergy is usually produced from human, animal, and plant-based products. Biomass energy contributes 8.48% of the total renewable energy production (Du et al. 2007). The biomass is constantly generates and decomposes as part of the natural biological cycle (Walmsley and Godbold 2010). The CO_2 and H_2O are converted into carbohydrates through photosynthesis by plants (Sinclair and Horie 1989) are broken down in a bio-production process (Lehmann 2007).

7.1.2.4 Geothermal and Tidal Energy

Geothermal and tidal are newer alternative energy methods that have gained interest recently (Fridleifsson 2001). Geothermal produces a clean energy by reaping the energy that is stored under the earth's crust in thermal form (Lund and Freeston 2001). The heat exchange from earth can be used to heat/cool water for residential and industrial processes. This thermal exchange process can also be used for steam generation (Barbier 2002) wherein steam pressure is used to turn steam turbines, generating electrical power (Demir et al. 2008). Geothermal energy produces 0.23% of the total renewable energy that supplies global demand (Barbier 2002).

7.1.2.5 Solar-Energy Based Alternative Energy Production

The sun is the most bountiful energy source for our planet with a continuous flow of clean energy (Glaser 1968). Solar light hits the earth at a rate of 120 petawatts per day (Karl and Trenberth 2003) which can provide an ample amount of electricity for 20 years worldwide (Erbs et al. 1982). This can highly beneficial and reliable since the energy use worldwide increases by 5% every year (Solangi et al. 2011). The energy emanated from the sun in 1hr is higher than the energy used by the world's population in 1 year (Mohandes et al. 1998; Lewis and Nocera 2006). Sun is the primary source of all energies available on planet earth while surprisingly only 47% of the light emitted by sun reaches the earth's atmosphere. 32.9% of this light can be utilized as a source for renewable energy while the remaining (14.1%) of the light is reflected back into space (Hansen et al. 2005). Efficiently harnessing a fraction of this available solar energy can provide, in principle, a permanent solution for our energy crisis resulting from dwindling fossil fuels (Lewis and Nocera 2006). Further, solar-based energy can also help in containing increase greenhouse gases in the atmosphere (Robertson et al. 2000), and an increasing energy demand for the masses that aspires to reach developed world life-style (Stainforth et al. 2005).

7.2 Photovoltaic-Based Devices and Energy Production

Photovoltaics (Green 2004; Antonanzas et al. 2016; Fan et al. 2015; El Chaar et al. 2011; Zhang et al. 2011; Reinders et al. 2017; Furchi et al. 2017) is one of the fastest growing renewable energy areas. It converts sunlight into electricity without concerns of energy supply or any interference from heat engines. Photovoltaic based energy production is clean, sustainable, and renewable. The efficiency of the photovoltaics depends on the design of the photovoltaics panel, climatic conditions, irradiation levels and local temperature where photovoltaic devices will be installed (Parida et al. 2011). Major challenges that limit the development and commercialization of photovoltaics include production cost, low photon-to-electron efficiency, and the lifetime of the device providing energy. The main source of photovoltaics is the unlimited supply of solar energy. Although this supply is free of cost, the cost associated with materials, equipment, and processing makes photovoltaics more expensive under current environment than that of fossil-based energy production (Fahrenbruch and Bube 2012). Despite these disadvantages, the growing of solar photovoltaic cells is promising and evident with its increase of 0.26–16.1 GW by 2010 and an annual growth rate of nearly 40% through research progress (Branker et al. 2011).

The average renewable energy production cost (Cost 2014) can be 2–5 times higher than fossil fuel based energy production (Table 7.1). Table 7.1 shows the cost of electricity production in US dollars/megawatt-hour for both renewable and non-renewable energy. This cost does not include future cost to repair damage or minimize loss of natural resources including plants, animals, land, rise of water level, droughts and flood damage, and possible detrimental effects on human and animal health (Gould and Higgs 2009).

7.2.1 History and Background of the Photovoltaics Technology

The photovoltaics effect was discovered by 19 year old Edmund Becquerel in 1839 during an experiment he conducted in his father's laboratory (Lewis 2007). He found

Table 7.1 Cost comparison of different energy sources (Cost 2014)

Energy type	Momentary cost per megawatt hour ($)
Coal	35
Gas	60
Solar	190
Biomass	70–158
Wind	80–120
Geothermal	70–87
Hydro-electricity	60–150

that when platinum electrodes coated with silver chloride immersed in an acidic salt solution generated potential between the two electrodes when illuminated with light (Williams 1960). In 1877, Adams and Day demonstrated a photovoltaic cell utilizing selenium (Ameta and Ameta 2015). Another important observation by Fritz in 1883 yielded photovoltaic cell with efficiency <1% (Singh 2013). In 1905, Albert Einstein explained the photoelectric effect (Einstein 1936) that states ejection of electrons from semiconductors and metals with low ionization potential when they expose to electromagnetic waves of sufficient high energy (Clauser et al. 1969). Einstein was awarded the Nobel prize in 1921 for his discovery of photoelectric effect (Einstein and Rosen 1935). Robert Millikan provided an experimental proof of Einstein's theory on photoelectric effect in 1916 (Millikan 1916). A major breakthrough in photovoltaic industry occurred in 1954 when D. Chapin, C. Fuller, and G. Pearson demonstrated silicon photovoltaic cell with 5–6% photon-to-electron conversion efficiency (PCE) that was further enhanced to 11% by Bell Laboratories (Chapin et al. 1954). The photovoltaics research and development between 1950 and 1970s focused on the application of photovoltaic devices to satellite and space programs (Green 2002a, 2009). In 1958, the first photovoltaic cell powered radio transmitters were sent into space on a satellite 'Vanguard I' (El Chaar et al. 2011; Easton and Votaw 1959). The development of highly efficient photovoltaic cells lead to further investment towards the development of the photovoltaics technology. Approximately 1000 satellites were incorporated with photovoltaic cells by 1972 (Nemet 2006). In 1970, the cost of electricity generated from photovoltaics technology was estimated to be ~200 times higher than the cost of electricity generated using fossil fuel combustion. Research and development efforts in photovoltaic cell technology were sparked by the oil embargo in 1973. The creation of U.S. Department of Energy (DOE), and the Photovoltaic Program in 1976 further aided in photovoltaic research (Gisser and Goodwin 1986). In the 1980s, different photoactive materials emerged including cadmium sulfide, gallium arsenide, and copper sulfide. Furthermore, the photovoltaic devices were also fabricated on flexible thin film substrates and installed on solar powered aircraft. Table 7.2 summarizes materials used in the photovoltaic cells, their efficiency, and the advantages and disadvantages of each material. Although the production cost of photovoltaic cells is high, the innovations and technology improvements on solar photovoltaics production are promising. It is expected that the cost of photovoltaic cells will decrease with advances in materials, processing, and fabrication (Singh 2013; Kim et al. 2016).

7.2.2 Types of Photovoltaic Cells

Table 7.2 *shows different generation of photovoltaic cells, PCE and some comments on advantages and disadvantages of these devices* (Zakutayev 2017*).*

Sockley-Queisser Limit Energy conversion efficiency of Si photovoltaic is thermodynamically limited between 30% and 40% and is refer as "Shockley-Queisser

Table 7.2 Different types of photovoltaic cells, PCE, and comments on advantages/disadvantages

Photovoltaic cell classification	PCE (%)	Comments
Monocrystalline or single crystal silicon (Masuko et al. 2014; Zhao et al. 1998)	25.6	Advantages: high efficiency, space efficient, durability
		Disadvantages: expensive
Poly or multicrystalline silicon(Green 2007)	20.8	Advantages: less expensive compared to monocrystalline silicon cells
		Disadvantages: lower heat tolerance, low PCE[a] and space efficiency
Amorphous silicon(Carlson and Wronski 1976)	10.2	Advantages: easier to produce, high absorption of light because of irregular surface
		Disadvantages: low PCE[a], shorter life times
CdTe(Sites and Pan 2007)	21.0	Advantages: simple mass production, flexible, temperature changes have less impact
		Disadvantages: low space efficiency, expensive, fast degradation
CIGS(Ramanathan et al. 2003; Repins et al. 2008)	20.5	Advantages: high PCE[a], less toxic compared to CdTe technology
		Disadvantages: use of Cd; limited Indium is available
GaAs (thin film) (Yamaguchi 2003)	28.8	Advantages: higher PCE[a], UV and heat resistance
		Disadvantages: high production cost
DSSC(Bach et al. 1998)	11.9	Advantages: easy production, less negative impact on the environment
		Disadvantages: low PCE[a] and shorter life times
Perovskites (Kojima et al. 2009; Lee et al. 2012)	21	Advantages: low cost of production, high PCE[a]
		Disadvantages: toxic chemical components such as lead, shorter life times

[a]Power conversion efficiency (PCE) is the efficiency of a photovoltaic cell to convert solar energy into electrical energy

(SQ)" limit (Shockley and Queisser 1961). In general, the PCE losses occur in at least two ways: (1) the "red losses" which refers to photon with energies less than the band gap not being absorbed and will not contribute to electrical signal; and (2) "blue losses" where the photon energies lose their excess energy in the form of heat (Brown and Wu 2009). William Shockley and Hans J. Queisser calculated the theoretical efficiency of a photovoltaic cell made from a single p-n junction (Vos 1980). For a single p-n junction cell, SQ limit is around 33.7% for a material with a bandgap of 1.4 eV using an AM 1.5 solar spectrum under standard test conditions (Conibeer et al. 2006). The remaining 67% of the incident energy is lost to surrounding: 47% of the solar energy gets converted to heat, 18% of the photons pass through the photovoltaic cell into the surroundings without being absorbed, and 2%

is lost in radiative and non-radiative recombination (Nayak et al. 2011; Toon and Pollack 1980; Hanna and Nozik 2006). Some environmental factors also appear to effect both PCE and stability of the photovoltaic cells (Krebs et al. 2005). The oxygen and moisture present in the atmosphere can degrade the materials of the photovoltaic cell, thereby, affecting the performance of the cell (Madakasira et al. 2005). The photovoltaic cells can be encapsulated within inert materials such as SiN_X, SiO_2, and silicones to reduce material degradation (Neugebauer et al. 2000). The performance and PCE of the solar photovoltaic cells has been observed to depend on solar energy, wind speed and environmental temperatures (Khatib et al. 2013).

7.2.2.1 First Generation Photovoltaic Devices

The first generation photovoltaic cells composed of mono-crystalline and/or poly-crystalline silicon semiconductors (to some extent Gallium-Arsenide) were more expensive for producing electricity compared to fossil fuel energy production (Green 2005; Masetti et al. 1983; Blakers et al. 1989). The monocrystalline Si (99.9% Si) photovoltaics yielded one of the highest PCE efficiency (~25.6%) (Aberle 2000). The crystalline Si atomic arrangement favors efficient charge transfer with minimized losses through radiative and/or non-radiative charge recombination processes (Green et al. 2015; Wenham and Green 1996). The first generation solar cells were also durable and reliable. However, silicon wafer growing, cutting and other post-processes are labor-intensive with more than half of the device fabrication cost is associated (Wang et al. 2012). Silicon grooves fabricated using a laser through an insulating layer were observed to increase the PCE and performance of photovoltaic solar cells by 20–30% (Green 1995, 2004).

7.2.2.2 Second Generation Photovoltaic Devices

The second generation of solar cells was evolved to reduce the production cost associated with the silicon wafer dominated first generation solar cells. These devices are a thin layer of solar cells composed of a small sheet of photoactive material evaporated on low-cost substrates.(Shah et al. 1999; Britt and Ferekides 1993) This has greatly reduced the percentage of semiconductor materials used and also enhanced commercial production as the thickness of the semiconductors were <1 μm. Thin film cells with different materials, namely hydrogenated alloy of amorphous silicon, cadmium selenide, copper indium gallium selenide (CIGS), copper indium diselenide, cadmium telluride (CdTe), nanocrystalline titanium dioxide, polycrystalline silicon were dominating the commercial market (Green 2004). Thin film photovoltaic devices were also fabricated on a variety of flexible, elastic substrates such as polyimide, polyethylene, polyethylene terephthalate, polyethylene-naphthalate, paper, and foil (Krebs 2009). Using thin film technology, transparent photovoltaic cells can be fabricated and incorporated on glass windows,

generating electricity for residential utilities (Brabec et al. 2001). The highest reported PCE of solar cells based on GaAs thin film technology is ~28% (Mitzi et al. 2008; Stolt et al. 1993). However, the use of toxic and heavy metals such as cadmium and tellurium is one of the main drawbacks of the second generation photovoltaic cells (Chen et al. 2012).

7.2.2.3 Third Generation Solar Devices

The third generation solar cells were intended to overcome the disadvantages of both first and second generation solar cells by cutting the production cost down to $0.20/W. Third generation solar cells were also designed to improve upon the durability and stability of PCE while maintaining the low production cost offered by thin-film deposition techniques (Green 2001). Increasing efficiency indirectly reduces the production cost, but to attain higher efficiency the device must overcome the SQ limit for a single bandgap which regulates the PCE efficiency (Conibeer 2007). Tandem cells or multiple cells, each with different bandgaps, were used so that photon with energy higher than a single bandgap could be utilized. The use of multiple band gaps stack of materials for device fabrication helped converting improved PCE. The photovoltaic cells developed based on these novel technologies are in the commercial production stage with double/triple junction cells (GaInP/GaAs/Ge) and quadruple junction devices with efficiencies of 30% and 40% respectively (Green 2002b). Multiple electron-hole pairs were also formed by the creation of more than one pair of electron hole pair through ionization expected to yield higher efficiency. Unfortunately measured efficiency was unsatisfactory and no advances were reported although theoretical calculations indicated an upper PCE of 85.9% (Green 2001, 2002b). Hot carrier cells were also reported to have a PCE of 86.8% for an infinite tandem cell stack (Saeed et al. 2014; Würfel 1997). On the other side of photovoltaics, thermo-photovoltaics (recently referred as thermophotonics) are also being investigated using a heating body source other than sun as a source of illumination (Green 2002a). The third generation technologies may also utilize organic conductive polymers, dyes, small molecules, nanoparticles, nanotubes, nanowires, and inks (Lewis 2007; Grätzel 2003). These photovoltaic devices can be printed on flexible substrates in mass production at lower cost compared to second generation solar cells (Green 2004; Krebs 2009; Vogelbaum and Sauvé 2017).

7.2.3 Förster Resonance Energy Transfer (FRET) Based Photovoltaic Devices

FRET incorporated photovoltaic cells are extensively investigated recently. In general, FRET occur between two chromophores separated by a short distance

(usually <10 nm), where non-radiative electronic energy of one molecule (donor) is transferred to another molecule (acceptor) through dipole-dipole coupling (Förster 1949). Quantum dots and organic dyes are considered as good donors in FRET because of its high molar extinction coefficients and broad absorption spectra. Two different ways of loading donor in the pores of titanium electrode have been reported; one method involved embedding of few nanometers of donor QDs below the sensitizing layer and other process utilizes dissolving organic relay dye in either the solid or liquid electrolyte. A simple FRET-based DSSC fabrication involves coating of QD antennas below an amorphous titania (TiO_2) layer and followed by an organic dye coating (such as squaraine dye SQ02) (Itzhakov et al. 2011; Geiger et al. 2009). FRET-based DSSC devices composed of quantum dots and dyes (such as CdSe/CdS quantum-dot (QD) donor and a D719 dye acceptor) are reported to yield high PCE over a wide wavelength range. The photovoltaic performance of FRET-based DSSC showed a short circuit photocurrent density of 12.4 mA/cm^2, open voltage 0.74V, fill factor 0.71, and PCE ~6.49 with various combinations of QD and D719 dye (Lee et al. 2013). Low cost photovoltaics are also possible through solid-state dye-sensitized solar cells (SS-DSCs) and organic solar cells (Li et al. 2010) utilizing FRET mechanism that enables enhancement of light harvesting and photocurrent generation. The concerns with FRET-based photovoltaics are charge transfer competition at the hetero-interface, low-power conversion PCE and limited choice of acceptor dyes (Mor et al. 2010; Shankar et al. 2009; Feron et al. 2012).

7.3 Perovskites Based Photovoltaic Devices

Recently, a new class of solar cells based on mixed organic-inorganic perovskites has gained interest with extensive research leading to an efficiency of 20% within a period (2009–2017) (Arjona-Esteban et al. 2017; Reinders et al. 2017). The perovskites based photovoltaic cells (Cao et al. 2015; Hao et al. 2014b, c; Liu et al. 2013; Lee et al. 2012; Snaith 2013; Snaith et al. 2014; McGehee 2014; Mailoa et al. 2015; Smith et al. 2014; Hoke et al. 2015; Munir et al. 2017) possess strong solar absorption leading to a high PCE efficiency, lower cost, easy fabrication and low non-radiative carrier recombination rates (Green et al. 2014).

7.3.1 Information on Perovskite Crystal Structure

Perovskites are named after a Russian mineralogist L. A. Perovskite who discovered the mineral in 1839 (Collavini et al. 2015). The basic crystal structure of perovskites is ABX_3, where A and B are cations of different sizes, and X is an anion such as oxygen or a halogen that bonds to both A and B (Navrotsky 1998) "A" cation is occupied in a cubo-octahedral site whereas "B" cation is occupied in an octahedral site. The crystal stability and the structure can be predicted by tolerance factor

Table 7.3 Efficiency of perovskites reported from 2009 to 2016

Perovskite sensitizer on TiO_2	Short circuit photocurrent density J_{sc} (mA/cm^2)	Open voltage V_{oc} (V)	Conversion Efficiency η (%)	Fill factor (FF)	Published year and reference
$CH_3NH_3PbBr_3$	5.57	0.96	3.13	0.59	2009 (Kojima et al. 2009)
$CH_3NH_3PbI_3$	11.0	0.61	3.81	0.57	2009 (Kojima et al. 2009)
$CH_3NH_3PbI_3$	15.99	0.629	6.20	0.55	2011 (Im et al. 2011)
$CH_3NH_3PbI_3$ on mesoscopic TiO_2	17.6	0.88	9.7	0.62	2012 (Kim et al. 2012)
Al_2O_3/TiO_2 $CH_3NH_3PbI_3$	17.8	0.80	10.9	0.63	2012 (Lee et al. 2012)
Mesoporous TiO_2 – $CH_3NH_3PbI_3$	16.5	0.99	12.0	0.727	2013 (Heo et al. 2013)
$CH_3NH_3SnI_3$	16.30	0.68	5.23	0.48	2014 (Hao et al. 2014a)
$CH_3NH_3SnIBr_2$	12.30	0.68	5.73	0.57	2014 (Hao et al. 2014a)
$CH(NH_2)_2PbI_3$	24.7	1.06	20.2	0.77	2015 (Yang et al. 2015)
NiO_x based $CH_3NH_3PbI_3$	20.5	1.07	16.47	0.72	2016 (Yin et al. 2016)
Mesoscopic $CH(NH_2)_2PbBr_3$	6.9	1.5	7.1	0.69	2016 (Arora et al. 2016)

$t = (R_A+R_X)/\sqrt{2}(R_B + R_X)$ and octahedral factor $\mu = R_B/R_X$, where R_A, R_B and R_X are ionic radii of the corresponding ions. For perovskites, the tolerance factor value lies between 0.81–1.11 and octahedral factor values within 0.44–0.90 (Green et al. 2014; Li et al. 2008). Some examples of perovskite crystals are $CaTiO_3$, $CH_3NH_3PbX_3$ (X= Cl, Br, and I), $CH_3NH_3SnI_3$, and $H_2NCHNH_2PbX_3$ (Eperon et al. 2014; Feng and Xiao 2014; Gonzalez-Pedro et al. 2014; Sasaki et al. 1987) (Table 7.3).

7.3.2 *The Device Architecture and Properties of Perovskites-Based Photovoltaic Devices*

The device architecture of the perovskite photovoltaic devices is similar to that of dye-sensitized solar cells (DSSC) (Grätzel 2003). Figure 7.2 shows one-step and two-steps coating methods for depositing perovskite ($CH_3NH_3PbI_3$) on mesoporous TiO_2. The devices composed with two-steps coating method is reported to have higher PCE of 13.9% than that of devices fabricated with one-step coating method (7.5%). Both the devices utilized CH_3NH_3I and PbI_2 solution for the fabrication (Im et al. 2014).

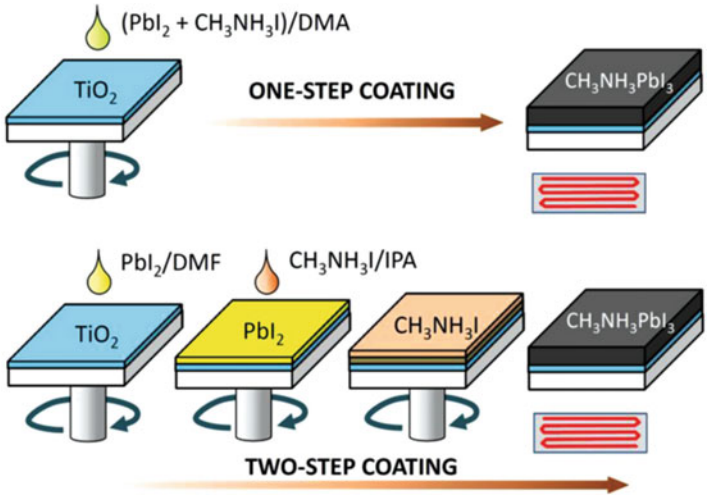

Fig. 7.2 One and two step methods of perovskite coating on mesoporous TiO_2 (Im et al. 2014)

Perovskite-based devices were first devised by its self-organization in nanoporous TiO_2 layer of DSSC by Miyasaka and coworkers (Kojima et al. 2009). Perovskite quantum dots/nanocrystals on TiO_2 showed PCE of 6.2% and which was observed to increase to 6.54% with application of surface modification using Pb $(NO_3)_2$ prior to deposition of QD on TiO_2 (Im et al. 2011). Further increase in PCE efficiency was obtained by devices having optional layers with scaffolds infiltrated by perovskites of different thickness (0.1–0.5 μm), mixed halide $CH_3NH_3PbI_{3-x}Br_x$ perovskites and two-step iodine deposition (Heo et al. 2013; Jeon et al. 2014). The growth of perovskites is rapid and is evident from the increase in PCE of perovskites from 3.9% to 21% between 2009 and 2016 (Ahn et al. 2015). Perovskites possess strong optical absorption property even at reduced thickness of absorbing layer (Yin et al. 2015). The density functional theory calculations showed that giant spin-orbit coupling in the conduction band dominates the bandgap of perovskites (Even et al. 2013). Direct-bandgap property calculations of perovskites are consistent with the absorption measurements and its two strong, spin-orbit split and electronic absorption thresholds are similar to direct band-gap III-V semiconductors while the reverse band-edge ordering results in a splitting of the conduction band rather than valence band (Even et al. 2013). Unlike tetrahedral coordinated semiconductors, an increase in band-gap was observed with increasing temperature in reverse band-edge ordering (Green et al. 2014; Ishihara 1994; Hao et al. 2014b). Perovskite based layers can be fabricated easily with large grain sizes, low intra-granular defects density, and low grain-boundary. These properties provide perovskites with a low radiative recombination as observed in conventional polycrystalline semiconductors (Edalati and Horita 2011). Perovskites with high open circuit voltage (V_{oc} ~1.5 V) (Arora et al. 2016; Tress 2016; Unger et al. 2014) and significantly long diffusion lengths (1–10 μm) (Gevorkian et al. 2016; Stranks et al. 2013a, b; Li et al. 2015) were

developed yielding PCE up to 20.2%. Concerns with perovskites are their chemical stability (Niu et al. 2015; Snaith et al. 2014) and the presence of lead in the devices that has negative impacts on the environment (Serrano-Lujan et al. 2015; Hodes 2013). Lead when consumed poses significant health risks to humans, plants, and animals. Particularly lead consumption in infants and children can lead to brain and nervous system damage (Mielke et al. 1999). Research is being now conducted to fabricate lead free perovskite solar cells to overcome this issue (Hao et al. 2014a).

Utilization of Photovoltaics for Residential and Industrial Settings The research on photovoltaics was initiated by many developed and developing countries after the 1973 oil crisis looking for an alternative energy source. Japan and European countries have been the main driving force initially followed by the enormous investment made by USA and China doubling the growth of photovoltaics and has further gained momentum worldwide (Hill 1989; McEvoy et al. 2003). The energy produced through photovoltaics process at a central power station for cities and for remote and difficult or inaccessible is anticipated in near future (Green 2004). Its commercialization has also increased its applications in several areas such as residential (powering homes, heating systems), space (satellites and aircrafts), solar powered vehicles, microscopy, portable power supplies (Fazelpour et al. 2013; Mok 2011; Janhunen 2004; Wang et al. 2000; Green 1982; Grätzel 2005; Baikie et al. 2013; Tejuca and Fierro 1992; Gao et al. 2014; Petek 2017).

The application and usage of photovoltaics in residential industry was first initiated in Germany in 1990s through '1000 roof' program' aimed at installing 1000 photovoltaic systems in private residences. Japan added strength to the role of photovoltaics in residence usage by the implementation of massive 4.6 GW by 2010. European countries and USA also made huge investments on photovoltaics during similar time (Green 2004). This approach of photovoltaics in residential sector led to its expansion by replacing conventional buildings with photovoltaics system using building-integrated (BIPV) and building applied photovoltaics (BAPV) modules. These modules involve the replacement of conventional building parts such as roof and windows using photovoltaic materials serving as a source of electrical power and reduce cooling load. Such modules have however limitation in terms of overall cost analysis and performance (Reinders et al. 2017; Karthick et al. 2017; Kim et al. 2017; Benemann et al. 2001; Oliver and Jackson 2001; Norton et al. 2011; Zahedi 2006; Agathokleous and Kalogirou 2016). Photovoltaics have also seen a wide range of applications in the space industry for space power, components of satellites and aircrafts (Iles 2000; Datas and Martí 2017). Nanostructured photovoltaics made of quantum dot enhanced solar cells (InAs, GaAs) possessing highest PCE implemented for space and satellite applications (Hubbard et al. 2009). Factors like radiation resistance, size and weight, power density, PCE, and cost influence the usage of photovoltaics in space station. Space components made of GaInP/GaAs high efficiency with 26.9% and thin films copper-indium di-selenide and amorphous silicon (based on chalcogenide absorbers) with multiple bandgaps have occupied space industry to wide extent (Bailey and Flood 1998; Tringe et al. 2000; Reinders et al. 2017). Thin films (III-V solar cells, $CuSbS_2$) and polymers (Quinoxaline) based

photovoltaics have recently gained attention in research for space industry (Yuan et al. 2017; Leest et al. 2017; Vinayakumar et al. 2017; Guo et al. 2017; Liu et al. 2017).

7.4 Photovoltaic Device Physics

Light is made up of packets of energy called photons. The energy of the photons depends upon the wavelength/frequency of the light. The shorter the wavelength of the photon, the higher energy it possesses (Factoran 1995) The wavelength of the solar radiation reaching earth's atmosphere ranges from cosmic to the near-infrared (NIR).

The photon energy is described by Eq. 7.1 (Nozik 2008)

$$E = \frac{hc}{\lambda} \tag{7.1}$$

where E is energy, h is the Plank's constant (6.625×10^{-34} Js), c is the speed of light in vacuum, and λ is the wavelength of light.

The operation of photovoltaics is based on the generation of the excitons through the absorption of appropriate energy photon by a semiconducting material (Kayes et al. 2005). Exciton is an electron-hole pair where electron and hole are weakly coupled through electrostatic coulombic interactions. The excitons are formed when a semiconductor material is illuminated with light (Fig. 7.3a), i.e. photo-excitation of the particle leads to electronic excitation to a higher energy level leaving a hole in the lower energy level. The typical lifetime for Si and organic materials is fraction of ns to tens ns range, whereas the diffusion lengths are ~10–50 nm for organic and ~1–10 μm range for perovskites (Kelzenberg et al. 2008). The excited electron may relax to ground state by through a number of relaxation mechanisms including radiative recombination, heat, electron and energy transfer to another particle (Najafov et al. 2010). Interaction binding energy between the electron and hole of an exciton is material dependent, for example, the binding energy of an exciton in highly ordered and crystalline inorganic materials is low due to the periodic structure with low defect density and high dielectric constants that lead to strong delocalization of the charges. Whereas in organic-based materials with low dielectric constant and long-range order, and geometry relaxation usually results in strong exciton binding interactions (Brédas et al. 2009). Geometric relaxations in the excited states also originate in an excited organic molecule.

Only photons with energy equal to or more than the optical bandgap of the material produce an electron in higher energy state of the material. If the energy of the photon (E_{ph}) < band gap (E_g) of the semiconductor, the interaction of electrons with the photons is minimum (reduced probability of photoexcitation). When the $E_{ph} = E_g$, the photon will be absorbed and an exciton pair will be generated. If the $E_{ph} > E_g$, the photon will be absorbed and the extra energy ($E_{ph} - E_g$) can be lost in

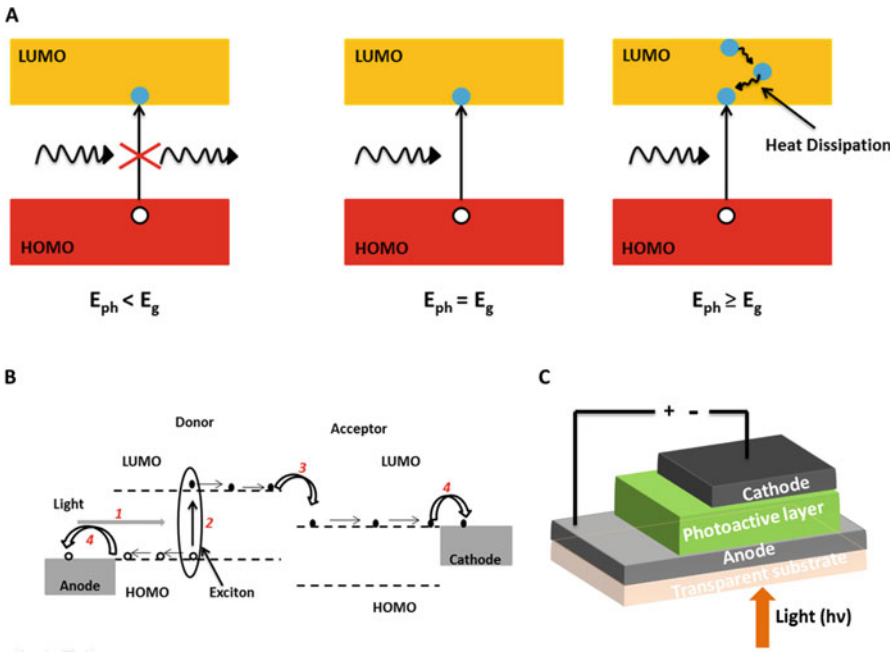

Fig. 7.3 (**a**) Photon absorption phenomenon of semiconductor. (**b**) Mechanism of the exciton generation. (**c**) The device architecture of a typical heterojunction photovoltaic cell (Zhou et al. 2010)

another form (thermal energy and vibrational relaxations). Figure 7.3a depicts the optical absorption process in a semiconductor. The mechanism of the exciton generation, charge generation and transport in a heterojunction solar cell is depicted in Fig. 7.3b. *1* represents the absorption of a photon with $E_{ph} \geq E_g$ by the donor, *2* denotes exciton generation, and *3* denotes the exciton dissociation at the donor and acceptor interface. *4* represents the charge extraction to the corresponding electrodes (Zhou et al. 2010).

The photovoltaics cell operates similar to a p-n junction diode device. p and n stand for positive and negative semiconductors respectively. p-type semiconductor is rich in positive charge carriers (holes), and n type semiconductor is rich in negative charge carriers (electron) (Tang 1986). A p-n junction is formed by combining p- and n-type semiconductor materials such that the electrons flow only in one direction (Kayes et al. 2005). When a photon of appropriate energy is absorbed by the active material in a photovoltaic cell, the electrons and holes are generated at the interface of a donor (D) and an acceptor (A) similar to p-n junction diode (Hagfeldt and Grätzel 2000). This active layer is usually composed of two or more (donors and acceptors) components with different ionization potentials (Yu et al. 1995). As displayed in Fig. 7.3b, (Koster et al. 2005) the active layer is sandwiched between two positive and negative terminals with different work functions (Tang 1986). The absorption of light generates excitons inside the active layer in the donor (Fig. 7.3b,

step 1) and can diffuse to the donor/acceptor interface (Fig. 7.3b, step 2) (Halls et al. 1996). The excitons dissociate into electrons and holes at the interface by overcoming the exciton binding energy (Fig. 7.3b, step 3). The dissociation takes place through a non-radiative transfer when the LUMO of acceptor is energetically lower than the LUMO of donor (Soavi et al. 2015; Gao et al. 2013). The dissociated charges (electrons and holes) are extracted at their respective electrodes by the application of an external bias. The exciton diffusion length limits the efficient charge separation and charge extraction to the respective electrodes (Forrest 2005). Only excitons that are capable of reaching the interface may undergo dissociation into charges. Excitons that are generated far from the donor/acceptor interface will not have a chance to dissociate within their lifetime and may undergo radiative or non-radiative recombination (Stübinger and Brütting 2001). These relaxation processes decrease the PCE. The radiative or non-radiative recombination phenomenon can be minimized in heterojunction solar cells by blending donor and acceptor molecules for reducing the inter-particle distance. The blending of donors and acceptors increases the charge generation by creating more donor/acceptor interfaces resulting in increased probability of dissociation of excitons (Huynh et al. 2002; Blom et al. 2007) thereby, reducing radiative recombination at the interface.

7.5 Photovoltaic Materials Characterization Techniques

This section discusses the characterization techniques used for the evaluation of materials for the photovoltaic devices (Sun et al. 2012). The optimized performance of individual phase in the complex photovoltaics active material mixture is the key to enhancing the photovoltaics device performance. The characterization of the materials for elemental composition, contaminations, structural properties, defects, and interface properties is important for the optimization of the photovoltaics characteristics (Carr and Chaudhary 2013).

X-ray diffraction spectroscopy (XRD) has been used to study the crystallinity and defects in photovoltaic active materials (CdSe, graphene, carbon nanotubes, P3HT, C60 and its derivatives etc.). XRD is also used to identify the crystal phase (amorphous and crystalline) and can also provide useful information about the grain size in graphene. Identifying the defects and crystal phases can help in optimizing the material performance for improving the device performance and efficiency (Talapin et al. 2001). Raman spectroscopy can provide information on chemical structure, crystal lattice order, heterogeneity in microscopic phases, and can also differentiate carbonaceous materials such as graphene, diamond, and amorphous carbon (Calizo et al. 2007). Structural information, contaminants identification, and chemical bonding interaction within active molecules can be characterized using FTIR (Kim and Hochstrasser 2005). SEM and AFM can provide the surface morphology, topography, and thickness of thin films at sub-nanometer resolution. TEM and electron diffraction provide the high-resolution imaging and long-range order of both carbon and inorganic-based materials useful for

photovoltaic devices. EDS can yield the elemental identification and composition of molecules and/or matrix system (Tung et al. 2009). UV-Visible spectroscopy can be applied to estimate the band gap for the photovoltaic materials (Moerner and Fromm 2003).

7.6 Current-Voltage (I-V) Characteristics of Photovoltaic Cell

This session discusses the I-V characterization of the photovoltaic devices. The photo-induced current-voltage characterization of photovoltaic cells is performed under both dark and light illumination. In the dark conditions, the current-voltage (I-V) characteristics of a solar cell bear resemblance to the response of a diode (Shah et al. 1999). Under light illumination, the photovoltaic device generates photocurrent in addition to the dark current yielding much higher current that can be used for powering a device (Villalva et al. 2009). I-V characteristics of a photovoltaic device can be described by the Shockley equation of a diode with an additional term that described the photocurrent (Eq. 7.2) (Martí et al. 1997).

$$I = I_{ph} - I_0[\exp(eV/nkT) - 1] \tag{7.2}$$

where I is the current density, V is the applied voltage, I_0 is the reverse saturation current density of the diode, e is the elementary charge, n is the ideality factor (emission coefficient), k is the Boltzmann's constant (1.38×10^{-23} J/K), T is the temperature (in K), and I_{ph} is the photocurrent upon illumination.

Figure 7.4 displays a typical I-V characteristic of a photovoltaic cell (Kawamura et al. 2003; Priambodo et al. 2013). The red and black curves represent the I-V responses in dark and under light illumination respectively. When light is

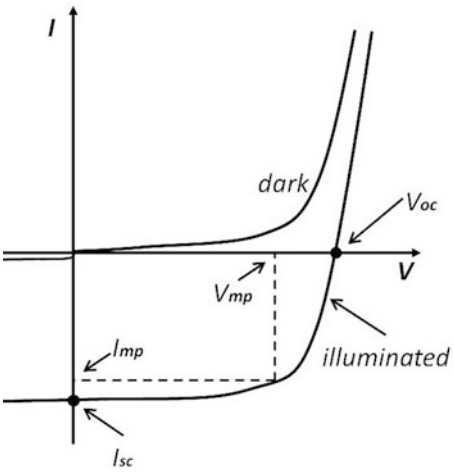

Fig. 7.4 Photovoltaic response of a photovoltaics cell under dark and light illumination (Kawamura et al. 2003; Priambodo et al. 2013)

illuminated on a photovoltaics device, the I-V curve is raised by the amount of photo-induced current (PIC) generated. V_{oc} is open circuit voltage at open-circuit ($I_{sc} = 0$). V_{oc} represents the maximum voltage a photovoltaics cell can produce when the circuit is open. I_{sc} is the maximum current that can flow through the external circuit at zero voltage (V_{oc}), i.e. two electrodes of the cell are being short circuited. V_{oc} and I_{sc} are the two important parameters for the evaluation of the performance of a photovoltaics device. P_{max} is the maximum power generated by a photovoltaics cell and occurs at V_{mp} and I_{mp}. Another factor that determines the efficiency of the cells is fill factor (*FF*). Higher FF is an indication of higher maximum power achievable in a photovoltaics device. *FF* tells how close V_{oc} and I_{sc} are to V_{mp} and I_{mp} (Eq. 7.3). In general, FF of a photovoltaics cell is in the range of 0.4–0.75 (O'Regan and Gratzel 1991).

$$FF = \frac{V_{mp}\ I_{mp}}{V_{oc}\ I_{sc}} \tag{7.3}$$

The power conversion efficiency of a cell is determined by the amount of incident light (I_L) per unit area that is converted into out power as shown is Eq. 7.4. PCE of a photovoltaics cell has a direct effect on V_{oc}, I_{sc}, *and FF* (see Eqs. 7.4 and 7.5).

$$\eta = \frac{V_{mp}\ I_{mp}}{I_L} * 100\% \tag{7.4}$$

From Eqs. 7.3 and 7.4 can be written as:

$$\eta = \frac{V_{oc}\ I_{sc}\ FF}{I_L} * 100\% \tag{7.5}$$

7.7 Conclusions

Photovoltaic is a solar energy conversion which is considered to play a vital role in future electricity generation. This article has emphasized the significance, history, development, and future of photovoltaic-based energy production and device fabrication. The existing and emerging photovoltaic technologies and materials utilized in photovoltaics devices are also presented. In particular, insight towards emerging photovoltaics namely the perovskites with their structure and properties are provided. The working principles of photovoltaic generation, device physics, and device characterization are discussed towards the end of the mini-review.

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Chapter 8
Nanomedical Applications of Nanoparticles for Blood Coagulation Disorders

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Contents

Abstract Nanotechnology has evolved as a novel multidisciplinary concept of the twenty-first century, abridging gaps in materials science, engineering, life sciences and medicine, with tremendous applications in diverse areas of human endeavours. Nanoparticles, which form critical components of nanoscience and nanotechnology, have also played prominent roles in extending the frontiers of applications of the

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emerging discipline. The metallic nanoparticles, owing to their unique optical, surface, chemical, biological, catalytic, electronic, and resonance properties have formed an epicentre of research in recent times, with major focus on synthesis and novel applications. A new line of application that has emerged is in the delivery of quality healthcare, leading to the offshoot of a sub-discipline, nanomedicine. A major health problem confronting man is the blood coagulation disorder, which often leads to cardiovascular diseases, with the attendant high mortality worldwide. The use of conventional drugs in the treatment blood coagulation has been plagued with problems of high cost, short-lived action and adverse severe reactions. Hence, there is need to search for newer treatment regimes with improved outcomes, of which nanotechnology holds a promising future. In this review, we focus on the emerging applications of metallic nanoparticles in the management of blood coagulation disorders; notably in the prevention of clot formation, dissolution of blood clots, and in the combined role of therapeutic and diagnostic agents. The review presents a comprehensive overview on blood coagulation disorders, synthesis and applications of metallic nanoparticles, and the novel management of blood coagulation disorders using nanoplatform deliveries. Emphasis has been placed on the prospects of the use of metallic nanoparticles such as silver, gold and silver-gold alloy nanoparticles as anticoagulant, thrombolytic and theranostic agents, with evidences of excellent performances in the prevention of blood clot formation, dissolution of blood clots, and enhanced imaging of thrombus (blood clot) in vivo. The increasing appraisals of these nanoplatforms, potent action, improved biocompatibility cum absence of complications of excessive bleeding are good indicators of potential future integration in the clinical management of blood coagulation disorders. However, diligent studies are needed to be conducted to establish the long-term safety of applications of these nanomedical materials. The compendium seeks to bring to the fore, the continued relevance of nanotechnology in the twenty-first century, and its potential dynamic integration into medicare programmes.

8.1 Introduction

There has been unprecedented progress in the synthesis and application of metallic nanoparticles in the last one decade, owning to the new range of techniques available for the fabrication of nanoscale materials, and the expanding diverse applications in industries, environment, agriculture and medical care. A major contributor to this development is the emergence of biosynthesis using myriad of biological molecules to drive the process of fabricating metallic nanoparticles in an eco-friendly, benign and cost effective way. In addition, the non-use of harmful procedures and chemicals in the process also expand the applications of those nanoparticles synthesized through the biological route for biomedical purposes as the particles are usually more biocompatible than those synthesized using chemical routes. An important emerging application of metallic nanoparticles is in the

management of blood coagulation disorders; particularly the prevention of clot formation (anticoagulant), the lysis of blood clot (thrombolysis) and in the dual action of therapeutic and diagnostic agents (theranostics).

Cardiovascular diseases are major killers throughout the world, with death rate of 235.5 per 100,000 recorded in 2010 (Devi et al. 2016). These diseases in most cases stemmed from the problems of formation of thrombi (blood clots) in blood vessels leading to thrombotic or blood coagulation disorders with unprecedented morbidity and mortality (WHO 2011; Uddin et al. 2013). Although, there are conventional drugs such as urokinase, streptokinase and tissue plasminogen activators that have been used in the treatment of thrombus, however, these drugs are plagued with serious complications including excessive bleeding and hemorrhagic side effects (Cicha 2015). The drugs also have low short-life and are expensive too (Devi et al. 2016). Therefore, new treatments are canvassed to remove the barriers associated with the use of the conventional drugs, particularly to improve performance, reduce dosage, side effects, and cost. Attempts in this area include the use of plant extracts to boost the actions of clot buster enzymes (Devi et al. 2016) and nano-based products (Ilinskaya and Dobrovolskaia 2013). The nanomaterials have been deployed as anticoagulants (Azeez et al. 2017a; Lateef et al. 2017), thrombolytic agents (Harish et al. 2015; Lateef et al. 2016a, 2017), carriers of thrombolytic drugs (McCarthy et al. 2012) or for the in vivo imaging of thrombi by computed tomography (Kim et al. 2015; Cicha 2015).

Nanotechnology is poised to enhance heath care deliveries in this area, in such a way that encumbrances associated with conventional treatment of blood coagulation disorders are eliminated, with the resultant effect of improved treatment regimes. While the use of several metallic nanoparticles and alloys as anticoagulant and thrombolytic agents is at infancy, this article seeks to document the milestone in this emerging discipline to spur more research activities that could lead to translational applications. The review examines the blood coagulation disorders, the synthesis of metallic nanoparticles and the application of nanotechnology in combating the disorders.

8.2 Haemostasis

Blood is a liquid organ of the body which has diverse functions including, transport and distribution of cells and molecules, protection against pathogens, wound healing, and thermoregulation of the body (Schaller 2008). The two major components of blood are cells and plasma, whereby the cellular component accounts for 45%, while the rest are made of plasma. The blood plasma is primarily made up of water which constitutes about 90% of plasma; and other materials such as soluble gases, low molecular weight lipids, carbohydrates, amino acids, metabolites, minerals, salts, and proteins (Schaller 2008).

To ensure continued survival of the organism, it is important for the body to exercise control over the flow of blood following injury done to the vascular system.

Therefore, it is remarkable that as blood clotting is very essential for life support after tissue damage, eventual dissolution of this clot is also inevitable, and this is termed haemostasis (Riddel et al. 2007). In order words, haemostasis is regarded as a dynamic process whereby coagulation of blood is initiated and terminated in a quick and closely regulated manner (Nathan et al. 2003). The loss of blood portends vascular system injury, as a result of which the termination of blood loss is highly essential part of defense mechanism of the host. Haemostatic mechanism protects the host against the threat of terminal hemorrhage through the interaction between the platelets and clotting factors leading to the generation of haemostatic plug that plays significant function in cessation of blood flow at the location of injury (Riddel et al. 2007).

8.2.1 Blood Coagulation System

According to Nichols and Bowie (2001), Hippocrates, Aristotle, Celcius and Galen once observed blood clot following internal and superficial bleeding, but could not establish a link between blood clot and the concept of haemostasis. However, French surgeon Jean-Louis Petit in 1720s noted that haemostasis after amputation of a limb was as a result of coagulation of blood at the site of the damaged blood vessels, and this relationship was also confirmed in 1828 by a Swiss Physician Friedrich Hopff (Nichols and Bowie 2001). Furthermore, description of blood clot and the ability to embolize by a German Pathologist, Rudolf Virchow in 1860 led to the classic theory of coagulation (Morawitz 1958; Nichols and Bowie 2001). Factors that are involved in the mechanism of blood coagulation include, von Willebrand factor (von Willebrand 1931), factor (F) V (Owren 1947), FVII (Alexander et al. 1951), FVIII (Patek and Stetson 1936), FIX (Aggeler et al. 1952; Briggs et al. 1952; Shulman and Smith, 1952) and FXI (Rosenthal et al. 1953). These coagulation factors are generally serine proteases which play vital roles in the creation of "thrombin burst" accompanied by instantaneous release of thrombin (Johri et al. 2011). Other elements involved in coagulation system include endothelium and platelets (Lefkowitz 2008).

Activation of blood coagulation begins majorly with interaction of the platelets, vessel wall and plasma proteins (Spronk et al. 2004). Disruption of the endothelial layer arises when the blood vessel is injured leading to the exposure of the underlying extracellular matrix containing both the VWF and collagen which in turn bind to the specific receptor and glycoproteins that are borne on the platelets (Spronk et al. 2004). Platelets passes through a chain of reactions such as adhesion, aggregation, release of granule content and morphological alteration culminating to the development of the platelet plug (Majerus 2001). Primary platelets adhesion occurs due to the interaction of platelets with von Willebrand factor which is a plasma protein composed of several disulphide-linked subunits (Sadler 1998; Ruggeri 2003). The von Willebrand factor facilitates adhesion of platelets by serving as a link between the tissue and the platelets which binds to collagen exposed at the sites of vascular

injury and the platelet membrane glycoprotein Ib-V-IX (GPIb-V-IX) (Clemetson and Clemetson 2001). This is followed by major structural changes of the platelets that involve reorganization of the membrane and exposure of negatively charged phospholipids and formation of far-reaching pseudopodia that help anchor the platelets (Majerus 2001).

Simultaneous formation and secretion of thromboxane A2 and release of ADP, calcium, and serotonin from the platelet granules result in the activation of additional platelets and contraction of smooth muscle cells of the vessel wall. An inside-out signal over the platelet membrane promotes a conformational change of the platelet integrin glycoprotein IIb-IIIa (GPIIb-IIIa) and exposure of binding sites for the adhesive proteins fibrinogen, von Willebrand factor, fibronectin, and thrombospondin (Woodside et al. 2001). The linking of these proteins with the platelets leads to the formation of platelet aggregates. The formation of the primary platelet plug is temporally and spatially coordinated with the activation of the blood coagulation system leading to the generation of thrombin and eventual formation of the fibrin clot (Monroe et al. 2002). The development of a steady fibrin clot depends on the capacity of thrombin to translate fibrinogen to fibrin (Fig. 8.1) and at the same time trigger factor XIII to XIIIa, which functions to stabilize the fibrin clot (Triplett 2000).

The process of managing coagulation and anticoagulation performance in blood can be achieved naturally. Fibrin is capable of actively controlling the self degeneration of clot through several relations with fibrinolytic and anti-fibrinolytic factors. The pathway followed for the self dissolution comprises of plasminogen, a range of activators and numerous inhibitors. The endothelial cells can also regulate the equilibrium of coagulation and anticoagulation mechanisms by liberating the plasminogen activator inhibitors, which can prevent fibrinolytic action and bestow a complete pro-coagulation effect. Thrombin also controls the appearance of urokinase-like plasminogen activator (which is deficient of fibrin binding activity) and tissue plasminogen activator (primarily produced by the microvascular endothelial cells), as well as fibrinolytic activities (Carpenter and Mathew 2008).

8.2.2 Blood Coagulation Disorders

Modification in the polymerization of fibrin, dissimilar fibrillation or abnormal structural configuration may cause formation of an unsteady thrombus. Anomaly in fibrin network can make thrombi extremely resistant to dissolution or too precarious to thrombolysis (Kim et al. 2011). The conformations of fibrin network and fiber diameters are factors upon which the binding of plasminogen to fibrin in the process of fibrinolysis are dependent. Blood clots with conformation that are fine and closely-packed are more lysis resistant than those with a loosely- packed and coarse fibrin conformation. Also, clots that consist of thin or gauzy fibers may be more susceptible to lysis than clots made of thick or broad fibers (Bhattacharjee and Bhattacharyya 2014).

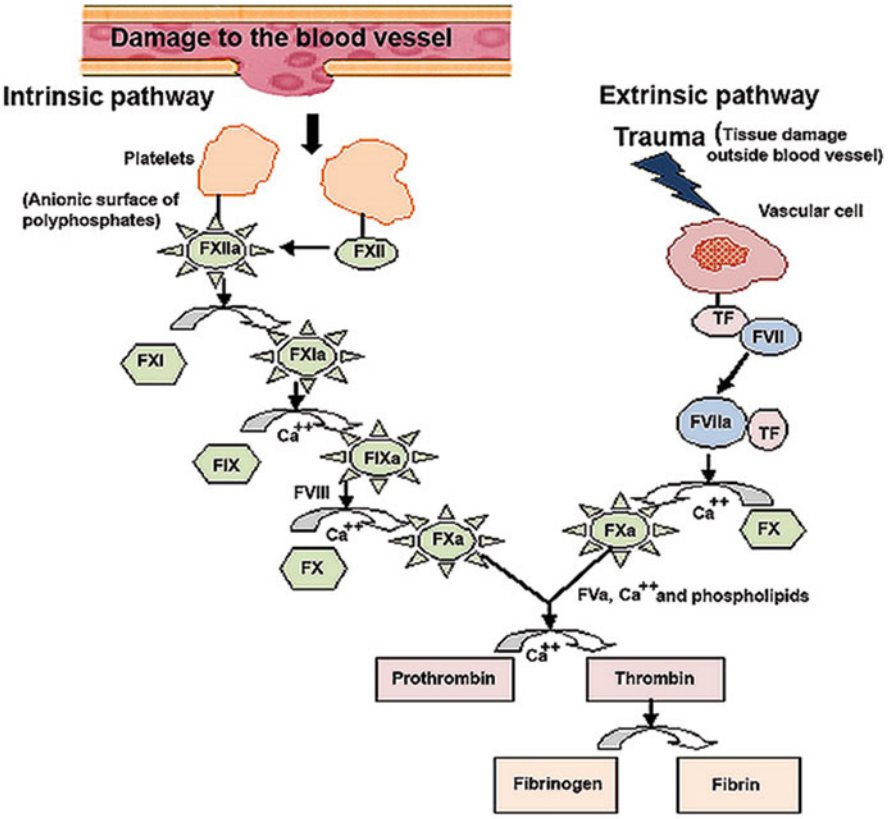

Fig. 8.1 The blood coagulation cascade (Bhattacharjee and Bhattacharyya 2014; reproduced with permission of authors). The coagulation of blood can occur through intrinsic and extrinsic modes in a series of events that lead to the eventual coagulation of blood

Factors like temperature, microgravity, pH, reducing agents and chloride concentration and concentration of calcium ions, which stabilizes the fibrinogen structure, quickens the formation of fibrin and can to some extent prevent fibrinogen from easy degradation which may influence the change of fibrinogen to fibrin (Nunes et al. 1995; Wolberg and Campbell 2008; Farahani and DiPietro 2008). However, the structure and performance of fibrin clot are controlled by certain genetic and acquired factors (Bhattacharjee and Bhattacharyya 2014). The genetic factors are inherited while the acquired factors may be as a result of either disease condition, side effects of certain medications (some anticoagulants or drugs), or nutritional deficiency.

Inherited or congenital coagulation disorders can be due to deficiency of a couple of factors or requirements that are necessary in the blood coagulation cascade or shortage of von Willebrand's factor. Examples of such factors are the antihaemophilic factor or factor VIII deficiency found in haemophilia A, which

causes joint synovitis and haemophilic arthropathies, pseudotumors, and intramuscular bleeds, retroperitoneal and central nervous system bleed which can be life threatening. Others include Christmas factor or factor IX deficiency found in haemophilia B (this can lead to catastrophic bleeding), plasma thromboplastin antecedent or factor XI deficiency (it is transmitted as an autosomal dominant trait, which has mild bleeding symptom), Hageman factor or factor XII deficiency, stuart factor or factor X deficiency (it is inherited as an autosomal recessive trait), proaccelerin or factor V deficiency (mostly results in soft-tissue hemorrhage), fibrin-stabilizing and fibrinogen or factors XIII and I deficiencies (both of which are autosomal recessive traits and may lead to moderate bleeding, and induce a state of hypercoagulation) (De Gopegui and Feldman 1997).

Disease- related acquired blood coagulation disorder or coagulopathies may be associated with liver diseases, deficiency of vitamin K or disseminated intravascular coagulation. Due to compromised protein synthesis, inhibitors of the clotting process and fibrinolytic systems are distinctly reduced in patients suffering from liver diseases and this may trigger a broad spectrum of haemostatic failure which is dependent on the extent of liver damage (Mammen 1994). Also, common in acute liver diseases are thrombocytopathy and thrombocytopenia. The deficiency of vitamin K is unusual but can be an implication of either insufficient dietetic intake, mal-absorption in the intestine, or damage of storage sites resulting from hepatocellular disease. Biliary tract obstruction and prolonged use of all-purpose antibiotics, especially cephalosporins can also cause deficiency of vitamin K. Also, disseminated intravascular coagulation is elicited by strong stimuli that activate both fibrin-stabilizing factor and tissue factor to primarily form microthrombi and emboli all through the microvasculature. Disseminated intravascular coagulation can be mild or chronic, however, in acute state, it can generate substantial haemorrhage and can also be life threatening (Patton 2003).

Drugs or anticoagulant-related acquired coagulopathies result as side effects of use of various anticoagulants and drugs. Anticoagulation is intentionally produced acutely or intensely using heparin, or as chronic or persistent oral therapy using coumarin drugs (Patton 2003). Heparin acts as a very effective anticoagulant that binds with antithrombin III to significantly hinder stimulation of factors IX, X, and XI, thereby lessening thrombin and fibrin formation. Heparin is usually used for severe anticoagulation because it has a fairly short period of potency of 3–4 h. The common indications for heparin treatment include prophylaxis or venous thromboembolism therapy. Moreover, complications in bleeding and thrombocytopenia are conditions that can be as a result of heparin use (Hirsch et al. 1998a).

Coumarin anticoagulants (dicumarol (coumadin) and warfarin) are used in preventing recurring thrombotic occurrences and treating atrial fibrillation (Hirsch et al. 1998b). Coumarin can also slow down thrombin production and formation of clot by hindering the activities of vitamin K. Also, the concentrations of vitamin K-dependent Factors II, VI, IX, and X (pro-thrombin complex proteins) are decreased. Some of the disadvantages of coumarin anticoagulants include that treatments with coumarin demands monitoring in the laboratory continually as

variations and changes can occur. Treatment with coumarin can result in bleeding that sometimes may be deadly.

Moreover, haematoma formation and intramuscular bleeding may be risks presented in anticoagulation patients. Also, there may be problems of some drugs to interact with coumarin drugs, due to susceptible interactions. Antibiotics such as erythromycin, metronidazole, cephalosporins, penicillin, tetracycline, and other drugs like ketoconazole, fluconazole, propoxyphene and chloralhydrate have high possibilities of increasing the actions of coumarin, but reduction in potency of coumarin is possible with ascorbic acid, barbiturates, nafcillin and dicloxacillin (Herman et al. 1997). The use of coumarin drugs combined with aspirin or NSAIDs have been observed to result in additive haemostatic condition (Patton 2003).

Polyphosphates, which has been used as a pro-coagulant and pro-inflammatory mediator is a polymer containing 60–100 phosphate residues that promotes the formation of thick and condensed fibrin aggregates that have turbidity up to three-fold higher (Smith and Morrissey 2008). Polyphosphates can also weaken the binding of tissue plasminogen activator and plasminogen to incompletely lyse fibrin, thereby resulting in protracted clot lysis (Smith et al. 2006). Also, homocysteine which results from the metabolism of methionine, raises the risk and chances for coronary artery disease and thrombosis. Moreover, fenfluramine, a drug that is used as a serotonin regulator has been described as a cause of abnormalities in blood clotting (Carr et al. 2001). Metformin which is an antidiabetic drug administered orally can adversely affect the configuration of fibrin by distorting fibrin polymerization (Standeven et al. 2002). S-nitrosoglutathione is used medically as an antithrombotic drug but at higher dose, the drug stimulates the development of abnormal fibrin structures and fibrin clusters to produce coarse network of clot (Bateman et al. 2012). Some other drugs that have the ability to cause clotting disorders are statin, glycosaminoglycans (chondroitin sulfate and dermatan sulfate etc) (Rottenberger et al. 2013) and Quinapril (Undas et al. 2006).

Various clinical laboratory tests are available to detect deficiency of elements required for coagulation or dysfunction in coagulation stages. Bleeding time and platelet count are the two major tests clinically used to evaluate primary haemostasis. Determination of the state of other features of haemostasis can be carried out by such tests as activated partial thromboplastin time, prothrombin time, international normalized ratio, fibrin degradation products, thrombin time, von Willebrand's antigen, coagulation factor assays, fibrinogen assay, and coagulation factor inhibitor screening assay (Patton 2003).

8.2.3 Physiopathological Conditions of Coagulation Disorders

Abnormal clots can lead to some physiopathological conditions which may be generated when emboli are embedded in vital body organs, interrupting the blood flow with possibly lethal consequences. Acute dysfibrinogenemia in patients with end stage liver disease is caused by the elevated sialic acid contents in the oligosaccharide of the anomalous fibrinogen which damages the polymerization of fibrin monomers (Roberts et al. 2001; Kujovich 2005) and the resulting haemostatic imbalance sometimes aids hypercoagulability (Lisman et al. 2001). In cases involving Ischemic stroke, congenital or hereditary fibrinolytic abnormalities such as deficiency of plasminogen activator, factor XII or prekallikrein, plasminogen and dysfibrinogenemia are linked to thrombosis. Extended ischemia can lead to a pathological condition termed myocardial infarction (death of cardiac myocytes).

Stimulation and clustering of platelets, assembly of thrombin and development of thrombus which blocks the blood vessels and obstructs the flow of blood is caused when the atherosclerotic plaque in the epicardial coronary artery bursts (Gutstein and Fuster 1999). Also, it has been reported that plasma fibrin clots in elderly and middle-aged peripheral arterial disease patients are formed faster, have smaller pores, thicker fibers and are lyzed at lesser rate than those collected from healthy individuals (Undas et al. 2011). Moreover, venous thromboembolic disorders is used to describe both deep vein thrombosis and pulmonary embolism. Deep vein thrombosis is a severe pathological condition which is caused by fractional or entire obstruction of blood flow due to lower or upper extremities of intravascular thrombosis, while pulmonary embolism is caused when an embolus settles in an arterial branch in the lungs (Bhattacharjee and Bhattacharyya 2014).

Less permeable clots that are formed more rapidly and also having a longer lysis time than in healthy individuals have been reported to be found in rheumatoid arthritis patients. The plasma secretion into joints in patients leads to amassing of increased concentration of coagulation elements at the synovial fluid and this is mostly associated by deposition of fibrin. In adult respiratory distress syndrome, the upsurged plasminogen activator inhibitors (which promotes compact clot structures formation and reduced fibrin degradation) (Undas and Ariëns 2011) and α2-plasmin inhibitor levels lead to reduced fibrinolysis and elevated deposition of alveolar fibrin (Idell et al. 1989). The condition also leads to lung fibrosis (Fan et al. 2000). Patients with coronary artery disease caused by atherosclerosis (thinning and toughening of arteries supplying blood to the cardiac muscles) have plasma fibrin clots that are thicker and less penetrated than healthy individuals.

The reduced fastening of tissue plasminogen activator and plasminogen to fibrin, decreased plasmin production on the clot surface and elevated cross-linking lead to the development of thick, less penetrable fiber with decreased lysability in diabetic (type 1 and type 2 diabetes) patients as evaluated against non-diabetic individuals

(Alzahrani and Ajjan 2010). Malformed fibrin clot with poor lysability add to the problem of hyperviscosity reported in retinal vein occlusion. Also in patients with end-stage renal disease, lesser permeable plasma fibrin clots, reduced fibrinolytic susceptibility, more rapid formation of protofibril and elevated clot fiber mass and size have been reported when compared with healthy persons (Undas et al. 2008). In normal circumstances, the blood brain barrier prevents circulating fibrinogen from flowing into the central nervous system while it passes through the brain and spinal cord vasculature (Davalos and Akassoglou 2012). But, in pathological situations like wound or diseases (such as Alzheimer disease), connected to infection, vascular disorder or inflammation, fibrinogen concentration is elevated and it flows into the central nervous system via the disrupted blood brain barrier. The combined effect of increased fibrinogen level and availability of Aβ peptide generate clots that are typically lysis-resistant in neurovascular diseases and this plays a significant role to reduce blood flow, increased infection and neuronal death (Ahn et al. 2010).

8.2.4 Management of Blood Coagulation Disorders

Antiplatelet, thrombolytic and anticoagulant agents are the three main classes of medications that are used for treatment of coagulation disorders. Antiplatelet agents are used to prevent coagulation of platelet, and among these medications are aspirin, dypyridamole, ticlopidine and glycoprotein IIb and IIIa (GP IIB and IIIA) inhibitors (Bhattacharjee and Bhattacharyya 2014) which may have excessive bleeding as side effects. Thrombolytic medications assist to lyze fibrin clots and these medications includes tissue plasminogen activator, urokinase also called urinary plasminogen activator, streptokinase and the modified recombinants. When streptokinase combines with plasminogen, the resulting streptokinase-plasmin complexes are more effective at lyzing fibrin clot than plasmin alone. However, the serious upshot of using these medications is excessive bleeding (Fedan 2003). Moreover, anticoagulants such as warfarin (Coumadin) and heparin which function by restricting and modifying stages in the coagulation cascade are also medications used but both drugs have many severe side effects.

Some fibrinolytic enzymes obtained from natural sources have been reported to have activities that resemble that of plasmin and plasminogen activators (Kotb 2012), but application in the prevention of development of abnormal fibrin clot is still yet to be reported. Also the prospect of these enzymes being upgraded into drugs is still at the stage of assumption or theory (Bhattacharjee and Bhattacharyya 2014). Similarly, phytochemicals from plant extracts have been used for lysis of blood clot. Recently, Devi et al. (2016) showed that leaf extracts of *Leucas aspera, Cynodon dactylon* and *Murraya koenigii* showed thrombolytic activities of 30.32–45.32%, proposing them to be new sources of natural thrombolytic agents, which can be used to improve the performance of clot buster enzymes such as Nattokinase and Staphylokinase. In recent times, various metallic nanoparticles have made inroads into various fields of science and technology and potential useful applications of

metallic nanoparticles as an alternative to conventional drugs or in combination with medical treatments mete against blood coagulation disorders have been reported in the area of biomedical sciences.

8.3 Nanoparticles

Nanotechnology is a vastly developing field which cuts across diverse fields of science and technology including physics, chemistry, biotechnology, medicine, material science and pharmacy (Huang et al. 2009). The study deals with the creation, exploitation and creation of nanometer sized materials (Rai et al. 2008). Metallic nanoparticles are metal particles whose size ranges fall within 1 and 100 nm, exhibiting different morphologies in terms of shapes which include sphere, rods and polygons. Often times, the extremely small-sized metallic nanoparticles display distinct and considerably interesting visible properties (optical, electronic, chemical, physical, catalytic, magnetic, antimicrobial among others) compared with the macro-scaled equivalents, and these have made syntheses and applications of metallic nanoparticles to be an attraction in various fields (Rai et al. 2009; Sau and Rogach 2010). Metallic nanoparticles, such as Cadmium (Cd), zinc (Zn), gold (Au), Titanium (Ti), Cu (copper), Silver (Ag), as well metal alloy nanoparticles, which have a high fraction of surface atoms, have been studied extensively because of the unique properties and higher surface area to volume ratio in contrast to the corresponding bulk materials (Kowshik et al. 2002).

8.3.1 Green Synthesis of Metallic Nanoparticles

Over the past few decades, wide varieties of synthetic approaches including physical and chemical methods have been employed in the synthesis of metallic nanoparticles. These methods include, ion exchange (Gamez et al. 2003), sol process (Qu et al. 2001), precipitation (Braun et al. 2001), pyrolysis (Senapati et al. 2005), reversed micelles (Ingelsten et al. 2001), ionizing radiation, radiolysis, heating technique, and laser irradiation (Abid et al. 2002; Huang and Yang 2004; Thirumalai et al. 2010) among many others with controllable size, shape and morphology. However, the problem associated with these methods is the requirement of the use of reducing agents such as sodium borohydride, sodium citrate and alcohols which are environmentally unfriendly with low nanoparticles production rate. Most of the chemicals are also toxic, flammable and also difficult to be disposed of as a result of environmental issues (Mohanpuria et al. 2008; Sharma et al. 2009). Furthermore, these methods are expensive and some of them involve the use of hazardous procedures (Ingle et al. 2008).

These problems have raised a lot of concerns in different areas of research in science and technology because of the need to protect human's health and the

environment; hence, the quest for methods which could effectively replaced the conventional methods of synthesis of metallic nanoparticles. The search for such methods has led to a "green" synthesis approach, involving the exploitation of cheap and ecologically friendly biological agents for the synthesis of metallic nanoparticles. The biological method has been proven to be a green approach in the synthesis of metallic nanoparticles due to availability of a wide range of biological resources such as bacteria (Lengke et al. 2007; Mokhtari et al. 2009; Samadi et al. 2009; Valdyanathan et al. 2010; Lateef et al. 2015c, 2016a; Ojo et al. 2016), fungi (Gade et al. 2009; Verma et al. 2010), plants' extracts (Mude et al. 2009; Raut et al. 2009; Sathyavathi et al. 2010; Lateef et al. 2015b, 2016b, c, d, e, 2017; Azeez et al. 2017a), enzymes (Lateef et al. 2015a; Lateef and Adeeyo 2015), as well as metabolites of arthropods (Singh et al. 2014; Lateef et al. 2016f, g). There are excellent reviews on the utilization of agrowastes, pigments, enzymes, arthropods and their metabolites for the benign and eco-friendly synthesis of nanoparticles (Adelere and Lateef 2016; Lateef et al. 2016h). These biological materials have abundance of biomolecules that can serve the purpose of simultaneous bioreduction of metal ions to metallic nanoparticles, and the capping of the biofabricated nanoparticles in a range of one-pot synthesis. The abundance of these biomolecules and diversity in occurrence are important factors that are driving the utilization of biological resources in creating myriads of nanoparticles of different properties and applications. The process is often simple, rapid and in several cases involves the use of aqueous extracts (Fig. 8.2).

Owing to their unique properties, various metallic nanoparticles have found useful applications in many areas of human endeavors and have remained a major attraction over the past several decades thus arousing the interests of many researchers in the field of science and technology. The usefulness of various metallic nanoparticles has been established in areas such as medicine, agriculture, paintings, fabrics, pharmacy, pollution control and technology (Kaida et al. 2004; Linkov et al. 2008; Skocaj et al. 2011; Weir et al. 2012; Azeez et al. 2017b; Olajire et al. 2017). Some of these are summarized in Table 8.1.

8.3.2 Application of Nanoparticles in the Management of Blood Coagulation Disorders

The incidence of bleeding as a consequence of administration of traditional anticoagulants has always been a major issue that requires constant monitoring. Coagulation system plays vital role in the balanced flow of blood, prevention of bleeding and spread of infectious agents (Esmon et al. 2011). Conversely, blood clots due to infection have injurious effects on tissues and organs and have ultimately led to cardiovascular disorders, allergic responses, injuries, cancer, and autoimmune reactions (Prandoni et al. 2007; Davalos and Akassoglou 2012). These conditions necessitate needs to control blood coagulation disorders. However, the development

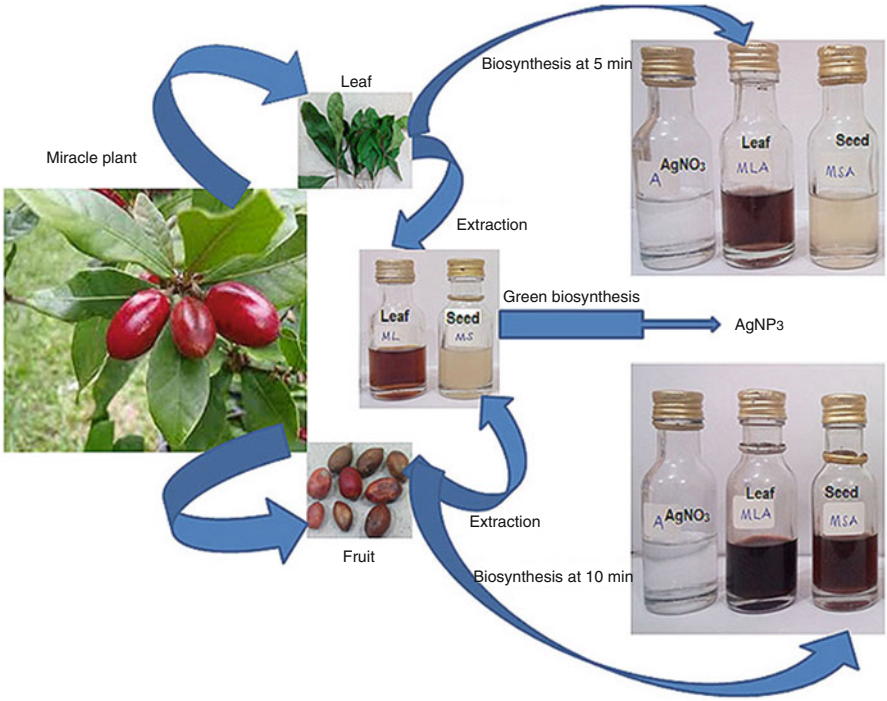

Fig. 8.2 Schematic view of the biosynthesis of AgNPs using leaf and seed extracts of *Synsepalum dulcificum* (Lateef et al. 2016d). Leaves and seeds of the plant were dried at room temperature, and then powdered. The powders were extracted in hot water, and the extracts were reacted with 1 mM $AgNO_3$ under benign condition to synthesize brown colloidal AgNPs with surface plasmon resonance of 438.5 and 440 nm for the seed and leaf extract-AgNPs respectively

of new anticoagulants is slow and that is why it is difficult to achieve the effect that can replace conventional anticoagulants (Tian et al. 2014).

Antiplatelet, anticoagulant and thrombolytic agents are the three principal classes of therapeutics used in the treatment of patients with thrombophilic disorders at present (Bhattacharjee and Bhattacharyya 2014). Several orally administered medications including aspirins, ticlopidine, dypyridamole and clopidogrel have been used to inhibit aggregation of platelets while intravenously administered glyprotein IIa and IIIa and non-steroidal anti-inflammatory drugs have also been used for the same purpose. Moreover, coumarin and heparin are commonly used anticoagulants as a result of the ability to alter coagulation cascades (Bhattacharjee and Bhattacharyya 2014), whereas thrombolytic medications including streptokinase, tissue plasminogen activator, urokinase as well as their recombinant alternatives serve to break up the fibrin clot. However, these medicaments have raised concerns due to eventual ill effects particularly, excessive bleeding that these drugs have on body system when administered (Fedan 2003).

Table 8.1 Applications of some important metallic nanoparticles

Type of nanoparticles	Applications	References
AgNPs	Electronics, silica-coated nanowires and electric circuits	Kvistek and Prucek (2005)
AgNPs	Silver- laden paper (hospital notes and medical files)	Dirienzo (2006)
AgNPs	Incorporation in interiors of automobiles and building materials	Blaser et al. (2008)
AgNPs	Antimicrobial additive in paint	Kumar et al. (2008), Gaylarde et al. (2011), Banach et al. (2014), Rajarathinam et al. (2014), Lateef et al. (2016b, c, f), and Oladipo et al. (2017b)
Ag and AuNPs	Anticancer	Bhattacharya and Mukherjee (2008) and Asharani et al. (2009)
Ag and AuNPs	Antimicrobial	Ahmad et al. (2013), Lateef et al. (2015a, b, c), Lateef et al. (2016a, b, c, f), Ojo et al. (2016), and Oladipo et al. (2017b)
AgNPs	Spermicides	Tolaymat et al. (2010)
AgNPs	Personal-care kits, female hygiene products, beauty soaps, cleansers and fabric softners	Luoma (2008)
AgNPs	Incorporation in textiles and fabrics	Tolaymat et al. (2010)
AgNPs	Larvicidal and mosquitocidal	Roopan et al. (2013), Lateef et al. (2016c), Azeez et al. (2017a), and Benelli (2016)
AgNPs	Coating medical tools used in surgery, anesthesiology, cardiology, and urology	Wijnhoven et al. (2009)
AgNPs and AuNPs	Enhanced healing of wounds	Dirienzo (2006) and Marazzi et al. (2007)
AgNPs	Coating of contact lenses and making artificial teeth	Wijnhoven et al. (2009) and Espinosa-Cristobal et al. (2009)
AgNPs, AuNPs and Ag-AuNPs	Synergistic effects with various antibiotics	Shahverdi et al. (2007), Lateef et al. (2015c), Azeez et al. (2017a), and Lateef et al. (2016f)
AgNPs	Orthopedics (additives in bone cement, bone prostheses and implant coatings for joint replacement)	Tolaymat et al. (2010)
AlNPs and TiNPs	Bone generation and repair	Sato and Webster (2004)
AgNPs	Integration into medical catheters, contraceptive devices, scaffolds, sterilization materials in hospitals, medical textiles and diabetic socks	Johnson et al. (2006) and Castellano et al. (2007)

(continued)

Table 8.1 (continued)

Type of nanoparticles	Applications	References
Magnetic iron oxide nanoparticles loaded with mitoxantrone	Anticancer	Lyer et al. (2006)
AuNPs	Identification, targeting and killing of tumor cells	Nam et al. (2009)
Magnetic iron oxide nanoparticles	Negative contrast agents	Laurent et al. (2008)
Super-paramagnetic iron oxide nanoparticles (SPIONPs)	Detection of neurodegenerative diseases	Cengelli et al. (2006)
SPIONPs	Atherosclerosis study	Hildebrandt et al. (2007)
AuNPs	Active sensors in detecting presence of analyte and its concentration	Sperling et al. (2008)
AuNPs	Detection of DNA and proteins	Krug et al. (1999) and Ni et al. (1999)

Arising from the use of these clinical drugs are many challenges. For instance, majority of these drugs have a short half-life, thereby necessitating repeated administration which may be very expensive and unaffordable. In fact their therapeutic effects are usually so high which may result to bleeding and hemorrhagic stroke with generation of antibodies that could neutralize the activities of recombinant coagulation factors, thus reducing the efficacy of drugs as well as producing detrimental side effects associated with clearance of immune complexes (Ilinskaya and Dobrovolskaia 2013). Modification of these clinical drugs into nanotechnology platforms is considered helpful to surmount these limits (Tian et al. 2014). Nanotechnology platforms are thus targeted at reducing the dosage, improving stability, attaining targeted delivery as well as overcoming immune recognition. A number of studies have shown the interactions of nanoparticles with blood through inhibition of platelets aggregation (Miller et al. 2009; Shrivastava et al. 2009). This makes metallic nanoparticles with anti-platelet or anticoagulant activity to be of huge importance in the development of antithrombotic nano-drugs (Tian et al. 2014). Largely, blood consists of two components; plasma proteins and cells. Therefore, the interaction of metallic nanoparticles with the blood can be grouped into two; and these are protein-nanoparticles interactions and blood cell-nanoparticles interactions (Shan and Bischof 2013). These interactions are capable of inducing downstream effects with medical impacts (Shan and Bischof 2013) (Fig. 8.3).

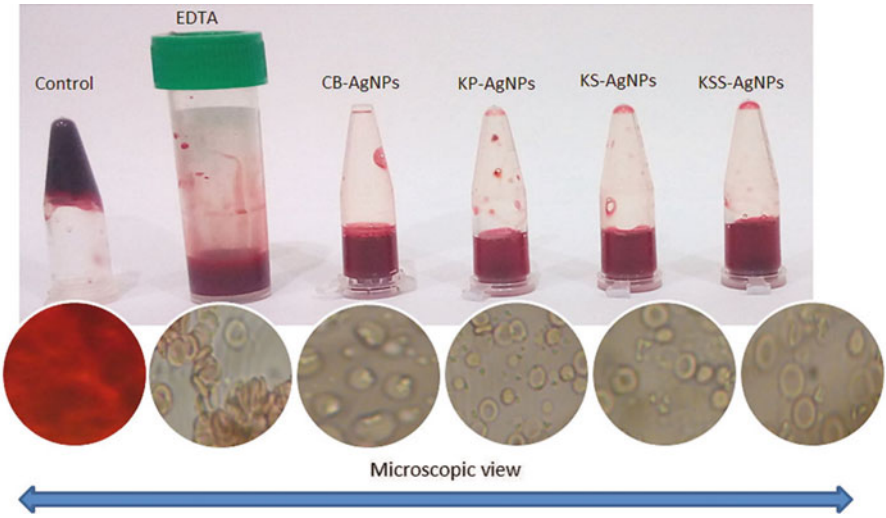

Fig. 8.3 Anticoagulant activities of biosynthesized AgNPs using extracts of cobweb (*CB*), kola pod (*KP*), kola seed (*KS*) and kola seed shell (*KSS*) (Lateef et al. 2017). Biosynthesized AgNPs were mixed with blood, and then observed for anticoagulation. EDTA was used as a positive control, while ordinary blood served as negative control. Smear from each tube was observed under optical microscope for cell morphological study. All the AgNPs prevented coagulation of blood, with the biconcave structure of red blood cell retained

8.3.2.1 Nanoparticles As Anticoagulants (Antithrombotics)

In order to ensure adequate blood flow and ultimately a healthy living, it is very important to exercise a good control over the coagulation system. Therefore, there is a need to prevent formation of thrombus (also known as blood clot) which is caused by aggregation of blood platelets (Shrivastava et al. 2009). Blood clots have deleterious effect on circulatory system and because of the association with various health threats including cardiovascular disorders, allergic responses, injuries, autoimmune reactions and cancer (Prandoni et al. 2007; Davalos and Akassoglou 2012). A number of authors have reported anticoagulant property of metallic nanoparticles. For instance, silver nanoparticles mediated by extracts of *Bacillus safensis* LAU 13, paper wasp nest, cobweb, pods, seeds and shell of *Cola nitida*, seed and leaf of *Synsepalum dulcificum,* as well as beans of *Theobroma cacao* prevented aggregation of platelets thus inhibiting the clot formation (Fig. 8.4) over an extended length of time as opposed to those without the nanoparticles (Azeez et al. 2017a; Lateef et al. 2016a, d, g, 2017). The result also compared well with EDTA-incorporated blood thereby suggesting the biosynthesized silver nanoparticles as excellent alternatives to the conventional drugs which are short-termed in circulation, capital intensive and as well have deleterious effects after a prolonged exposure of vital organs to such drugs. Similarly, we have demonstrated the use of gold, and silver-gold alloy nanoparticles as potent anticoagulants (Lateef et al. 2016e; Ojo et al. 2016; Oladipo

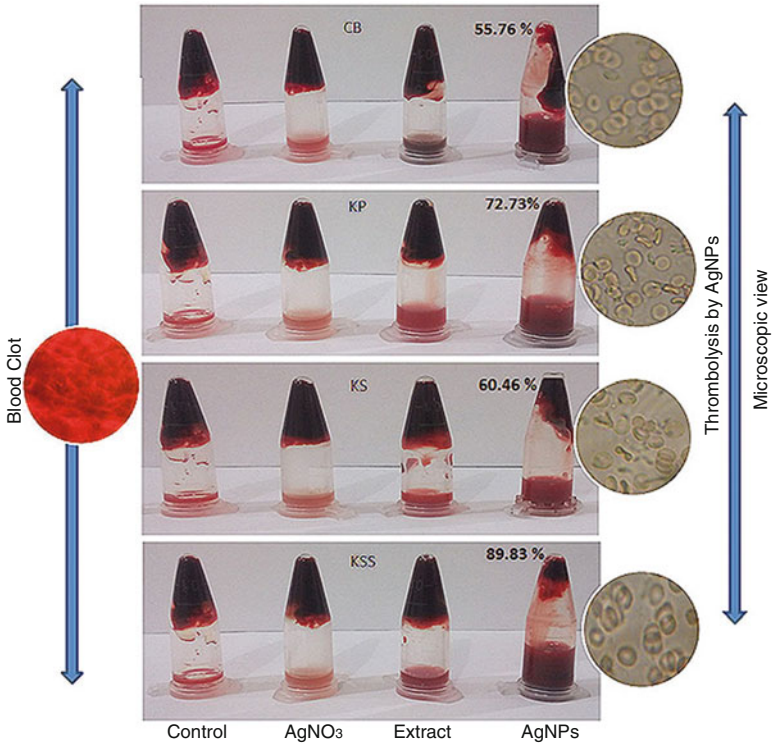

Fig. 8.4 Thrombolytic activities of biosynthesized AgNPs using extracts of cobweb (*CB*), kola pod (*KP*), kola seed (*KS*) and kola seed shell (*KSS*) (Lateef et al. 2017). Freshly prepared blood clot were exposed to biosynthesized AgNPs, and incubated together at 37 °C for 1 h, thereafter the tubes were inverted to release the lyzed clot. By difference, the weight of lyzed blood was obtained to determine thrombolysis (lysis of blood clot). The lyzed clots were examined microscopically to study the morphology of red blood cells. Extracts and $AgNO_3$ solution were used as control. The AgNPs caused tremendous dissolution of blood to the tune of 55.76–89.83%, with biconcave structure of red blood cell retained

et al. 2017a). These nanometer-sized metallic particles impinged differently on the blood, and are reported to be due to their compositions, sizes, shape and charge (Ilinskaya and Dobrovolskaia 2013; Ojo et al. 2016).

Non-metallic polystyrene nanoparticles of different sizes reportedly bound irreversibly to the surface of red blood cells after mixing, thereby leading to the improvement of blood circulation time (Chambers and Mitragotri 2004). Zhao et al. (2011) revealed that metallic nanoparticles of smaller sizes could bind to the membrane of red blood cells without inducing any deformity, whereas the larger sizes induced localized deformation of the membrane. For instance, mesoporous silica nanoparticles of approximately 100 nm in size bound to membrane of red blood cells without inducing any deformation on the cell membrane. However, large mesoporous silica nanoparticles of approximately 600 nm induced localized

membrane deformation and change in cell shape with subsequent hemolysis (Zhao et al. 2011). Cocoa bean mediated-AgNPs of diameter sizes between 8.96 and 54.22 nm showed antiplatelet activity which prevented coagulation of blood without any alteration in the morphology of the cells (Azeez et al. 2017a).

Gold nanoparticles had been used to engineer anticoagulant surfaces (Ehmann et al. 2015). Prior to the deposition of gold nanoparticles on surfaces, the ability of the nanoparticles to prevent coagulation was determined using activated partial thromboplastin time (aPTT) technique which involves addition of small volumes of nanoparticles to the blood plasma of patient suffering from blood coagulation disorder. It is the most essentially used method in diagnosis of a patient that is suspected to have coagulopathy. Subsequently, the activity of the gold nanoparticles immobilized onto solid substrate showed them as highly efficient anticoagulant after exhibiting prolonged coagulation time when reacted with blood plasma (Ehmann et al. 2015). Kim et al. (2013a), reported improvement in the anticoagulant activities of heparin coupled with gold nanoparticles that was biosynthesized using the earthworm extract. The heparin-gold nanoparticles produced improvement of 118.9% over the clotting time of heparin alone. In addition, Shrivastava et al. (2009) reported silver nanoparticles in a dose dependent manner to be highly effective for the inhibition of platelet functional responses such as secretion, aggregation, adhesion to immobilized collagen or fibrinogen and retraction of fibrin clot which are often mediated by integrin.

8.3.2.2 Nanoparticles As Thrombolytic Agents

The roles of metallic nanoparticles in dissolution of blood clot cannot be over emphasized. It is very paramount to sustain a balance and healthy biological system. In recent times, several potential applications of metallic nanoparticles as thrombolytic agents have been documented, thus providing a vista in nanomedicine to explore them as an alternative therapy (either singly or in combined forms with other molecules) against various blood coagulation system disorders and also to help reduce dependence on conventional therapy which often comes with various problems; typically serious bleeding complications associated with reocclusion and reinfarction (Ragaseema et al. 2012). Silver nanoparticles mediated by using wheat bran induced clot dissolution when added to preformed blood on clean glass plate within 5 min with high consistency when juxtaposed with the positive control containing the blood clot and sodium citrate (Harish et al. 2015).

Similarly, in our laboratory, we have demonstrated timely dissolution of blood clot using series of silver nanoparticles that were biosynthesized using extracts of paper wasp nest, cobweb, pod, seed and seed shell of kolanut, seed and leaf extracts of miracle fruit plant, and cell-free extract of *Bacillus safensis* LAU 13 (Lateef et al. 2016a, d, g, 2017). We have reported thrombolytic activities of 55.76–89.83% for some of these biosynthesized silver nanoparticles (Fig. 8.4). Similarly, biosynthesized gold nanoparticles using cell free extract of *Bacillus safensis* LAU 13 was able to induce the dissolution of clot when treated with blood clot within

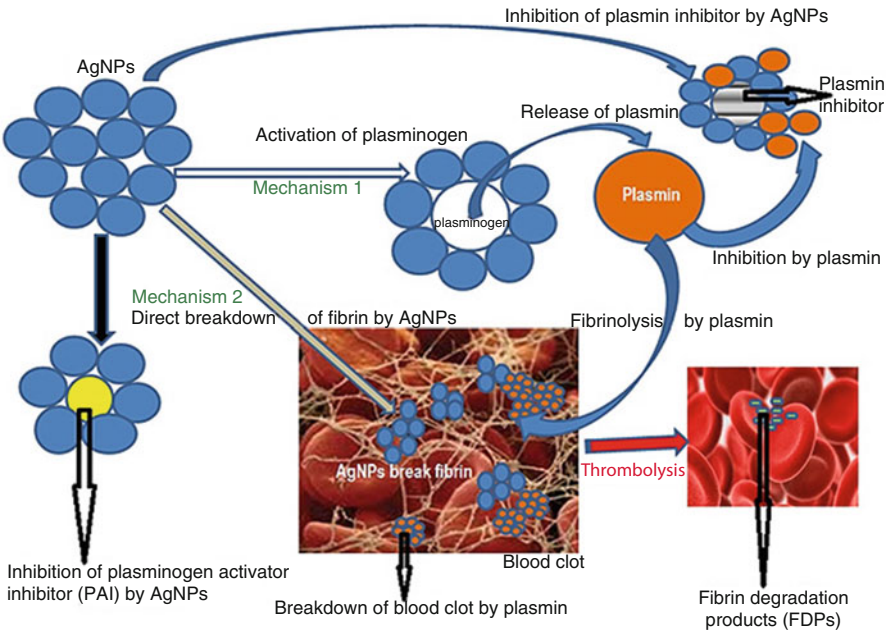

Fig. 8.5 The possible mechanisms of thrombolytic activities of the biosynthesized AgNPs (Lateef et al. 2016a, d). The nanoparticles can act directly on fibrin (mechanism 2) to break it down as evidenced from the plate assay of Harish et al. (2015). In the alternative, AgNPs can activate plasminogen to release plasmin which then breaks the blood clot (mechanism 1). In addition, the nanoparticles can inhibit the activities of inhibitors that may prevent activation of plasminogen and plasmin

5 min of reaction (Ojo et al. 2016), while similar results were obtained when silver-gold alloy nanoparticles biosynthesized using the leaf, pod, seed, and seed shell extracts of *Cola nitida* were used as thrombolytic agents (Lateef et al. 2016e). In a similar study, thrombolytic activities of 9.4–94.6% were achieved using gold nanoparticles that were biosynthesized using the cell-free extracts of non-pathogenic *Enterococcus* species (Oladipo et al. 2017a). We have recently proposed the mechanisms of thrombolytic activities of silver nanoparticles (Fig. 8.5). The nanoparticles can act directly on fibrin (mechanism 2) to break it down as evidenced from the plate assay of Harish et al. (2015). In the alternative, silver nanoparticles can activate plasminogen to release plasmin which then breaks the blood clot (mechanism 1). In addition, the nanoparticles can inhibit the activities of inhibitors that may prevent activation of plasminogen and plasmin. It is envisaged that the two mechanisms could occur together, thereby leading to the pronounced thrombolytic activities as obtained in these studies.

Shrivastava et al. (2009) also demonstrated and established that silver nanoparticles effectively inhibited functional responses of integrin-mediated platelets which include aggregation, adhesion to immobilized fibrinogen and retraction of fibrin clot in a dose-dependent manner and this report makes the nanoparticles a

potential antiplatelet therapeutic agent. Dextran-coated iron oxide nanoparticles have found application for magnetically targeted thrombolytic therapy. Urokinase was conjugated to the nanoparticles and local thrombolysis was achieved in vivo with an external magnetic field focused on the site of thrombus (Bi et al. 2009).

The D-phenylalanyl-L-prolyl-L-arginyl-chloromethyl ketone perfluorocarbon nanoparticles is an effective anticoagulant owing to apparent sequestration of numerous ligands at the site of thrombosis that continue to maintain prolonged surveillance against any subsequently activated thrombin after the initial binding event (Cicha 2015). These nanoparticles help in delaying localized occlusive thrombosis at the same time as rapidly minimizing systemic effects on bleeding times, and indeed appear more effective than a selected conventional anti-clotting agent. Although the drug is used as the active pharmaceutical ingredient in this case, the antithrombotic nanoparticles act as a unique inhibitor regardless of the drug that is conjugated to the particle. Rather than serving simply as a vehicle that delivers and releases an antagonist to the thrombin target, the particle holds onto the inhibitor and acts against thrombus formation by maintaining localized thrombin-absorbing surfaces that are not disabled after locating a thrombin target (Cicha 2015). The use of nanoparticles as anticoagulant and thrombolytic agents continues to unfolds, and poised to define milestone as novel nanomedical approach in the management of blood coagulation disorders.

8.3.2.3 Nanoparticles As Theranostic Agents

The term theranostics is made up of two words; therapeutics and diagnostics. Theranostics is defined as an integrated therapeutic system that provides therapy and helps in the diagnosis and monitoring of therapy through imaging (Warner 2004). Clinicians are able to identify responders and non-responders by imaging tumors during the course of treatment through theranostics. This is of importance in determining the correct line of treatment for an individual patient. Consequently, the diagnosis, treatment, and monitoring of the response to the treatment can be achieved using a single approach (Jeelani et al. 2014).

Nanoparticles may be highly useful for imaging applications because of the high surface area-to-volume ratio (relative to larger particles) as well as having the potential for numerous sites for chemical modification that may be used to amplify imaging sensitivity (Hahn et al. 2011). Metallic nanoparticles have gained momentous attention in recent years because of the unique physical (plasmonic resonance and fluorescent enhancement) and chemical (catalytic activity enhancement) properties. These properties make metallic nanoparticles appropriate for drug delivery and targeting (Cole et al. 2011). Owing to the larger surface area and area-to-volume ratio, several specific physicochemical properties have been exhibited by metallic nanoparticles, thereby useful for the treatment of cancer (cytotoxicity after interaction with cancer cells). In addition, owing to the aforementioned inherent properties, metallic nanoparticles have also been explored for diagnostic and imaging purposes (Ahmed et al. 2012; Khan et al. 2013; Li et al. 2013; McCarthy and Jaffer 2011;

Mukherjee et al. 2014). This emerging technology is now being applied in the management of blood coagulation disorders.

The leading causes of mortality worldwide have been linked to cardiovascular diseases including stroke and myocardial infarction. The distinctive fundamental pathology is the development of thrombi and vessel occlusion which could either be at the origin of thrombosis or at spots of embolization. As far as myocardial infarction is concerned, atherosclerosis is one key condition that contributes to the condition, and this is driven by an inflammatory response caused by apparatuses including oxidation and lipids build-ups (embolus) in the wall of the artery (Mackman 2008; Weber and Noels 2011).

Systemic administration of fibrinolytic drugs is the most active pharmacological therapy and administration of tissue plasminogen activator in the dissolution of the offending thrombus. Tissue plasminogen activator is the only therapy approved by the FDA for acute ischemic stroke treatment, however, dosing of the drug is often either deficient or disproportionate, and these lead to either low rates of thrombolysis or high rates of hemorrhagic problems and complications (Kim et al. 2013b). Nearly 60% of patients living with stroke die or become dependent on intravenous tissue plasminogen activator (Kirmani et al. 2012), but bleeding complications are quite common and this risk as such restricts the extensive use of the drug. Furthermore, due to non-availability of rapid non-invasive imaging technology, many thrombotic events are missed or diagnosed just only when ischemic damage has already occurred (Wang et al. 2016).

New diagnostic and therapeutic strategies are needed as patients present themselves at late stages of disease or more commonly, after cardiovascular events. In addition, sub-categories of patients do not respond to current therapeutic methods (Libby 2005). Therefore, the availability of various nanoplatforms provides the opportunities for better drug carrier design with imaging functionality (Duncan 2003; Peer et al. 2007). The nanoplatforms which are clinically pertinent include polymer-drug conjugates, dendrimers-polymer micelles, and liposomes amongst others. These nanoplatforms can conjugate or entrap drugs thereby offering a number of benefits over conventional preparations in certain applications (Duncan 2003). Due to the nano-sized particulate nature of nanomaterials, nanoplatforms can lengthen the circulation time of the drug and control drug release by delivery systems responsive to a stimulus such as pH, temperature, light, ultrasound, or enzyme degradation, leading to a desired drug release rate and concentration at the site of action (Tong and Cheng 2007). Additionally, one important advantage of nanoplatforms is the integration of diagnostic and therapeutic components with targeting moieties (Sahoo and Labhasetwar 2003; Bae et al. 2011). The exponential growth of the field of nanoplatform-based theranostics is an indication of advances in nanotechnology and the call for personalized medicine.

Theranostic approaches combining diagnostic and therapeutic capabilities in a single agent and imaging microbubble have attracted major attention, with the promise of specific, and individualized therapies with fewer side-effects for various diseases (Sun 2010; Kievit and Zhang 2011; Kelkar and Reineke 2011; Ahmed et al. 2012). The main advantage of theranostic methods is the ability to offer

simultaneous diagnosis and treatment, as well as the ability to dependably and appropriately monitor the outcome of the treatment (Wang et al. 2016). Nanoparticles that hold both therapeutic drugs and diagnostic labels are therefore popularly referred to as theranostic nanoparticles. Nonetheless, the field on nanotheranostics does not just focus on the use of theranostic nanoparticles, but also includes a variety of combinations of nanomedicine, targeted therapy, and imaging (Janib et al. 2010).

There are three distinct categories of nanotheranostics in terms of usefulness. First, the use of nanoparticulates as contrast agent-aided imaging to evaluate the effectiveness of therapy; second, the use of imaging to assess and evaluate nanotherapy; and third, the use of theranostic nanoparticles for the purpose of diagnosing, treating, and subsequently evaluating disease (Tang et al. 2012). In a 4-in-1 system, Mukherjee et al. (2014) demonstrated the green synthesis of AgNPs using the leaf extract of *Olax scandens* for nanobiomedical applications as antibacterial, anti-cancer, drug delivery vehicle, and imaging facilitator agent. Current computed tomography -based thrombus which is used in imaging involves the use of iodinated intravenous contrast to opacify the blood pool and indirectly demonstrate thrombi as filling deficiencies in the vessels (Jaberi et al. 2014). This method has a lot of limitations, the foremost problem being the failure to successively track cerebral thromboemboli in vivo and there are also difficulties in distinguishing between thrombus and underlying atherosclerotic plaque, both of which could contribute to stenosis or occlusion (Kim et al. 2015).

Kim et al. (2015) demonstrated direct imaging of cerebral thromboli using computed tomography and fibrin-targeted gold nanoparticles. Computed tomography-based fibrin-targeted glycol-chitosan coated nanoparticles produced was able to clearly image cerebral thromboembolism as well as carotid thrombosis better than the non-targeted agent used without showing any noticeable neurobehavioural or systemic toxicity both in in vitro and in vivo models of in situ thrombosis, embolic infarction and therapeutic thrombolysis. In addition, the conjugated nanoparticles in conjunction with micro computed tomography also made the visualization of recurrent and persistent thrombosis possible without necessarily giving additional doses of the particles. Presence or absence of targeting peptides on gold nanoparticles and physicochemical clot properties such as fibrin and gold nanoparticles concentration gradient-dependent diffusibility in this case were reported as part of the multiple factors that could influence the movement of synthesized gold nanoparticles into and within the clot thereby determining the equilibrium distribution of the imaging agent within the thrombus and blood compartments (Diamond and Anands 1993).

Various nanotechnological applications are being investigated for treatment of atherosclerosis and restenosis, including nanocarriers for drug delivery. Among such drugs used are cytotoxics that inhibit smooth muscle cell growth (e.g. paclitaxel, cytarbine, etoposides, doxorubicin), platelet-derived growth factor receptor antagonists and antibiotics. Encapsulation of drugs and biomolecules such as liposomes in nanoparticles provides protection from enzymatic degradation and allows for prolonged release profiles, and these therapeutic strategies have been thoroughly

reviewed (Brito and Amiji 2007; Buxton 2009). Therefore, particles integrating diagnostic imaging and therapeutic components, or "theranostic" agents, gained much recent interest as a valuable advance for drug delivery (Cyrus et al. 2008), with numerous potential advantages that allow precise, temporal and spatial monitoring of the therapeutic agent as well as treatment outcomes. In addition, due to the need for powerful magnetic fields and radio frequency waves in cardiovascular imaging by magnetic resonance imaging, theranostic nanoparticles have been used for the enhancement of cardiovascular imaging techniques (which includes T1, T2* and off-resonance) in order to produce a brighter contrast images during diagnosis of cardiovascular disease (Godin et al. 2010). Manganese nanoparticles have been effectively used as T1 enhancing contrast agent, while magnetite (Fe_2O_3 and Fe_3O_4) nanoparticles typically enhanced T2 (Cunningham et al. 2005; Sosnovik et al. 2008; Pan et al. 2009).

Sanhai et al. (2008) reported the ability of theranostic nanoparticles to monitor biodistribution and dynamics of nanoparticles in the body. Iron oxide nanoparticles-enhanced magnetic resonance imaging as a method for noninvasive imaging was used for the evaluation of drug therapy in patients with atherosclerosis, particularly peripheral artery disease. The condition often leads to reduced blood flow and oxygenation of tissue that consequently lead to claudication or critical limb ischeamia (Tang et al. 2009; Weinberg et al. 2011). Peters et al. (2009) produced a micelle-based theranostic nanoparticles, in which anti-coagulation drugs and peptides that specifically bind to clotted plasma proteins were incorporated into the synthesized nanoparticles. The nanoparticles showed specific in vivo targeting to atherosclerotic plaques as revealed by in vitro fluorescence imaging. When the nanoparticles were loaded with an anti-thrombosis peptide (hirulog), the nanoparticles showed better anti-thrombosis effects than the free hirulog even at the same molar concentrations in apolipoprotein E-deficient knockout mice (Peters et al. 2009). It is important to know that inhibiting angiogenesis is known to stop the progression of atherosclerosis (Moulton 2006). Using $alpha_v beta_3$-integrin paramagnetic nanoparticles doped with anti-angiogenesis drug, Winter et al. (2006) in an in vivo experiment evaluated response to treatment by measuring changes in signal enhancement in atherosclerotic plaques with the aid of magnetic resonance imaging. The decrease in the signal enhancement seen at the end of the treatment was clear indication of reduced angiogenesis and this showed the dual purpose characteristics of theranostic nanoparticles in atherosclerosis. Proliferation of smooth muscle cell is often times inevitable, especially after revascularization treatment. Lanza et al. (2002) reported the ability of antiproliferation drugs (doxorubicin and paclitaxel) loaded with perfluorocarbon nanoparticles to inhibit the proliferation of smooth muscle cells in vivo.

Moreover, it is important to know that plaques contain numerous inflammatory cells particularly macrophages and these can lead to inflammatory atherosclerotic plaques destabilization and disruption which could lead to stroke and myocardial infarction (Libby 2012). McCarthy et al. (2010) experimented with a novel theranostic platform that targeted macrophages. The synthesized iron oxide nanoparticles were coated with dextran loaded with near-infrared fluorophores and

phototoxic agents, and these specifically targeted macrophages. Once fluorophores were activated by light, apoptosis was induced in the targeted macrophages. In vitro histology staining revealed that the nanoparticles were able to induce considerable death of macrophages thus allowing free blood flow without obstruction and these also showed less skin toxicity compared to the photo-free phototoxic agents (McCarthy et al. 2010).

Nanoparticles for instance, perfluoroalkane nanoparticles were considered an artificial blood substitute to improve clinical outcome (Lanza et al. 2002; Braun et al. 2006). Perfluorocarbon nanoparticles previously considered as artificial blood substitutes (Tran et al. 2007; Cyrus et al. 2008); have been developed into a nanoplatform technology for targeting drug delivery and quantitative detection with the help of magnetic resonance imaging. Inhibition of stenosis was made easier and more effective using $\alpha_v ß_3$-targeted rapamycin nanoparticles (Cyrus et al. 2008). After treatment, histological analysis showed a drastic reduction in stenosis in the region of all affected arteries.

A lot has been done in the area of theranostics to create new and effectual therapeutic and diagnostic horizons against cardiovascular diseases including atherosclerosis, myocardial infarction, and stroke resulting from embolism. There are quite a large number of theranostic nanoplatforms, in which biodegradable and metabolizable polymer nanoparticles were designed and tested in small animal models. The advantages of these particles include biosafety, long circulation in life and loading of therapeutic and contrast agents with ease of assessment of biodistribution and targeting efficiency of conjugated or entrapped therapeutic agents.

8.4 The Future

The general understanding of some metal precursors used in the synthesis of nanoparticles as being inert materials may have deterred some investigators from considering these studies. Nevertheless, it is important to pay close attention to the reducing species employed in the synthesis of the metallic particles and see how best the process can be harnessed for the benefits of mankind. Completion of the characterization of synthesized metallic nanoparticles could be ensured in terms of size, shape and surface characteristics in the context of platelet interactions and coagulation pathway because future drugs that make use of new pathways would help in making decision on thrombolytic therapy for patients. Also, apart from concentrations of the metallic nanoparticles, more clarifications on the impact of sizes and shapes on blood as well as target-specificity could be made, so as to reduce the need for laboratory monitoring in treatment of various blood disorders.

8.5 Conclusion

Nanotechnological advancement through utilization of particles at nanoscale levels has so far been harnessed for the creation of new therapeutic horizons. Metallic nanoparticles have proven to be indispensable for treatments of various infections, prevention of microbial attacks and improvement of quality of impregnated-products. The increasing evidence in recent times have also suggested that metallic nanoparticles could be used in the area of nanomedicine to produce novel products which may have useful potential applications in the control and management of blood coagulation disorders, thereby mitigating the age long debilitating effects posed by conventional drugs when used for the treatment of various problems associated with blood coagulation disorders. However, clinical safety and feasibility of the use of metallic nanoparticles as potential nano-therapeutic agents must be assured prior to application in patients. It is evidently clear that nanomedicine offers a leverage to combat health issues and challenges in the twenty-first century, and it is a technology that is envisaged to drive beneficial healthcare in the future.

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Chapter 9
Cyclodextrin Nanosponges in Drug Delivery and Nanotherapeutics

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Abstract The drug delivery technology landscape has become highly competitive and rapidly evolving as more and more developments in delivery systems are being integrated to optimize the efficacy and cost effectiveness of therapy. Currently, extensive research in the field of nanotechnology and nanomedicines is ongoing with a major focus towards manipulating materials at nanoscale; which can subsequently lead to advancements in diagnosis, imaging as well as treatment of a broad spectrum of diseases. In wake of recent findings, cyclodextrin based nanosponges comprising of hyper-crosslinked cyclodextrin polymers, are trendsetting in modern times with nanostructured three-dimensional network. Nanosponges based systems can address the issues related to solubility, absorption, penetration, bioavailability, in vivo stability, and can achieve sustained and targeted delivery with maximum therapeutic efficacy for a number of pharmaceutical entities. Molecules having molar mass between 100 and 400 Da, and with less than five condensed rings can be easily entrapped into nanocavities. For synthesizing nanosponges, melt method, solvent method, quasi-emulsion solvent diffusion, ultrasound and microwave assisted method can be adopted. Nanosponges synthesized via microwave method exhibits narrow size distribution, and higher crystallinity and drug loading (~2 fold) than the counterparts synthesized via conventional methods. Among diverse types, carbamate nanosponges have notable ability of binding to the organic molecules with loading capacity of 20–40 mg per cm^3, and ~84% of dissolved organic carbon can be taken away from waste water; hence mostly used for water purification. However, polarity and flexible dimensions are the distinct features of carbonate nanosponges, and via synthetic reaction under different conditions, carbonate nanosponges can be obtained in amorphous or semi-crystalline form. Ester nanosponges have ability to host apolar organic molecules together with the cations, owing to presence of free polar carboxylic group. Lately, stimuli-responsive, intelligent or smart polymeric nanosponges have also been proposed for controlled delivery of low molecular weight and macromolecular drugs. In all, cyclodextrin nanosponges based drug delivery systems have achieved two to tenfolds improved stability, four to 25-folds enhanced solubility and three to fivefolds increased drug targeting efficiency; when compared to direct injection. The extension of nanosponges based drug delivery systems is an exhilarating and demanding research pasture, predominantly to overcome problems allied to existing formulations and for the further progressions in the field of pharmaceutical sciences and technology. Herein, nanosponges has been extensively reviewed as novel nanocarrier and adjunct with an all-inclusive focus on the suitability, versatility and characteristics of cyclodextrin based nanosponges for the promising applications in the fields of drug delivery and nanotherapeutics. Additionally in this chapter, development of nanosponges with a major focus on cyclodextrin based nanosponges has been well covered, and special importance has been given on discussing the preparation methods, characterization techniques and prominent applications of these novel drug delivery carriers for therapeutic purposes.

9.1 Introduction

A meteoritic rise in research towards developing new drug entities for substituting current drug delivery approaches and strategies has gained much focus in the wake of recent clinical findings as well as greater healthcare expenses. Advancement in technology has further augmented the study, production and development of new drug delivery tools. For optimizing a cost effective therapy, the ongoing research towards developing an advance drug delivery system is highly scrutinized. Further, novel categories of pharmaceuticals and biopharmaceuticals of drug delivery technology are boosting the progression for its development. Yet, to deliver these novel entities, the currently available conventional systems are neither feasible nor efficient. To address this snag, research towards developing localized and targeted delivery systems are gaining much attention (Osmani et al. 2015a; Saxena and Nacht 2005).

The term "nanotechnology" was coined in the year 1974 by Norino Taniguchi, a researcher from University of Tokyo, Japan (Taniguchi 1974). The term "nanotechnology" was then broadly defined as the design, synthesis and manipulation of structure of particles with dimension less than 100 nm (Sadowski 2010). Nanoparticles are sub-nanosized colloidal structures that are synthesised using synthetic or semi-synthetic polymers (Vyas and Khar 2004). In modern times, the synthesis of these sub-colloidal nanosized structures has become an integral part of research, for the various applications in the field of electronic, information storage, magnetic, material science, optoelectronic, sensing devices, catalysis, recording media, drug delivery and medicine (Mallikarjuna et al. 2011). The technology allows a researcher to engineer material properties through size control; which has further driven research in the direction of the potential uses for nanomaterials. The reduction of materials dimension has pronounced effects on diverse properties that may be significantly different from the corresponding bulk material (Benjamin and Bharathwaj 2011). These properties make the technology favourable towards reducing the number of doses, better treatment and cost effectiveness. Drugs those are difficult to administer due to the restricted solubility (E.g. paclitaxel), have been successfully overcome by these nano-based technologies. Recently, the technology is employed to deliver the existing, fully developed off-patented drugs, the so called "low-hanging fruit" of nanotechnology-based delivery. Hence, nanotechnology should not be overlooked as a single technique which only affect specific areas, but rather should be seen as a broad "catch-all" term for science which is benefiting a whole array of areas, from the environment, to healthcare, to hundreds of commercial products (Duncan 2006; Wen et al. 2016).

Owing to the remarkable efficiency in augmenting therapeutic index of many actives used in therapeutics, much research has been focussed in the field of nanotechnology and nanomedicine over the past few years. The major underlying reason that compromise the therapeutic index of these actives includes insufficient drug concentration at the site of action and the drug related toxic side effects. Additionally, development of resistance of the body cells towards actives due to

frequent use over a prolonged period of time leads to development of multidrug resistance, and this further retards the efficiency of therapy (Ali et al. 2011; Couvreur 2013; Riehemann et al. 2009; Sagnella et al. 2011). Moreover, this further complicates the therapy as the body develops resistance against those drugs too that have not been prescribed in the chemotherapy regimen (different chemical structure and mode of action). For almost four decades, extensive research on multidrug resistance has highlighted different ways via which cells escape the chemotherapy, further establishing the fact that for each and every drug resistance does exist, even for new chemical entities. This raises a question as how effective are the currently existing conventional chemotherapy for fatal diseases like cancer, and the concern remains over the frequency of multidrug resistance that is associated with the pharmacotherapy for such diseases (Chen 2010; Couvreur et al. 1977; Maeda et al. 2000; Matsumura and Maeda 1986; Lammers et al. 2012). This makes it quite clear that identifying and evading these drug related resistance can improve the efficacy of the currently existing therapy. This subsequently highlights the need for designing such effective formulations with the ability to bypass the "drug efflux barrier", presenting one of the major challenges that have to be overcome. Literature on research based on developing polymeric nanoparticles shows promising potential of these systems in terms of cellular uptake, in prevailing drug resistance by modulating or reversing the P-glycoprotein (P-gp) activity and thereby allowing controlled delivery of the drug with improved efficacy (Arima et al. 2010; Decuzzi et al. 2010; Ferrari 2005; Jeong et al. 2009; Liu et al. 2009; Maeda et al. 2013; Skinner et al. 1990; Wang et al. 2007).

Nanomedicine (medicine from nanotechnological origin) aims at improving the current existing drug delivery systems and treatment via use of nanoparticulate systems. Also parameters such as solubility, pharmacokinetics, distribution as well as sustained release and cellular targeting of drugs can be improved by utilizing these nanosystems (Allen and Cullis 2013; Desai et al. 2006; Gabizon 2001; Wang and Thanou 2010). Intracellular delivery of drugs using nanoparticles and efficient penetration of nanoparticles were first discovered by "Couvreur" (Desai et al. 2006; Lee et al. 2011). Further, active or passive targeting enables site and tissue specific delivery of drugs (Guo et al. 2008; Trotta and Tumiatti 2003). Till date, umpteen nanoparticulate systems have been synthesized, fabricated and explored like nanoparticles, dendrimers, nanocrystals, micelles, nanotubes, liposomes, inorganic structures (Dodziuk 2006; Girek and Ciesielski 2010; Li and Ma 1999, 2000; Swaminathan et al. 2007; Vyas et al. 2008), to list a few. Surprisingly, out of the numerous systems claiming to have achieved effective targeting with minimized toxic effects (Trotta 2011), the FDA approval has only been granted to few of these innovations and have been marketed (Cavalli et al. 2007a; Duchene et al. 1999). Therefore, a persistent need of research for developing novel supramolecular nanostructures, nanocarriers and biomaterials to address the limitations associated with already existent and new active pharmaceutical ingredients (APIs) still remains in pipeline.

Recently in the field of nanotechnology, for diagnostic and therapeutic purposes, focus has been heightened towards developing supramolecular assembly of simple components. Presently, mesoporous and nanoporous (organic and inorganic nanosponges) systems are being assessed for potential applicability in the field of

drug delivery and nanotherapeutics (Bilensoy et al. 2008; Cavalli et al. 2007b). Risks associated with biodegradability complications of metal based inorganic systems leading in vivo toxicity, has directed the research towards organic nanosystems. Hence, nanoscale based biomaterials possesses structural characteristics that are expected to impart potential applications in the field of drug delivery and nanotherapeutics. Therefore, keeping in mind all the potential benefits and drug delivery efficiency offered; cyclodextrin nanosponges based approaches, current progress and outcomes have been profusely covered in this chapter along with promising applications in the field of drug delivery and therapeutics.

9.2 Cyclodextrins

9.2.1 Structure and Properties of Cyclodextrins

In the early 1950s, fundamental physicochemical characteristics of cyclodextrins were discovered, and thereafter, cyclodextrins are known and used as realistic as well as cost-effective way to enhance the physicochemical and pharmaceutical properties viz. stability, solubility, and bioavailability of drug molecules (Osmani et al. 2015b). Cyclodextrin compounds are majorly classified into three classes such as hydrophilic, hydrophobic, and ionic derivatives (Loftsson and Brewster 1996). These compounds belong to the family of compounds (cyclicoligosaccharides) which are made up of sugar molecules bound together in a ring. Enzymatic degradation of starch via cyclodextrin-glycosyltransferase leads to the production of cyclic oligomers (Radi and Eissa 2011). Cyclodextrins are crystalline, non-reducing, water soluble, and cyclic oligosaccharides composing five or more anhydrous α-D-glucopyranoside units (AGU) (Bricout et al. 2009) connected together via a-1,4-bond (Dodziuk 2006). Generally, six, seven or eight AGU are present in cyclodextrins, and are known as α, β and γ-cyclodextrin, respectively (Fig. 9.1). Molecules of cyclodextrins are like cone in shape with secondary hydroxyl groups at C2 and C3 positions (as a result of chair formation of glucopyranose units), widening from the broad edge, and also with primary hydroxyl groups at C6 position exposed from opposite side of the narrow edge (Girek and Ciesielski 2010; Radi and Eissa 2011). Atomic arrangement of these molecules shows cylindrical cavity (hydrophobic inner part) and truncated cone (hydrophilic outer part) (Li and Ma 1999; Swaminathan et al. 2007). Moreover, cyclodextrins have well-defined cylindrical cone structure containing a cavity of about $5–10 \times 10^{-10}$ m in diameter and $7.9–8 \times 10^{-10}$ m deep, depending on the number of glucose units (Li and Ma 2000). Several key characteristic features of α, β, and γ-cyclodextrins are listed in Table 9.1 (Bilensoy and Atilla Hincal 2010; Osmani et al. 2015b; Vyas et al. 2008).

Besides, cylindrical cavity of cyclodextrins expresses apolar character with Lewis base properties and high electron density (Loftsson and Brewster 1996). Basically, cyclodextrins have structure like a cage (as mentioned in Table 9.1), and because of

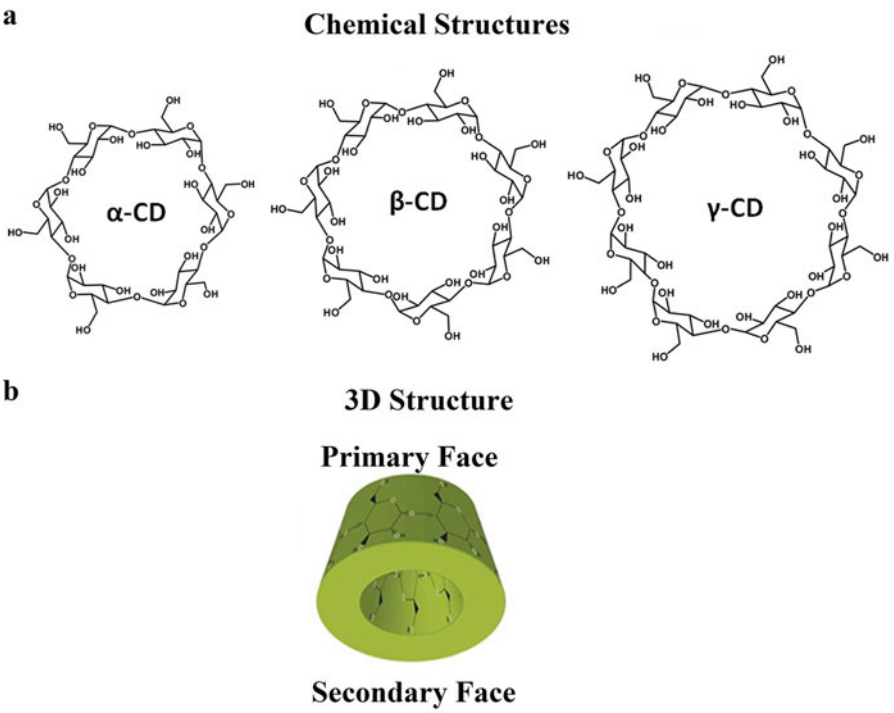

Fig. 9.1 Cyclodextrins (CDs) are cyclic oligosaccharides consisting five or more anhydrous α-D-glucopyranoside units (AGU) connected together via a-1,4-bond. See (**a**) chemical structures and (**b**) 3D structure of α-, β- and γ- cyclodextrin with six, seven and eight AGU, respectively

Table 9.1 Important characteristic features of α, β and γ-cyclodextrins

Characteristics	α-cyclodextrin	β-cyclodextrin	γ-cyclodextrin
Molar mass (g mol^{-1})	972	1135	1297
Internal diameter (10^{-10} m)	4.9	6.2	7.9
External diameter (10^{-10} m)	14.6	15.4	17.5
Depth-height cone (10^{-10} m)	7.9–8	7.9–8	7.9–8
Cavity volume	174	262	472
Water solubility (g per 100 cm^3) at 25 °C	14.5	1.85	23.2
Crystal water (m, %)	10.2	13.2–14.5	8.13–17.7

the peculiar shape, cyclodextrins are able to form stable inclusion complexes with molecules having suitable size and polarity in aqueous solutions. Covalent bonds absence and driving force presence for the complex formation by release of enthalpy-rich water molecules from the cavity part is the mechanism for complexation.

For improving the characteristics of native cyclodextrins, various derivatives have been synthesized. Cyclodextrins act as novel drug carriers owing to the ability to form a complex with wide range of compounds (Duchene and Bochot 2016;

Trotta and Cavalli 2009). Furthermore, cyclodextrins play vital role as multi-functional drug carriers, followed by inclusion complexes or via formation of cyclodextrin-drug conjugates (Celebioglu et al. 2014; Kaur et al. 2015; Liu et al. 2014). Above 30% of new pharmaceutical goods comprising cyclodextrins are in the global market (Vyas et al. 2008). To enhance the loading capacity of particulate drug delivery systems such as nanoparticles, liposomes, and microparticles, cyclodextrins as well as cyclodextrin derivatives have been employed as solubilizers (Swaminathan et al. 2010a). One of the examples of polymeric nanoparticles containing cyclodextrins is nanoparticles of poly(butylcyanoacrylate). To get the nanoparticulate systems, modified cyclodextrins have also been implemented as matrices (Erdogar et al. 2016; Huarte et al. 2016; Iohara et al. 2016). Modification of cyclodextrins on the secondary face with C6 aliphatic esters via nanoprecipitation technique has been made to form the nanospheres and nanocapsules (Trotta et al. 2007). Due to low intrinsic solubility of the drug or because of the low stability constant of a drug-cyclodextrin complex, the efficiency of solubilizing may be insufficient, and therefore, researchers are gaining so much of interest in cyclodextrin complexes, and the end product is an inventive nanosponge. β-cyclodextrin has the highest complex forming ability and stability with crosslinking agents as compared to other natural cyclodextrins (α- and γ-cyclodextrin) and hence, nanosponges are usually prepared by using β-cyclodextrin. β-cyclodextrin possess exhilarating characteristics, helping to form nanochannels to incorporate the drug molecule in cage and its complex network. Furthermore, cavity dimensions and economy as well as higher productions are some of the advantages of β-cyclodextrin (Trotta et al. 2009). In a research study, different types of cyclodextrins have been reacted with crosslinkers such as a carbonyl or dicarboxylate compounds, confirming the superiority of β-cyclodextrin (Swaminathan et al. 2010a; Trotta et al. 2012). Consequently, β-cyclodextrin became widely accepted and preferred for the fabrication of nanosponges. Diverse techniques are available for the fabrication of nanosponges by using such materials.

9.3 Nanosponges

Nanosponges are novel colloidal structures derived from a new category of hyper-crosslinked polymers, and comprising of solid colloidal nanoparticles with cavities of nanosized. Nanosponges have three dimensional network or scaffold with a long length polyester backbone. The polymer in solution form is mixed with a small molecule, crosslinker, which acts like small seizing locks to hold different parts of the polymer together, thereby forming roughly spherical particles with cavities to store the drug molecules in it. The polyester breaks down gradually in body owing to its biodegradable nature, and as a result, it releases the drug molecule in a predictable fashion. Numerous nano systems unload the drug molecules in rapid and uncontrolled fashion after reaching to the target (recognized as burst effect), leading to difficulty in determination of effective dosage levels. On the contrary,

nanosponges offer foremost advantage of predictable release of drug molecules from the system as compared to other nano based delivery systems (Osmani et al. 2015b, 2016a).

Moreover, other primary benefit of nanosponges is that nanosponge particles are water soluble. Encapsulation of drug molecule in nanosponges allows the use of hydrophobic drugs; which are difficult to dissolve readily in water. This phenomenon avoids the mixing of drug with adjuvant reagent which may reduce the efficacy of drug and can acquire adverse effects. Furthermore, by varying the proportion of polymer to crosslinker, it is possible to control the size of nanosponges particles (nanosponges particles can be tailored). As per the research, the drug delivery systems smaller than 100 nm (about the profundity of the lowest points on the surface of a compact disc) have shown the best performance. Another benefit of these systems is the simple chemistry required, and thus, researchers have developed simple high-yield "click chemistry" methods to fabricate nanosponges particles, and for attaching the linkers which are made from the peptides. Unlike nanosponges, other drug delivery systems need complicated chemistry which is intricate to scale up for the commercial production. In addition, the type and nature of polymer determines the type of nanosponges to be fabricated, and hence, various types of nanosponges can be designed and developed on the basis of polymer used. Few well-known examples of nanosponges include titanium-based nanosponges (Guo et al. 2008), silicon nanosponges particles (Farrell et al. 2006), hyper-crosslinked polystyrene nanosponges (Dakankov et al. 1996) and cyclodextrin based nanosponges (Bencini et al. 2008; Binello et al. 2008; Cavalli et al. 2009; Li and Ma 1998; Moya-Ortega et al. 2012; Swaminathan et al. 2010a). Cyclodextrin based nanosponges have gained vast consideration amongst all the types, and thus widely studied.

9.3.1 Salient Features of Nanosponges

- Nanosponges disclose the dimensions in the range of 1 μm or less with tunable polarity of voids. Nanosponge particles are of specific expected size, and variable polarity could be synthesized via adopting different polymer: crosslinker proportions (Trotta et al. 2007).
- Based on the applied synthesis conditions, nanosponges may either be crystalline or para-crystalline in nature. By point of drug complexation, crystal structure of nanosponges is extremely important, as degree of crystallization significantly affects loading efficiency of nanosponges. As per the literature, para-crystalline nanosponges have shown a range of drug loading ability (Swaminathan et al. 2010a).
- Nanosponges are proven to be stable across the pH range of 1–11, and also upto 130 °C.
- Nanosponges are non-toxic, biodegradable, and porous polymeric entities which can resist higher temperature (Subramanian et al. 2012).

- Encompassing a three dimensional structure, nanosponges offer encapsulation, transportation, and perceptive release of APIs as well as other numerous compounds.
- Nanosponges give clear to opalescent colloidal suspension in water, and could be easily regenerated via solvent extraction, thermal desorption by ultrasound and microwaves (Setijadi et al. 2009).
- Targeted delivery of encapsulated substances can be achieved due to ability of nanosponges to link with different functional groups, which can be further improved through chemical linkers primarily binding to the target sites.
- By loading magnetic properties in a system of nanosponges by addition of ferrite and other magnetic agents during synthesis, external magnetic field can also be applied for targeted release (Swaminathan et al. 2010a).

9.3.2 Materials Used for Nanosponges Preparation

The list of polymers and crosslinkers mostly used for synthesizing nanosponges are presented in Table 9.2.

9.3.3 Factors Influencing Nanosponges Formation

9.3.3.1 Type of Drugs and Medium Used for Interaction

Apart from the type and nature of polymer and crosslinker used, type of drugs to be loaded and solvents can also affect the nanosponge formation. Drug molecules should possess precise characteristics to get entrapped in nanocavities successfully. Molecules having molecular mass between 100 and 400 Da, and with less than five condensed rings can be easily entrapped into nanocavity. Melting point of molecules should be under 250 °C and solubility should be less than 10 mg/ml in water (Osmani et al. 2016a; Vyas et al. 2008). Compounds with higher melting points do not hold higher stability constant values after loading in the nanosponges and

Table 9.2 Generally used polymers and crosslinkers for the synthesis of nanosponges

Polymers	Hyper cross linked polystyrenes, cyclodextrins and cyclodextrin derivatives like methyl β-cyclodextrin, alkyloxycarbonyl cyclodextrin, 2-hydroxy propyl β-cyclodextrin and copolymers like poly(valerolactone-allylvalerolactone), poly (valerolactone-allylvalerolactoneoxepanedione), ethyl cellulose and polyvinyl alcohol
Crosslinkers	Diphenyl carbonate, diarylcarbonates, di-isocyanates, pyromellitic anhydride, carbonyldiimidazole, epichloridrine, glutarldehyde, carboxylic acid dianhydrides, 2,2-bis(acrylamido) acetic acid and dichloromethane

therefore, the stable complexes between drugs and nanosponges are unable to obtain. Briefly, higher melting point of drug notably affects the drug loading. Moreover, with melting of compounds at higher temperature, lower loading of drug can be observed; which can be attributed to the structural rigidity of compound. Medium plays important role in interaction between nanosponge cavities and targeted compounds; hydrophilic medium will oblige the organic guest molecules into the hydrophobic cavities and an organic solvent tends to release the organic molecules trapped in nanosponges. This powerful attraction between host and guest molecules lies on optimized physical and chemical interactions like structural properties, size, mutual matching of polarity, and hydrophobic environment (Li and Ma 1999).

9.3.3.2 Type of Polymers and Crosslinkers

Type of polymer used can affect the performance and formation of nanosponges. Capable crosslinkers switch molecular nanocavities into three dimensional nanoporous structures. Consequently, by changing the degree of crosslinking, either hydrophilic or hydrophobic components are formed that can entrap targeted compounds. Water soluble or insoluble nanosponge structures are formed depending on the nature of crosslinkers (Guo et al. 2016; Vyas et al. 2008).

Hydrophilic nanosponges can be synthesized by application of epichlorohydrin as a crosslinker (Girek and Ciesielski 2010; Li and Ma 1999; Rajeswari et al. 2005). Such nanosponges can modify drug release rate with improved drug absorption across the biological barriers, and can also be used as an effective drug carrier in immediate release formulations. Hydrophobic nanosponges can be developed by application of diphenyl carbonate (Cavalli et al. 2006a; Modi and Tayade 2007; Swaminathan et al. 2007, 2010b; Trotta and Cavalli 2009) or pyromellitic anhydride (Mele et al. 2011), diisocyanates (Layre et al. 2005; Swaminathan et al. 2007) and carbonyldiimidazoles (Ansari et al. 2011a; Swaminathan et al. 2009; Torne et al. 2010; Trotta and Cavalli 2009; Trotta and Wander 2005) as crosslinkers, and may act as carriers for sustained release drug delivery of hydrophilic drugs including proteins and peptides (Swaminathan et al. 2010a; Trotta et al. 2007). Table 9.3 represents different examples of polymers used with preparation method of nanosponges, and potential application as reported in the literature.

9.3.3.3 Degree of Substitution

Nanosponges complexation ability may get influenced by number, position, and type of the substituent on the polymeric molecule (Rajeswari et al. 2005; Semalty et al. 2014). The type of substitution is crucial as the β-cyclodextrin derivatives are broadly available in various forms by means of differing in functional groups present on the surface of cyclodextrin derivative. When complexed together via crosslinker, different types of complexed material (β-cyclodextrin nanosponges, cyclodextrin-carbonate nanosponges, cyclodextrin-carbamate nanosponges) can be obtained by

Table 9.3 Nanosponges prepared by diverse methods along with the potential applications

Polymer	Method of preparation	Reported particle size	Use	References
Titanium dioxide	Co-polymerizing polymerizable surfactants with styrene	100–130 nm	Coating of polystyrene microspheres	Guo et al. (2008)
Cyclodextrins and cyclodextrin derivatives	Simple thermal desorption, extraction with solvents and/or use of microwave and ultrasound techniques (diphenylcarbonate or pyromellitic anhydride as crosslinkers)	Below 500 nm	For solubility enhancement, cytotoxicity, haemolytic, antifungal, antiviral activity	Cavalli et al. (2006b), Osmani et al. (2016a) Swaminathan et al. (2010b), and Trotta and Cavalli (2009)
β-cyclodextrin and copolyvidonum	Simple thermal desorption, extraction with solvents and/or use of microwaves and ultrasounds	NQ[a]	Saturation solubility study	Mele et al. (2011)
Ethyl cellulose and polyvinyl alcohol	Emulsion solvent diffusion method	230–470 nm	Antifungal, irritation study	Sharma et al. (2011)
Poly(valerolactone allylvalerolactone) and poly (valerolactone – allylvalerolactone-oxepanedione)	Crosslinking using targeting units, e.g., peptides	NQ[a]	Drug release study	Trotta et al. (2012)

[a]*NQ* Not quoted

different functional groups. The degree of crosslinking and number of substitutions present are proportional to each other directly, thereby suggesting that higher number of substituents could led to the greater probability of undergoing higher degree of crosslinking that can yield highly porous nanosponges as an outcome of more interconnections between polymers, resulting in the mesh type network formation. Also, the position of substitution depends on the diverse conditions of system production. Change in process of production could lead to the formation of materials with different physicochemical properties due to occupancy of different position by functional group on parent compound. For an instance, physicochemical properties of hydroxypropyl-β-cyclodextrin (HP-β-CD) samples with same degree of substitution may not be identical if produced under different production conditions; which could be attributed to the probable residence of hydroxypropyl groups on parent cyclodextrin molecule at

different positions. Hence, the production processing and purity of material have significant impact on final quality of nanosponges, demonstrating the importance of degree of substitution of polymer.

9.3.3.4 Complexation Temperature

As mentioned above, the type and nature of polymer determines the type of nanosponges which is to be fabricated, and hence, various types of nanosponges can be designed and developed on the basis of polymer used. Few well-known examples of nanosponges include titanium-based nanosponges (Guo et al. 2008), silicon nanosponges (Farrell et al. 2006), hyper-crosslinked polystyrene nanosponges (Dakankov et al. 1996) and cyclodextrin based nanosponges (Binello et al. 2008; Cavalli et al. 2009; Li and Ma 1998; Moya-Ortega et al. 2012; Swaminathan et al. 2010a). Cyclodextrin based nanosponges have gained vast consideration amongst all the types of nanosponges, and thus widely studied.

9.4 Cyclodextrin Based Nanosponges

The ability of cyclodextrins is the inclusion of various compounds with compatible size and polarity with the cavity. On the other hand, certain hydrophilic compounds or macromolecules cannot be included in native cyclodextrins. In addition, β-cyclodextrin causes toxicity after intravenous administration and also has low aqueous solubility (1.85% w/w at 25 °C), and hence, to conquer these drawbacks and to obtain suitable materials for the pharmaceutical applications, numerous efforts have been taken for chemical modification of cyclodextrins. Literature have described the well-structured molecules and random mixtures, and dimers, trimers, and polymers have also been obtained (Gidwani and Vyas 2014; Mohtar et al. 2016; Ouerghemmi et al. 2016; Tripodo et al. 2013; Trotta et al. 2012; Tungala et al. 2013). Many synthetic approaches envisage cyclodextrin based polymers and nanosponges fabrication (Berto et al. 2007; Cavalli et al. 2010; Gelderblom et al. 2001; Lembo et al. 2013; Lundberg 2011; Malingre et al. 2001; Osmani et al. 2016b; Seglie et al. 2011; Swaminathan et al. 2013).

Long time ago, insoluble crosslinked cyclodextrin polymers were first reported by reacting parent cyclodextrin with epoxides, dialdehydes, diacyl chlorides and epichlorohydrin. In 1998, the term cyclodextrin nanosponge was first used by DeQuan Li and Min Ma. Li and Ma were the first researchers who reported the preparation of cyclodextrin based nanosponges by β-cyclodextrin crosslinking with diisocyanates for the production of inexplicable network possessing higher inclusion capacity towards the organic pollutants (Agueros et al. 2009; Swaminathan et al. 2016). However, Trotta et al. have anticipated the nanosponge's possible applications as nano drug delivery system followed by developing cyclodextrin based nanosponges by means of reaction of native cyclodextrin and crosslinker (Osmani et al. 2016a). Afterwards, numerous efforts have

been taken for the synthesis of nanosponges by using various crosslinkers with different synthesis conditions and ratios (Cavalli et al. 2010; Cina et al. 2017; Moreira et al. 2016; Shende et al. 2015a, b).

Crosslinking of cyclodextrins has led to a production of solid nanoporous system with numerous interconnected nanochannels, and when analyzed by techniques such as FT-IR, solid state NMR, and Raman spectroscopy, results revealed that primary hydroxyl groups of cyclodextrins chiefly concerned the network formation. As the of structure nanosponges grips both the hydrophilic as well as hydrophobic domains, nanosponges can skilfully encapsulate various agents by inclusion and non-inclusion complexation (Kaur et al. 2015; Swaminathan et al. 2016; Trotta et al. 2012). Schematic structures of cyclodextrin nanosponges synthesized using different crosslinkers are depicted in Fig. 9.2. For diverse biomedical applications, carbonyl compounds like carbonyldiimidazole or diphenyl carbonate can be used as crosslinkers to obtain carbonate nanosponges with spherical morphology and size less than 500 nm (Bilensoy and Atilla Hincal 2010; Duchene and Bochot 2016).

For nanosponges, linear dextrins and diverse types of cyclodextrins (α, β, and γ) are used as building blocks. Nanosponges with flexible properties enable them for drug delivery via diverse routes including the oral route. Also, the porous nature of nanosponges matrix provides the ease of loading different molecules such as hydrophilic or hydrophobic ions, liquids, and macromolecules (Ansari et al. 2011b; Hamada et al. 2006; Mognetti et al. 2012; Park 2010; Torne et al. 2010). Moreover, β-cyclodextrin nanosponges hold the gas encapsulation potential and hence, have positively depicted better storing capability for oxygen, carbon dioxide, and 1-methylcyclopropene (Cavalli et al. 2010; Seglie et al. 2013; Torne et al. 2013).

9.4.1 Methods of Cyclodextrin Nanosponges Preparation

To synthesize cyclodextrin-based nanosponges, either melt procedure or solvent method is used. Briefly, nanosponges are the result of crosslinking of different types of cyclodextrins with a crosslinker, carbonyl or a dicarboxylate compound (Swaminathan et al. 2010a). Numerous crosslinkers may modulate significant parameters like hydrophilicity, hydrophobicity and swellability of the end nanoporous polymer.

In case of melt procedure, crosslinker is treated with cyclodextrins to melt, and all the ingredients are homogenized properly and transferred in a 250 ml capacity flask followed by heating at 100 °C. The reaction is generally carried out under magnetic stirring for 5 h. Finally, the reaction mixture is allowed to cool and final product is broken down followed by repeated washing with suitable solvents for removal of unreacted excipients as well as by-products.

In case of solvent method, the melting step is removed. Crosslinker is solubilised in solvents like dimethylsulfoxide (DMSO) or dimethylformamide (DMF) and the polymer is generally treated with a suitable solvent (mostly a polar aprotic solvent). Polymer mixture is then added to the excess quantity of cross linking agent and

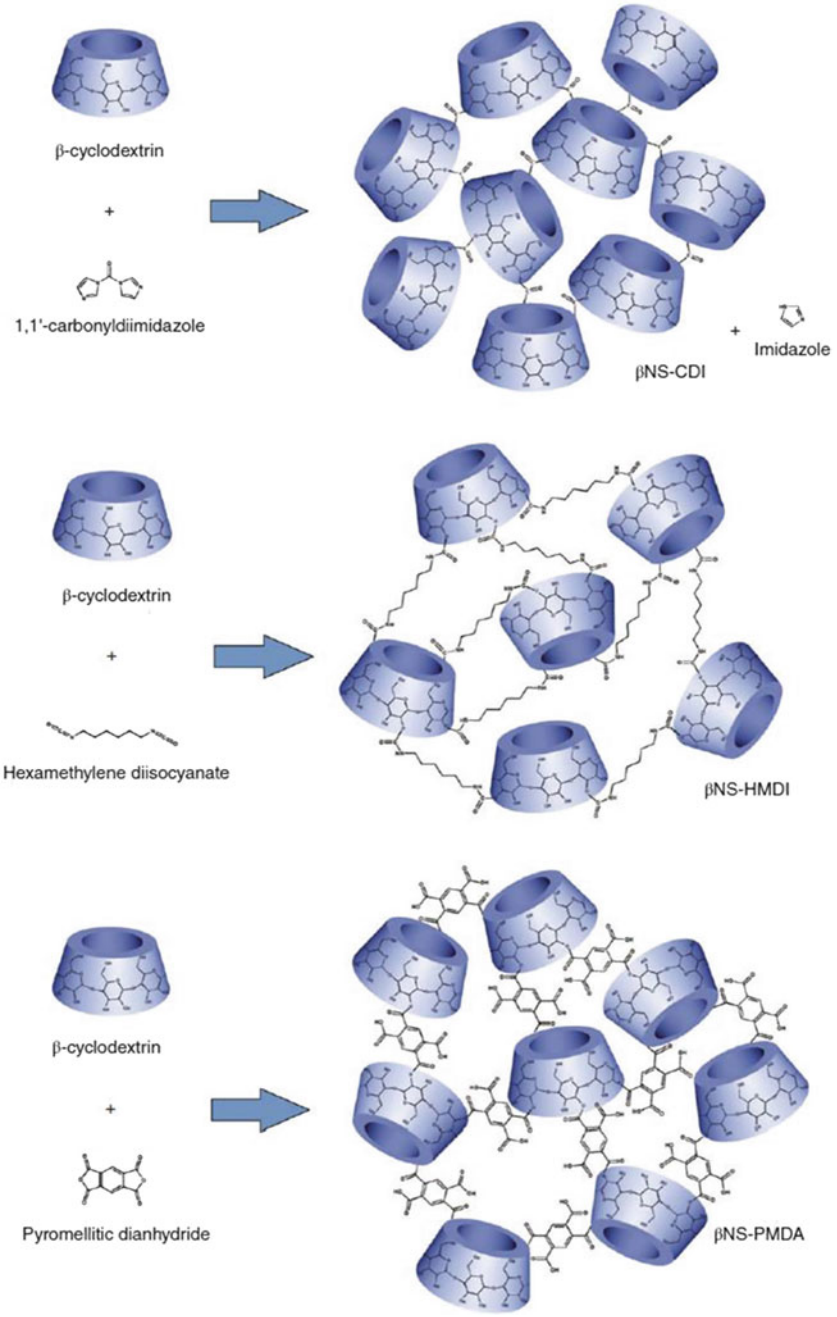

Fig. 9.2 Schematic structures of cyclodextrin nanosponges (CD NS) synthesized using different crosslinkers. Carbonyl compounds like carbonyldiimidazole (CDI) or diphenyl carbonate (DPC), isocyanates like hexamethylene diisocyanate (HMDI), and double carboxylic acid anhydride like

process optimization is performed by varying the molar ratio of crosslinker: polymer. The reaction is carried out at different temperatures for different time scales (temperature scaling from 10 °C to the reflux temperature of solvent and time scaling from 1 to 48 h). Carbonyl compounds such as dimethyl carbonate, diphenyl carbonate, or carbonyl diimidazole act as ideal crosslinking agents for the reaction to be carried out. Finally, by adding the cooled solution to excess of double distilled water, the product is obtained. Filtration is done for the recovery of product under vacuum and purification is done by the prolonged Soxhlet extraction (Osmani et al. 2015b; Trotta et al. 2009). The outcome is formation of solid nanoparticles with a spherical morphology having very high solubilizing efficiency for poorly water-soluble molecules either by forming inclusion or non-inclusion complexes. After completion of condensation polymerization, the transparent block of hyper-crosslinked cyclodextrins can be subjected to the incubation with drug for loading. Synthesized nanosponges can be transferred to the size reduction process carried out by means of high pressure homogenization technique in which an aqueous suspension of nanosponges is homogenized initially with an Ultra Turrax at fixed speed (rpm) for 10 min. This homogenized suspension is then transferred into a high pressure homogenizer and subjected to several homogenization cycles. For instance, Swaminathan et al. have homogenized a 2% m/V aqueous suspension of swellable β- cyclodextrin-polyamidoamines-nanosponges by an Ultra Turrax at 24,000 rpm for 10 min. This homogenized suspension was then transferred into a high pressure homogenizer and subjected to 12 homogenization cycles comprising 5 cycles at 7000 psi, 5 cycles at 5000 psi and 2 cycles at 5000 psi for 5 min in a recirculation mode. The obtained polyamidoamines-nanosponges aqueous nanosuspensions were used for the characterization and protein complexation studies. The nanosponges with narrow size distribution can be obtained by this technique and the obtained product can be stored safely in refrigerator at 4 °C without any aggregation (Swaminathan et al. 2010b).

Ultrasonication technique can also be used for the synthesis of nanosponges. In this technique, polymers are reacted with crosslinkers under sonication without solvents. This method for the fabrication of nanosponges is discussed by Trotta et al. (2007). In that method, anhydrous β- cyclodextrin and diphenyl carbonate were taken and mixed properly in a 250 ml flask, and that flask was placed in an ultrasound bath filled with water for heating at 90 °C with sonication for 5 h. Further steps for the production, crystallization, and purification of obtained product were similar to the steps followed for the melt or solvent method. Probe sonication, a process with high energy input, can be a substitute to the ultrasonication technique due to absence of organic solvents as an advantage. Trotta et al. have synthesized ultrasound assisted nanosponges by using ultrasound probes (Trotta et al. 2007). In a recent study, Anandam et al. have assessed

Fig. 9.2 (continued) pyromellitic dianhydride (PMDA) have already been reported as efficient crosslinkers by several researchers for obtaining nanosponges with spherical morphology and size less than 500 nm. (Reproduced with permission from Shende et al. 2015a, Copyright 2015 Wiley Periodicals, Inc. and the American Pharmacists Association)

two different heating methods of nanosponges preparation (microwave and conventional) for assessing the effect on crystallinity, morphology and size distribution of resultant nanosponges (Anandam et al. 2016). Significant structural diversities were observed among the nanosponges prepared by two approaches. Reportedly, nanosponges synthesized via microwave method had revealed narrow size distribution, and higher crystallinity and drug loading (~2 fold) than that of the counterparts synthesized via conventional method. In all, wide-ranging structural characterization and other studies by researchers validated preferential and distinct promising effects of microwave method.

By applying these explained techniques, nanosponges can be synthesized, crystallized, and purified. Purification, the last step of preparation method, is most critical and important. Based on the crosslinking agents used, by-products of different chemical structure and nature are formed, and hence, removal of formed by-products should taken seriously under consideration as the toxicity exerted by formed by-product resides in the final product.

9.4.2 Types of Cyclodextrin Nanosponges

Linkage or bonding between two molecules of cyclodextrin mainly depends on the type and nature of crosslinker used, and based on the crosslinker used; various types of nanosponges with diverse linkages are obtained.

9.4.2.1 Carbamate Nanosponges

In this type, cyclodextrins in presence of DMF solution are reacted with appropriate diisocyanates such as toluene-2,4-diisocyanate (TDI) and hexamethylene diisocyanate (HDI) under nitrogen atmosphere at 70 °C for 16–24 h. After reaction, residual DMF is removed carefully by washing with acetone, and the powder of crosslinked polymer is obtained. These nanosponges have ability of binding to the organic molecules, and used mostly for purification of water. Nitrophenol for example, is separated even at very low concentrations from its water solution. The capacity of these nanosponges to load organic molecules ranges from 20 to 40 mg per cm^3. Nearly 84% of the dissolved organic carbon can be taken away by nanosponges from waste water (Mamba et al. 2008). Because of such property, these nanosponges are applied for the process of removal of unwanted compounds from water such as 2-methylisoborneol and geosmin, which have been removed successfully by cyclodextrin based carbamate nanosponges (Mamba et al. 2007). Cyclodextrin based carbamate nanosponges were studied by Tang et al. for adsorption of aromatic amino acids namely, L-phenylalanine, L-tyrosine, and L-tryptophane from the phosphate buffer. The order of adsorption efficiencies of aromatic amino acids on cyclodextrin based carbamate nanosponges was as L-tryptophane greater than L-phenylalanine greater than L-tyrosine (Tang et al. 2006).

9.4.2.2 Carbonate Nanosponges

In case of this type, active carbonyl compounds are used as crosslinkers such as diphenyl carbonate, carbonyl diimidazole, and trifosgene. Carbonate bonds are observed between two cyclodextrin monomers resulting in carbonate nanosponges (Fig. 9.3). Either by employing the melt method or solvent technique, the processing can be carried out at 80–100 °C or at room temperature in presence or absence of a solvent (Cavalli et al. 2006b).

Polarity and flexible dimensions of the cavities are the significant properties of carbonate cyclodextrin based nanosponges, and also, by reaction under diverse conditions, carbonate nanosponges can be obtained in amorphous (by solvent technique) or semi-crystalline (by melt method) form. Carbonate nanosponges have been widely used for the encapsulation of numerous drug molecules like doxorubicin, flurbiprofen, dexamethasone, paclitaxel, progesterone, camptothecin, 5-fluorouracil, resveratrol, itraconazole, oxcarbamazepine, cilostazol, tamoxifen, and nelfinavir mesylate, to list a few. Wetting as well as solubility property of such poorly water-soluble drugs is advanced by nanosponges.

Carbonate nanosponges do not affect the surface tension of water significantly. Being non-hygroscopic in nature, carbonate nanosponges do not lose crystalline structure while absorption and desorption of the moisture (Cavalli et al. 2006b). Based on the degree of crystallinity, these carbonate- cyclodextrin-based

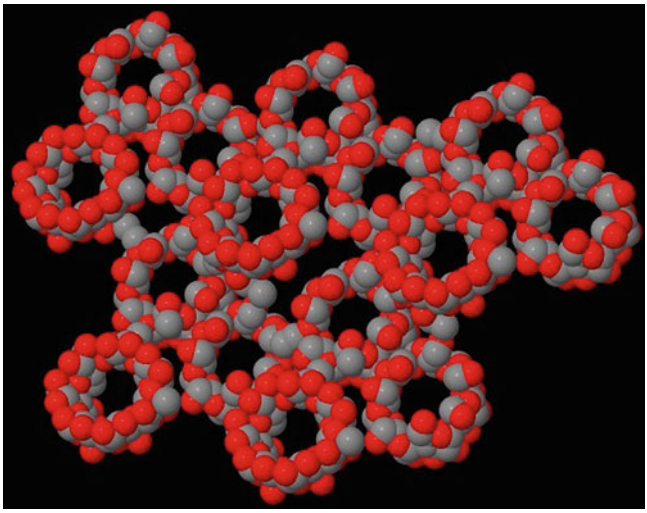

Fig. 9.3 Molecular structure of cyclodextrin carbonate nanosponges synthesized using a suitable cross-linker molar ratio. Structure depicts cyclodextrin molecules connected by nanochannels to form a cage-like structure; where the primary hydroxy groups are mainly involved in the formation of a network. (Reproduced with permission from Trotta et al. 2012, Copyright 2012 Trotta et al.; licensee Beilstein-Institut)

nanosponges have ability to enhance the solubility. For example, acyclovir, widely used antiviral agent, was solubilised twice as much by amorphous nanosponges, while dexamethasone, an eminent anticancer agent, was fourfold solubilised by crystalline nanosponges (Osmani et al. 2015b).

9.4.2.3 Polyamidoamine Nanosponges

These nanosponges are generally prepared by carrying the reaction in water. In this case, polymerization of β-cyclodextrin with acetic acid 2,20-bis(acrylamide) takes place after long standing of 94 h at room temperature, followed by cyclodextrin swelling in water (behaviour is pH dependent) and having both the acidic as well as basic residues. On contact with water, translucent gel is formed instantly by the polymer, and the stability of such gel for upto 72 h was confirmed in bio-relevant media by time dependent swelling studies.

Albumin, a protein exhibiting around 90% of encapsulation efficiency, was used for the study, and in vitro studies for the drug release have shown the possible modulation of protein release upto 24 h. Furthermore, sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS PAGE) technique was used for investigating the product stability; which confirmed the stability of formulation. Formulation was found to remain stable for several months (Trotta et al. 2012).

9.4.2.4 Ester Nanosponges

For fabrication of ester nanosponges, pyromellitic anhydride, a suitable dianhydride is used as a crosslinker. The rate of exothermic reaction for crosslinking is so fast that it completes within few minutes, and can be carried out at room temperature. The reaction involves dissolution of cyclodextrin and dianhydride in solvent DMSO in presence of an organic base like triethylamine or pyridine for acceleration of reaction in forward direction.

Ester nanosponges have ability to host apolar organic molecules simultaneously with the cations, owing to presence of polar free carboxylic acid group (Cavalli et al. 2006b). A variety of heavy metal cations like Mn, Al, Ni, Co, Cu, Cd, Pd, U, and Zn can be complexed with ionic moiety of nanosponges-pyromellitic anhydride at different pH values. Different pH values have an influence on exchange of cations as well as on synchronize properties, thereby enhancing the complexation activity of native cyclodextrin toward the metal ions. The inclusion abilities of nanosponges-pyromellitic anhydride via high resolution magic angle spinning (HR MAS) NMR technique were studied by Mele and co-workers. Investigation was done for water diffusivity and interaction of fluorescein in inner cavities of nanosponges (Mele et al. 2011).

9.4.2.5 Modified Nanosponges

By altering the reaction conditions, carbonate nanosponges can be modified for the application to be achieved. Fluorescent derivative is obtained by reacting carbonate nanosponges with fluorescein isothiocyanate at 90 °C for few hours in solvent DMSO, and these fluorescent nanosponges are found useful in cancer therapy. Similarly, carboxylated nanosponges can be obtained by using cyclic organic anhydride such as maleic anhydride or succinic anhydride (Osmani et al. 2015b; Trotta et al. 2012).

Such type of nanosponges reacts with biologically significant carriers like chitosan, proteins, or biotin to supply a hopeful targeting activity towards specific receptor for certain drug compounds. Moreover, powder X-ray diffraction (PXRD) studies reflected the amorphous nature of such nanosponges. These nanosponges are non-cytotoxic and non-haemolytic. The carrier systems of carboxylated nanosponges seems to be a hopeful and safe for drug delivery as reported in delivery of anticancer agent camptothecin (Swaminathan et al. 2010b). Characteristics requisite parameters for different β-cyclodextrin nanosponges preparation methods are listed briefly in Table 9.4.

9.5 Cyclodextrin Based Nanosponges in Drug Delivery and Nanotherapeutics

9.5.1 Drug Carriers

Cyclodextrin based nanosponges have been visualized as promising drug carriers in diverse pharmaceutical formulations. To address drug related issues such as solubility and permeability, drug interactions with cyclodextrin based nanosponges and encapsulation at molecular level helps to overcome the aforementioned problems and further assists safer and efficient delivery of drugs (Cavalli et al. 2006b; Trotta et al. 2012). The versatility offered by these nanosponges includes solubility enhancement, protection of fragile molecules, and function as a multifunctional carriers and achievement of sustained release of drug.

A number of compounds including volatile oils, BCS class-II and class IV drugs can be encapsulated into nanosponges, thereby capitalizing on the solubility, dissolution and stability of such drug moieties. Nano-pores present in the nanosponges further aides in entrapping flavours and odours via adsorption, which can be useful in masking the unpleasant taste and odours of certain materials, and also provide a platform for converting liquids into solid powders (Osmani et al. 2016a, 2015b). Early literatures have claimed that β-cyclodextrin based nanosponges drug delivery systems have achieved three to fivefolds increase in drug targeting efficiency when compared to direct injection. One such example in this field was achieved for carbonate nanosponges containing anticancer agents viz camptothecin and paclitaxel

Table 9.4 Characteristic requisites for various β-cyclodextrin nanosponges fabrication methods

Type of β-cyclodextrin nanosponges	Method	Crosslinker	Functional group formed	Solvent	Temperature (°C)	Reaction time (h)	Nature of the material	Type of drug to be included
Cyclodextrin-based carbonate nanosponges	Melt method	Carbonyl or dicarboxylate compound	Carbonate bond	None	100	5	Crystalline	Any drug
Cyclodextrin-based carbonate nanosponges	Solvent method	Diphenyl carbonate, dimethyl carbonate, carbonyldiimidazole	Carbonate bond	DMF or DMSO	10 to the reflux temperature of solvent	1–48	Amorphous	Any drug
Cyclodextrin-based carbamate nanosponges	Solvent method	Diisocyanates like HDI, TDI	Carbamate bond	DMF or DMSO	70	16–24	–	Any drug; chiral compounds can be separated
Cyclodextrin-based ester nanosponges	Solvent method	Dianhydride such as pyromellitic anhydride	Ester bond	DMF or DMSO and a base as a catalyst	Room temperature	Complete within few minutes	–	–
Cyclodextrin-based Polyamidoamine nanosponges	Solvent method	Acetic acid 2,20-bis (acrylamide)	Polyamidoamine	Water	Room temperature	96	Gel like material	Peptides and proteins to be separated
Modified type nanosponges	Solvent method	Fluorescein isothiocyanate and carbonate nanosponges	–	DMF or DMSO	90	A few hours	Amorphous	Cancer therapeutics

DMF Dimethylformamide, *DMSO* Dimethylsulfoxide, *HDI* Hexamethylene diisocyanate, *TDI* Toluene-2,4-diisocyanate

(Swaminathan et al. 2010b; Torne et al. 2010). Reportedly, in another research vocation, acetylsalicylic acid, a NSAID belonging to BCS class-III, was formulated into β-cyclodextrin nanosponges crosslinked with pyromellitic dianhydride (Shende et al. 2012). Particle size determined as per TEM analysis indicated an average size ranging between 40 and 60 nm for acetylsalicylic acid loaded nanosponges with regular spherical shape. Zeta potential recorded for the prepared formulation was high enough to sustain a colloidal formulation. A slow and prolonged release of acetylsalicylic acid from pyromellitic crosslinked β-cyclodextrin nanosponges over a period of 24 h was observed from in vitro and in vivo release kinetic profiles. When administered orally using an oral gavage in carrageenan induced rat paw edema, a significant reduction in inflammation (p less than 0.01 and p less than 0.05) for the prepared acetylsalicylic acid as nanosponge formulation was observed when compared to that of the control group. The results reflect that acetylsalicylic acid nanosponge formulation can be employed for oral delivery of the drug.

Recently, influence of carbonate nanosponges on the solubility of telmisartan in water at a concentration of 9.9 μg/ml resulted in enhanced bioavailability as per the findings by Rao et al. (2013). Additionally, the research also explored the effect of ternary component alkalizer ($NaHCO_3$) on solubility of telmisartan. Comparison of saturation solubility and in vitro dissolution of β-cyclodextrin complex of telmisartan, plain telmisartan and nanosponge telmisartan revealed that solubility of telmisartan increased by almost 8.53-fold in distilled water, 3.35-fold in 0.1N HCl and 4.466-fold in pH 6.8 PBS by incorporation of $NaHCO_3$ in the drug-nanosponges complex. By incorporating the ternary $NaHCO_3$ into the nanosponges based complex, enhanced dissolution of telmisartan via synergistic action of the component was achieved by modulating the microenvironment pH as well as by changing the amorphization of drug. The maximum solubility and in vitro drug release was exhibited by inclusion complex comprising of nanosponges and $NaHCO_3$. Further, an increase in area under curve (AUC) by 54.4% was observed for ternary nanosponges complex, whereas β-cyclodextrin ternary complex exhibited an increase by 79.65%.

Another medicinal application can be use of nanosponges in topical application of gels and creams (Friedrich et al. 2015; Pando et al. 2015). One such attempt to showcase nanosponges topical applicability was made by Ansari et al. Resveratrol, a polyphenilic phytoalexin known for its anti-oxidant properties and present in various plant sources, plays a crucial role in prevention of many human diseases (Chauhan 2015; Rauf et al. 2016). Resveratrol was encapsulated in nanosponges, and this incorporation led to marked increase in the solubility as well as stability of the drug. In vitro studies on porcine skin and on rabbit buccal mucosa showed enhanced drug permeation from resveratrol-loaded nanosponges permeation (Ansari et al. 2011b). In another research vocation, researchers have developed and characterized minoxidil loaded nanosponges based hydrogel system for topical application on to the scalp, in order to overcome the limitations associated with marketed minoxidil topical solution. Solvent evaporation method was implied for nanosponges synthesis using diphenyl carbonate as crosslinker. Minoxidil was loaded in the nanosponges using solid dispersion technique. The nanosponges and minoxidil-nanosponge

complexes were characterized by Fourier transform infrared (FT-IR), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). Further, drug-loaded nanosponges were incorporated in hydrogel formulations and were evaluated for appearance, homogeneity, gelling, pH, viscosity, spreadability, drug content and in vitro drug release. Nanosponges based hydrogel reportedly exhibited promising results compared to minoxidil topical solution (Ansari et al. 2014).

Conte et al. have reported pyromellitic dianhydride cross-linked β-cyclodextrin nanosponges as multifunctional ingredient in semisolid formulations for delivering drug to the skin (Conte et al. 2014). The role of nanosponges on solubilization and stabilization of the photosensitizer benzoporphyrin-derivative monoacid ring A (BPDMA) and all-trans retinoic acid (atRA) as well as effect on skin permeation of diclofenac was investigated. Gels, aqueous solutions and cream-gels were prepared by mixing nanosponges and a conventional gelling agent at specific ratios. Incorporation of BPDMA in nanosponges aqueous solutions avoided nanosponge aggregation and resulted in highly photo and kinetically stable complexes that generates singlet oxygen upon irradiation. atRA incorporated in the nanosponges containing gel demonstrated remarkable stability as compared with the formulation without nanosponges, resulting in 18-fold increase of atRA lifetime. Skin permeation studies explored that nanosponge in gels and cream-gels containing diclofenac significantly decreased the amount of drug permeated through the skin while increased drug amount in stratum corneum and viable epidermis. Researchers concluded swellable nanosponges to be a multifunctional co-ingredient with potential applicability in topical monophasic and biphasic formulations for stabilizing photo-sensitive drugs and for localizing the highly penetrating drugs action in outer skin layers.

Glaucoma is one of the principle irretrievable causes leading to blindness cases across the globe. Taking this fact into consideration, Galloway et al. have developed a novel image-guidance system for the controlled delivery of neuroprotective drugs in form of nanosponges. Characterization and performance assessment of developed system was carried out on animal models and ex vivo human tissue; which reflected promising results (Galloway et al. 2014). In another approach, Lambert et al. have fabricated nanosponges encapsulating hypotensive drugs viz Brimonidine, Travoprost and Bimatoprost, and evaluated nanosponges based delivery system for efficacy to reduce intraocular pressure in mice over extended period of time. For inducing bilateral ocular hypertension in mice, microbeads were injected into the anterior lobe followed by intravitreal injection of drug loaded nanosponges. Retinal ganglion cell (RGC) uptake and retinal deposition were also examined post Neuro-DiO nanosponges intravitreal injection using confocal microscopy. As per the study results, nanosponges encapsulating all the three hypotensive drugs significantly lowered intraocular pressure with varied percentage and time duration as: brimonidine (12–30% intraocular pressure lowering upto 6 days), travoprost (19–29% intraocular pressure lowering upto 4 days) and bimatoprost (400 nm size nanosponges, 24–33% intraocular pressure lowering upto 17 days; 700 nm size amorphous crosslinker nanosponges, 22–32% intraocular pressure lowering upto 32 days; 700 nm size crystalline crosslinker nanosponges, 18–26% intraocular

pressure lowering upto 32 days). Besides, Neuro-DiO released from nanosponges was found to be up taken by RGCs and Neuro-DiO deposition in retina was increased with extending time. This study established promising potential of nanosponge carrier in effective ocular delivery of hypotensive and other drugs. In addition, one can also design nanosponges based systems that would be able to target RGCs and neurons that gets degenerated in glaucoma (Lambert et al. 2015).

"Stimuli-responsive", intelligent or smart responsive polymeric nanoparticles have been proposed for controlled delivery of low-molecular weight and macromolecular drugs. The environmental responsive nanoparticles alter the structure and release profile of the above-mentioned drugs in response to external stimuli such as change in pH, temperature and irradiation (Hoffman 2013). Several literatures have been reported for glutathione (a tripeptide found in high concentration intracellularly, and increases further in cancer cells)-responsive nanosystems successfully designed for targeted intracellular delivery (Cheng et al. 2011; Ejaz et al. 2011). In animal cells, glutathione and glutathione disulphide are the chief redox combination, and based upon this, novel bioresponsive nanosponges of glutathione as anticancer drug carriers have been recently explored and designed. In chemo-resistant cells, intracellular concentration of glutathione increases by many folds when compared to extracellular environment and this glutathione further act as an external stimulus for intracellular drug release by destabilizing the nanocarriers and intracellular cleavage of disulphide bond. Using one step synthesis, a series of disulphide nanosponges with varied disulphide bridges were tailored and subjected to size reduction by means of high-pressure homogenization to obtain a homogenous dispersion with a narrow size distribution range.

Previously it has been observed that the disulfide nanosponges retained a superior swelling capacity in experiential pyro-nanosponges. The release of glutathione in a responsive manner to external stimuli has been promisingly achieved with the prepared nanosponges, and safety was validated with absence of any cytotoxic action of blank glutathione responsive nanosponges on numerous cancer cell lines. Camptothecin and doxorubicin, previously encapsulated in other type of nanosponges, were compared to the prepared nanosponges for the delivery aptitude. In vitro release data reflected that glutathione responsive doxorubicin release from nanosponges was achieved as a function of cellular concentration of glutathione, with absence of any toxic effects when tested in vivo after intravenous administration of disulfide nanosponges in rats (Cavalli et al. 2014; Trotta and Cavalli 2013). Therefore, one can postulate that disulfide nanosponges can be seen as promising innovative carriers for targeted drug delivery, with an equal potential and applicability in cancer therapy.

Lately, Lockhart et al. have reported the synthesis and encapsulation of tamoxifen and quercetin co-loaded polyester nanosponges (Lockhart et al. 2015). The dual drug formulation was made with varied crosslinking densities (4% and 8%) and evaluated for effect on loading, release, metabolism and release kinetics. The formulation exhibited significant loading of drugs and in vitro metabolism was abridged appreciably. Cytotoxicity study was carried out against 4T1 mouse breast cancer cells, results of which revealed the comparable efficacy to free dual drug formulations and

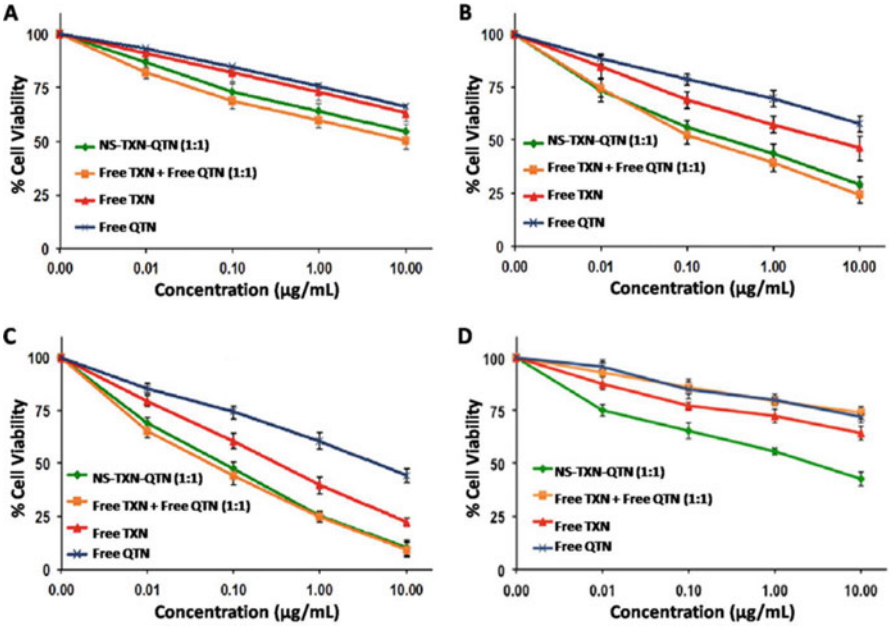

Fig. 9.4 Cell cytotoxicity of free tamoxifen (TXN), free quercetin (QTN), combined free TXN and QTN [1:1] and tamoxifen-quercetin-nanosponges (NS-TXN-QTN) after (**a**) 24 h, (**b**) 48 h, (**c**) 72 h, and (**d**) recovery condition. Each data point represents the mean ± SD ($n = 3$). Cytotoxic evaluation was carried out against 4T1 mouse breast cancer cells; outcomes of which revealed the comparable efficacy of nanosponges to free dual drug formulations and yet improved anti-cancer activity in the recovery condition. (Reproduced with permission from Lockhart et al. 2015, Copyright 2015 Elsevier B.V.)

yet improved anti-cancer activity in the recovery condition as shown in Fig. 9.4. As of this research vocation, researchers concluded for suitability and applicability of the nanosponges in developing novel dual release drug delivery system with a controlled and regulated metabolism. Thus, proven the fact that crosslinking variation enables tailored release kinetics and improved bioavailability via reduced drug metabolism.

Nanosponges exhibits several promising characteristics and thus ensure widespread applicability in numerous fields such as medicine, engineering, agriculture, water purification and many more. In a study, Shende et al. have designed diverse nanosponges formulations using varied crosslinkers (like carbonyl diimidazole, hexamethylene diisocynate, pyromellitic dianhydride) and preclinically evaluated toxicity of nanosponges. Organisation for Economic Co-operation and Development (OECD) guidelines 423 and 407 were followed for acute dose toxicity (14 days period) and repeated dose toxicity (28 days period) studies, respectively. The results for studies indicated that all nanosponges formulations were safe in experimental animals with maximally tolerated dose of 2000 mg/kg (Shende et al. 2015a).

Dopamine deficiency is the underlying cause for Parkinson's disease, afflicting about 0.3% of the population with symptoms like rigidity, tremors, bradykinesia and akinesia (Cooper and Chahine 2016; Davis and Racette 2016; Skogar and Lokk 2016). During Parkinson's disease, administration of dopamine remains ineffective due to dopamine's inability to penetrate the blood-brain barrier. In contrast, L-DOPA reaches the central nervous system and converts to dopamine via decarboxylation by neuronal amino acid decarboxylase (Eslami et al. 2012; Puiu et al. 2010). Precisely, L-DOPA acts as a prodrug, is absorbed through small intestine and subsequently carried through blood stream to the brain. Recently, Trotta et al. have fabricated molecularly imprinted cyclodextrin nanosponges for delivering a non-proteinogenic amino acid and dopamine precursor L-DOPA [(S)-2-amino-3-(3,4-dihydroxyphenyl) propanoic acid] in a prolonged and controlled manner (Trotta et al. 2016). Reportedly, the researchers team have synthesized molecularly imprinted nanosponges by crosslinking β-cyclodextrin using carbonyl diimidazole in presence of template L-DOPA molecules. The amount and affinity of L-DOPA entrapped in nanosponges was determined by implying quantitative NMR spectroscopy. Reportedly, molecularly imprinted nanosponges exhibited a sluggish and more prolonged release profile compared to that of non-imprinted nanosponges. Moreover, no significant L-DOPA degradation was noted even after long term storage study; validating significance of molecularly imprinted nanosponges in Parkinson's disease therapy.

As being solid, nanosponges can be easily formulated in any dosage forms (oral, topical, parenteral, inhalation dosage forms). Oral dosage form like tablets or capsules can be formulated by dispersing these complexes in excipients, adjuvants, lubricants and diluents matrices with suitable anti-caking agent. Simple dispersions of complex made in saline, sterile water or other aqueous solutions for parenteral delivery and incorporation in hydrogels and other topical dosage forms are effective for topical delivery.

One of advanced materials that are nowadays emerging extensively in drug delivery and therapeutics are biofunctional textiles; which are combination of conventional textile and novel drug delivery approach for getting fabrics capable of delivering APIs via skin. Recently, Mihailiasa et al. have synthesized carbonate nanosponges for melatonin delivery through skin (Mihailiasa et al. 2016). Melatonin complexation with three dimensional porous structures at molecular level was confirmed by FT-IR, DSC and PXRD studies. Later, melatonin nanosponges were dispersed onto substrate fibers (cotton) having durable adsorption capacity. These functionalized fibers subjected to in vitro release study followed zero order kinetics attributing to a model diffusion controlled system (Fig. 9.5).

9.5.2 Biocatalysts and Biomers Carrier

Nanosponges can serve as carriers for delivery of antibodies, enzymes, proteins and vaccines. In industry, different processes that involve chemical transformation are

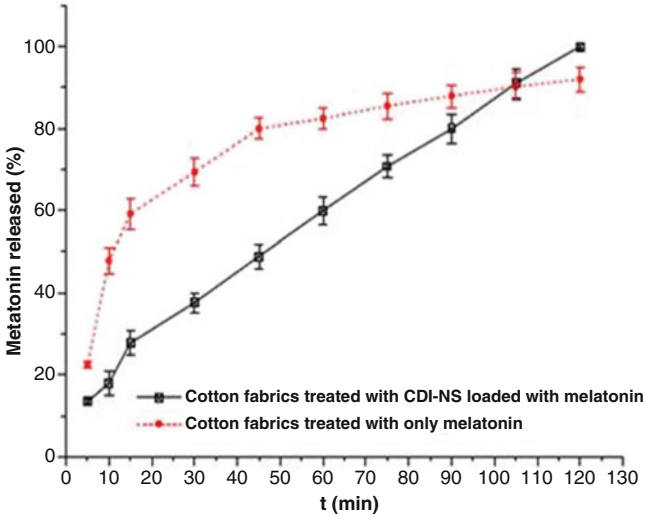

Fig. 9.5 Release curves of the fabrics samples treated with free melatonin and with melatonin loaded carbonyl diimidazole-nanosponges (CDI-NS). As shown in the figure, a sustained release profile was noted in case of melatonin loaded carbonyl diimidazole-nanosponges following zero order kinetics. (Reproduced with permission from Mihailiasa et al. 2016, Copyright 2016 Elsevier B.V.)

associated with operational disadvantages. Non-specific reactions lead to less yields consequently leading to persistent operations at higher temperature and pressure that consumes large amounts of energy and cooling water for downstream process. These drawbacks can be addressed by utilizing enzymes as biocatalyst; since enzymes work under mild reaction conditions, specific in nature, and act quicker. Enzymes reduce the consumption of energy and production of pollutants, thereby suggesting the beneficial impact on environment. Recent advances in genetic engineering have propelled the industrial applications of enzymes by increasing stability, economy and specificity of enzymes. Some enzymes that have found increasing applicability in industry include alpha amylase, trypsin, cellulose, pectinase (clarification process in fruit juice), ligninase (to breakdown lignin), and lipase. This catalytic activity of enzymes is attributed to the exact orientation of the active site (Osmani et al. 2015b; Vyas et al. 2008).

Proteins, peptides and enzymes are highly functional in the biomedical and therapeutic field. For treatment of cancer or type I mucopolysaccharidosis, proteolytic enzymes can be utilized, whereas deoxyribose nucleic acid (DNA) and oligonucleotides are employed for gene therapy. However, difficulty in administering these molecules brings about limitations in the use. Protein drugs as such are poorly absorbed by the biological membrane owing to hydrophilic nature, molecular size, high surface charge, degree of ionization, and chemical and enzymatic instability. Increasing the dose or use of absorption enhancers can lead to sever toxicity problems (Swaminathan et al. 2010a; Trotta et al. 2012). Various systems like

nano and micro particles have been developed to address the issues related to delivery of enzymes, proteins; and have been proven to modify pharmacokinetics and stability in vivo. However, similar to the benefits offered by these systems to proteins, concerns relating to protection and stability of enzymes, vaccines and antibodies still present a conundrum. Cyclodextrin based nanosponges are presumably found to be suitable carriers to adsorb proteins, enzymes, antibodies and macromolecules. Enzymes in particular have reaped the benefits of the carrier, since enzymes can maintain the activity, efficiency, and are capable of prolonging operation under different pH and temperature range. Either by encapsulating or adsorbing these biomers in cyclodextrin based nanosponges, enzymes can be delivered across the biological membrane more efficiently or site-specific targeting can also be achieved (Gilardi et al. 2009; Vyas et al. 2008). In a research vocation, Deshmukh et al. have developed surface active nanosponges by lysozyme impregnation to uphold lysozyme's conformational stability, to shatter bacterial cell wall via 1,4-β-linkages hydrolysis between N-acetylmuramic acid and N-acetyl-d-glucosamine residues occurring in peptidoglycan layer and to control calcium release in hypocalcemia (Deshmukh et al. 2016). Carbonyl diimidazole crosslinked blank and calcium carbonate ($CaCO_3$) loaded cyclodextrin nanosponges were fabricated by polymer condensation method followed by lysozyme impregnation. FT-IR and DSC outcomes confirmed successful lysozyme impregnation on and calcium loading in nanosponges. The developed nanosponges reflected monomodal distribution with average particle size ranging between 347.46 ± 3.07 and 550.34 ± 5.23 nm. Additionally, zeta potentials of nanosponges were found to increase further upon lysozyme impregnation, imparting more stability to formulations. As expected, controlled release of lysozyme and calcium from surface active nanosponges was noted over 24 h; proving cyclodextrin nanosponges as promising antibacterial protein and calcium nanocarrier; for superseding antibiotics associated hypocalcemia.

9.5.3 Drug Stability Enhancement

In order to improve the drug-complex stability, β-cyclodextrin have been previously conjugated with a variety of polymers that favours attachment of many cyclodextrin units to a polymer molecule (Girek and Ciesielski 2010). Also, the possibility of polymer contributing along with β-cyclodextrin for enhancing drug-complex stabilization increases. Such concepts have been adopted for protein and peptide molecules due to the molecules being less stable, allergic and also due to immunological latency, high production cost, protease stability and poor bioavailability (Swaminathan et al. 2010b). Few proteins such as Bovine serum albumin (BSA) need to be stored in lyophilized state due to lack of stability in solution form. However, lyophilization of proteins is also associated with denaturation of proteins, and many proteins tend to lose native confirmation and structure post lyophilization. The most critical parameter while formulating proteins is to retain the native structure that can be

stored for over a longer period of time. To overcome this anomaly, nanosponges technology allows encapsulation of such molecules in swellable cyclodextrin based poly(amidoamine) nanosponges with enhanced stability, thereby retaining BSA's native properties and structure (Swaminathan et al. 2009).

In powder forms, nanosponges exhibits higher stability for prolonged periods and offers protection from degradation by encapsulation of moieties (Trotta et al. 2012). As per previous literature, carbonate nanosponges are deemed to be thermally stable upto a temperature of 300 °C, thereby permitting sterilization as per USP protocol (autoclaving at 121 °C and 2 bar for 15 min). Absence of any degradation prior and post sterilization was confirmed by FT-IR and NMR analyses (Trotta 2011). Additionally, carbonate nanosponges can be easily dispersed in aqueous media as do not exhibit surfactant properties. The mean diameter was within the colloidal size of less than 1 μm with a narrow size distribution, and forms opalescent suspensions upon dispersing in aqueous media. A zeta potential of about −25 mV further ensures a stable aqueous suspension that remains stable over longer course of time.

Under acidic (0.1 N HCl) and basic conditions maintained at 60 °C, the stability for carbonate nanosponges was tested. Results showed a limited release of cyclodextrin units under acidic environment at the end of 2 h, which is mainly due to degradation of the nanosponge structure, while no such influence was observed when compared to stability study carried out in basic environment. In contrast, carboxylated nanosponges tailored using pyromellitic dianhydride as a cross-linker was found to be less chemically and thermally stable, and could swell almost 30-folds more in water. This is as a result of more negative zeta potential, and nanosponge ability to simultaneously host cations, organic molecules and even macromolecules (Rossi et al. 2014; Trotta et al. 2012).

Molecules that are prone to photo, chemical and enzymatic degradation can be delivered using nanosponges, as nanosponges serve as a more protective tool in the delivery of sensitive molecules. To assess the same, 30% 5-fluorouracil as model drug was loaded into β-cyclodextrin nanosponges. It was reported that only 60% of in vitro drug release was achieved at the end of 2 h at pH 7.4, thereby indicating drug-nanosponges interaction. Also, increased protection of encapsulated 5-fluorouracil by nanosponges keeps cytotoxic potential unaltered against MCF-7 cells for a duration of 6 months (Trotta et al. 2012). The results highlight the significance of 5-fluorouracil nanosponge encapsulation and nanosponge ability to impart sustained release of hydrophilic drugs.

Long before, in an approach Aynie et al. have synthesized alginate nanoparticles resembling sponge as novel carrier for oligonucleotides (Aynie et al. 1999). The ability of the carrier system to protect encapsulated oligonucleotides from degrading was investigated in presence of bovine serum media, and tissue distribution and pharmacokinetics of loaded oligonucleotides post intravenous administration have been assessed. Reportedly, synthesized nanocarriers were able to protect loaded oligonucleotides and also aided in modified biodistribution of oligonucleotides across lungs, liver and spleen. These results were attributed to efficient association in colloidal state between oligonucleotides and calcium alginate, and researchers claimed these nanosponges to be promising for targeted delivery to vital organs.

Another example highlighting the importance of nanosponges for enhancing the stability and protection was for encapsulation of camptothecin into cyclodextrin nanosponges. A typical quinoline alkaloid derived from *Camptotheca acuminate*, provides a potent DNA topoisomerase-I inhibitory effect including extensive anti-cancer potency. A major setback is hydrolytic degradation of camptothecin and poor solubility that consequently limits its clinical applications (Hatefi and Amsden 2002). However, a couple of synthetic and semi-synthetic analogues like topotecan, irenotecan have been developed, and are being currently used for the chemotherapy. Numerous nanotechnology approaches to decrease or limit camptothecin related side effects such as lactone ring instability and administration related side effects, and to increase camptothecin stability and bioavailability have been previously reported (Davis 2009; Luo et al. 2014; Min et al. 2008). In wake of this challenge, Swaminathan et al. have carried out the first formulation study relating to developing most appropriate nanosponge type capable of protecting camptothecin lactone ring hydrolysis by complexation. The researchers have fabricated β-cyclodextrin based carbonate nanosponges with different crosslinking ratios like 1:2, 1:4 and 1:8 (on molar basis with crosslinker). Amongst the prepared crystalline and paracrystalline nanosponges formulations, the former offered higher drug loading capability. For all the prepared formulations the particle size was within the range of 450–600 nm with less polydispersity indices and high zeta potential, thereby resulting in a stable colloidal nanosuspension in aqueous media. In vitro release profile indicated slow release of camptothecin upto 24 h. Further, under physiological conditions, nanosponges based formulations could successfully seclude the camptothecin lactone ring (80% w/w intact) against the plain drug (about 20% w/w). Higher cytotoxic potential of nanosponge formulation than plain camptothecin was established post 24 h cytotoxic studies using HT-29 cells (Swaminathan et al. 2010b).

Gamma-oryzanol, a ferulic acid ester mixture, is widely utilized as a natural antioxidant, food stabilizer and as a sunscreen in cosmetics. Due to high instability and photodegradation, applicability of gamma-oryzanol is limited. By encapsulating in nanosponges, gamma-oryzanol photodegradation can be prevented. An O/W emulsion and a gel for gamma-oryzanol loaded nanosponges was formulated and in vitro permeability and accumulation was tested on porcine skin. Over a period of time, high accumulation of gamma-oryzanol was observed which was attributed to the ability of nanosponges to increase the uptake of guest molecule by the skin (Sapino et al. 2009). Further, the nanosponges could possibly enhance the solubility of the molecules at the surface of the skin which has been previously reported for cyclodextrin.

Following the same path, Ramirez-Ambrosi et al. have encapsulated the potent antioxidants and nutraceutical apple polyphenols viz rutin, phloridzin and chlorogenic acid in β-cyclodextrin nanosponges to overcome allied photo and thermostability issues (Ramirez-Ambrosi et al. 2014). Higher encapsulation efficiencies were recorded for all the molecules. In vitro dissolution studies of encapsulated polyphenols showed that rutin and phloridzin get better dissolved in ethanol, while chlorogenic acid was better dissolved in water. Besides, Thermogravimetric analysis

(TGA), DSC, FT-IR spectroscopy and X-ray powder diffraction (XRPD) were used as characterization techniques and taking into account the obtained results, it was confirmed that the solid products formed were not physical mixtures but inclusion complexes.

Quercetin is an extensively distributed flavonoid compound (in fruits and vegetables) that exhibits strong antioxidant potential, but lacks abundant use and applications amid of poor solubility and stability issues. Anandam et al. have designed cyclodextrin based nanosponges of quercetin for enhancing dissolution and stability. Five different batches of nanosponges were prepared by varying the molar ratio of β-cyclodextrin and diphenyl carbonate via freeze-drying method. FT-IR spectroscopy, Raman spectroscopy, DSC and PXRD studies were adopted for confirming interaction between quercetin and nanosponges. Particle sizes of blank and quercetin loaded nanosponges were found to be within 100 nm with least polydispersity indices and zeta potential was sufficiently high to obtain a stable colloidal nanosuspension. Furthermore, particle sizes measured from TEM images were in agreement with DLS results. The dissolution of quercetin nanosponges was found significantly higher compared with the pure drug. Stability of quercetin encapsulated nanosponges was tracked in a simulated intestinal fluid; which depicted marked improvement in the photostability. In addition, the antioxidant activity of quercetin nanosponges was more effective than pure quercetin on DPPH scavenging, anti-superoxide formation and superoxide anion scavenging (Anandam and Selvamuthukumar 2014, 2016).

9.5.4 Drug Release Modulation

Frequent administration of dosage is one of the major drawbacks of conventional drug delivery systems. In contrast, drugs encapsulated in nanosponges can be released over an extended period of time. Therefore, drug release rate from hydrophilic cyclodextrin based nanosponges can be modified that subsequently aides in absorption across the biological membrane, and also provides an efficient drug carrier for immediate release dosage forms. For hydrophobic cyclodextrin based nanosponges, sustained delivery for proteins, peptides and water soluble drugs can be attained, as previous in vitro study on flurbiprofen encapsulated in β-cyclodextrin exhibited slow release with only 10% release post 130 min (Cavalli et al. 2006b). In another report, doxorubicin encapsulated in nanosponges was protected during stomach passage and delivered to colon, thereby highlighting the efficiency of nanosponges for pH specific or colon targeted drug delivery (Trotta et al. 2012).

For storing and prolonging the release of volatile molecules such as essential oils, linalool (liquid component of numerous essential oils with boiling point of 198 °C) was encapsulated in various types of nanosponges as a liquid oil model (Cavalli et al. 2006b). About 8% w/w of linalool can be incorporated into β-cyclodextrin nanosponges matrix. Entrapment was confirmed by DSC analysis. In vitro release studies by using linalool β-cyclodextrin complex. After 2 h, linalool release from

nanosponges was half of that from the β-cyclodextrin complex, thereby showing that molecule was stabilised in nanosponge structure. In a reported study, Vavia et al. have prepared nelfinavir mesylate (a protease inhibitor with low bioavailability) loaded nanosponges for enhancing nelfinavir mesylate solubility. It was conferred that the release of drug from nanosponges was slow when compared to its release from β-cyclodextrin complex (Vavia et al. 2006), which proposes that nanosponges can prolong the release of drug over a period of time and can achieve sustained release when delivered orally.

Shende et al. have fabricated cyclodextrin based nanosponges of calcium carbonate ($CaCO_3$) by polymer condensation method as novel carriers for controlled delivery of calcium in the treatment of hyperphosphatemia (Shende et al. 2013). FT-IR and DSC study results confirmed nanosponge encapsulation of $CaCO_3$ and SEM analysis revealed roughly spherical shape of nanosponges with porous nature and mean particle size of about 400 nm. The percent Ca encapsulation and moisture content of fabricated nanosponges were in the range of 81–95% and 0.1–0.7%, respectively. The optimized formulation was reported to offer enteric release in a controlled manner; which was claimed to be promising in the management and treatment of hyperphosphatemia.

Few researchers have also prepared polyester nanosponges with varied degree of crosslinking densities of ~4%, ~7% and ~10% with an average nanoscopic size of 100 nm. Wide-ranging crosslinking densities and respective influence on release kinetics of a BCS class IV drug (paclitaxel) was assessed in gastrointestinal fluid and buffer (separately for individual and mixed particles) to illustrate entirely modifiable release rates appropriate for intravenous and oral delivery (Stevens et al. 2014). Deshpande and Patel have designed cyclodextrin based nanosponges of atorvastatin as novel carriers by condensation polymerization and interfacial polymerization, to modulate atorvastatin release in desired manner, for the treatment of dyslipidaemia. FT-IR spectroscopy and DSC results confirmed atorvastatin compatibility with β-cyclodextrin and complete encapsulation in nanosponge structure. Results of encapsulation efficiencies of all formulation trials revealed condensation polymerization as the best method for nanosponge formation with higher encapsulation ranging in 72–86%. SEM images revealed porous nature, mean particle size was about 328 nm and zeta potential of nanosponges was sufficiently high giving enough stability to formulation. In vitro drug release study depicted good dissolution profile (greater than 75% releases within 1 h in 0.1 N HCl); indicating enhanced atorvastatin solubility post nanosponges encapsulation. During accelerated stability studies, no significant changes were recorded in formulation upto 3 months period (Deshpande and Patel 2014). Whereas, in another study Raja et al. have developed nanosponges for sustained release and for the delivery of antiulcer agents, taking ciprofloxacin as a model drug (Raja et al. 2013). As the drug was formulated in nanoparticles the density was found to be increased. Nanosponges reported to exhibit sustained drug release with an optimized batch depicting 90.80% drug entrapment and 99.4% drug release.

In an attempt Rao and Bhingole have formulated oral dry suspension of gabapentin; a bitter drug with low bioavailability (~60%) and short half life

(5–7 h), with a rationale of attaining controlled release, enhanced bioavailability and taste masking (Rao and Bhingole 2015). Cyclodextrin nanosponges were synthesized via conventional melt method followed by drug loading. Gabapentin nanosponges complexes were not only evaluated by FT-IR, DSC and PXRD studies, but also assessed for saturation solubility and taste analysis. Complexes were coated with ethyl cellulose and Eudragit RS-100 using suspension layering method and prepared dry gabapentin suspension was subjected to redispersibility, taste, sedimentation, leaching, in vitro dissolution and pharmacokinetic analysis. The results of study indicated maximum drug entrapment by nanosponges complexes, controlled release upto 12 h (due to polymers coating) with insignificant leaching and effective taste masking. In addition, in vivo studies outcomes revealed enhanced gabapentin bioavailability (by 24%) with respect to plain gabapentin.

In another study, Shende et al. have developed inclusion complexes and nanosponges of meloxicam using β-cyclodextrin for enhancing meloxicam solubility, stability and to prolong meloxicam release over the time (Shende et al. 2015b). A schematic presentation of β-cyclodextrin-meloxicam inclusion complex and meloxicam nanosponge formation is shown in Fig. 9.6. Different techniques like kneading, physical mixing and sonication were implied. Prepared nanosponges were characterized for zeta potential, particle size, encapsulation efficiency, stability, in vitro and in vivo drug release. Interaction of meloxicam with nanosponges was confirmed via FT-IR spectroscopy and DSC; which consequently resulted in amorphous meloxicam state as evident from PXRD study results. SEM micrographs of nanosponges revealed particle sizes in range of 350–765 nm. Observed zeta potential

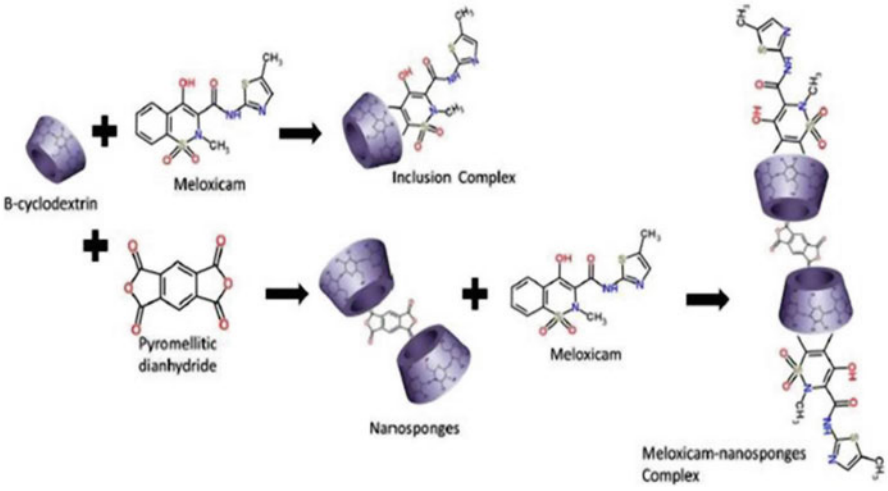

Fig. 9.6 Schematic presentation of β-cyclodextrin-meloxicam inclusion complex and meloxicam nanosponges formation using pyromellitic dianhydride as crosslinker. Reportedly, nanosponge encapsulation of meloxicam resulted in significant reduction in crystallinity, optimum particle size, higher stability and prolonged in vitro-in vivo release. (Reproduced with permission from Shende et al. 2015b, Copyright 2015 Elsevier B.V.)

was sufficiently high to attain greater stability. Moreover, as desired a prolonged meloxicam release from nanosponges was noted upto 24 h of in vitro and in vivo studies. Thus, researchers proposed adoption of nanosponges based systems in delivering analgesic and anti-inflammatory drugs in a controlled manner.

9.5.5 Solubility Enhancement

Most drugs due to inherent characteristics pose dilemma in the efficient delivery limiting allied clinical use. Mainly drugs belonging to BCS class-II offer limited aqueous solubility and about 40% of new drug entities fall under this category, hence this problem can be resolved through nanosponges technology (Swaminathan et al. 2007; Trotta et al. 2012). Cyclodextrin based nanosponges present crosslinking and cyclodextrin pockets that allows interactions with different drugs and augments the solubilization of drugs. Interactions of drug with cyclodextrin based nanosponges, inclusion complexes or solid dispersion reduces drug crystallinity that subsequently favours enhanced solubility and dissolution rate. This improvised solubilisation is because of masking of hydrophobic groups of less soluble drug inside cyclodextrin core thereby manifesting hydrophilic groups exposed on the outer side, and thus forming a hydrophilic complex (Alongi et al. 2011; Duchene and Bochot 2016; Vyas and Sharma 2012).

Methylated cyclodextrins with low molar substitution are substantiated as potential solubilizers amongst all the different available cyclodextrin derivatives. Cyclodextrin based nanosponges enhancing the drug release has been reported for ketoprofen and naproxen (Osmani et al. 2015b; Vyas et al. 2008). Enhanced permeability of hydrophobic drugs is an immediate result of improved solubility and dissolution by cyclodextrin without altering the lipid barriers of biological membrane.

Complexation of drug with nanosponges prevents crystallization through molecular dispersion of the same in nanostructure. Paclitaxel has been well established as a potent anticancer agent and is being used as first line chemotherapy against various types of cancer cells (He et al. 2013; Malingre et al. 2001). With a mortality rising at 42%, about 1.2 million women are being diagnosed with breast cancer and over half a million die every year around the globe. This has led to an increased demand since past decade and a market share of about 31.6 billion USD of various *Taxus* species made paclitaxel world's best anti-cancer drug. Paclitaxel, with a very less aqueous solubility of 30 μg/ml is currently being used for clinical application by solubilising in a mixture of ethanol and Chremophor® EL (polyoxyethylated castor oil). But a series of drawbacks associated includes Chremophor® allied hyperlipidaemia, neurotoxicity, hypersensitivity reactions as well as distorted paclitaxel kinetics (Gelderblom et al. 2001; Surapaneni et al. 2012). Leaching of plasticizer diethylhexyl phthalate from polyethylene tubing and PVC infusion bags further adds up the toxicity (Goldspiel 1999). All the afore-mentioned problems associated with paclitaxel have led to an extensive research on designing and developing

alternate delivery system for safe and adequate delivery of paclitaxel. Apart from the approved Abraxane®, other formulations are in pipeline and currently undergoing clinical trials such as Genexol-PM, NK 105. Other approaches include solid-lipid nanoparticles, polymeric nanoparticles, micelles and lipid capsules are also being currently explored as alternative formulations for paclitaxel solubilization (Agueros et al. 2009; Cavalli et al. 2000; Erdogar et al. 2016; Lundberg 2011; Mu and Feng 2003; Peltier et al. 2006; Zhang et al. 2016).

For solubilizing paclitaxel, cyclodextrin inclusion complexation with a variety of cyclodextrins and cyclodextrin derivatives has been previously reported (Hamada et al. 2006; Park 2010). Mognetti et al. have worked on developing cyclodextrin based paclitaxel formulation free of Chremophor® or any surfactants (Mognetti et al. 2012). The work exhibited that prepared carbonate nanosponges with a size of about 450 nm displayed effective complexing and solubilizing of paclitaxel. One milliliters (1.5% w/w) aqueous nanosponge suspension solubilized 2 mg of paclitaxel to make a homogenous dispersion that is devoid of paclitaxel crystals. The physical stability of aqueous dispersion of paclitaxel was found to be superior for about 6 months. Nanosponges stored in aqueous suspension at 4 °C formed a stable colloidal system that lacked any drug crystals, with absence of any signs of aggregation, stable particle size and distribution and highly charged negative surface. No burst release upon in vitro paclitaxel release explains the paclitaxel complexation in nanosponges and showed no presence of uncomplexed or weakly absorbed drug. Upon dilution with PBS at 37 °C, paclitaxel was released completely over a period of 2 h which reflects better drug solubilization with no crystallization and depleted of any surfactant or solubilizing agent. Haemolytic analysis for paclitaxel loaded aqueous nanosponges suspension revealed insignificant haemolytic potential post incubation with red blood cells (RBCs) at 37 °C. Further, blank nanosponges did not affect the cell vitality thereby confirming the biocompatibility of the prepared nanosponge formulation and making them a potential candidate that can be subjected for evaluating anticancer potential. Cytotoxicity evaluation against AT84 cell lines has reflected effective inhibition of cell proliferation by paclitaxel- nanosponges in contrast to plain paclitaxel. This can be as a result of higher paclitaxel- nanosponges cell uptake, and further incubation with cells stipulated that very less amount of plain paclitaxel (0.2×10^{-8} μg/cell) was extracted, whereas for paclitaxel-nanosponges extracted drug amount was found to be 3.6×10^{-8} μg/cell. The result evidences that paclitaxel loaded nanosponges not only offers a way of overcoming Chremophor® EL related toxicity but also enhances the uptake of paclitaxel by tumor cells, significantly lowering paclitaxel IC_{50} and augmenting the drug pharmacological efficiency (Mognetti et al. 2012). When tested against MCF-7 cell lines, similar results were attained by Ansari et al. (2011a).

Torne et al. have tested the in vivo behaviour of lyophilized paclitaxel-nanosponges with a particle size and drug loading of 350 nm and 500 mg/g respectively, on rats. The freeze-dried particles were dispersed in pH 7.4 PBS and ingested orally as well as bolus into the tail at a fixed dose of 10 mg/kg to different groups of rat. Commercial Taxol® (Bristol-Meyers Squibb) was utilized as reference

for both of the experiments. Almost threefold increase in oral bioavailability was observed for the paclitaxel concentration in plasma (Torne et al. 2010).

Dexamethasone is a drug with poor aqueous solubility and limited clinical applications in ocular disorders owing to its deprived corneal permeability. Considering this, Swaminathan et al. have fabricated dexamethasone nanosponges for ocular delivery using diphenyl carbonate crosslinker. Synthesized nanosponges were claimed to be hyper-branched polymeric colloidal systems with ultra high encapsulation efficiency. The study aimed at formulating complexes of dexamethasone with three types of β-cyclodextrin nanosponges (obtained with different cross-linking ratio) for ocular applications. Nano-encapsulation was done by incubation-lyophilization technique to yield various nanosponges formulations. XRPD, DSC and FTIR-ATR studies were implied to confirm the interactions and encapsulation of dexamethasone with nanosponges. In vitro release studies results reflected controlled release of dexamethasone for around 5 h. Particle sizes of loaded nanosponges formulations were traced between 350 and 660 nm with low polydispersity indices, and zeta potentials were sufficiently high (−20 to −27 mV) to obtain a stable colloidal nanosuspension. In addition, transmission electron microscopy (TEM) and atomic-force microscopy (AFM) results confirmed spherical colloidal nature of nanosponges. Moreover, no adverse reactions have been reported for safety assessment study carried out ex vivo on bovine cornea; confirming safety of the system. Corneal permeability of dexamethasone from optimized nanosponge formulations was assessed on excised bovine cornea in corneal holders; which depicted higher permeability than the marketed formulation (Swaminathan et al. 2013).

Itraconazole loaded cyclodextrin based nanosponges was formulated by Swaminathan et al. with an aim to enhance the solubility of the anti-fungal drug inheriting a poor aqueous solubility of just 1 ng/ml at physiological pH. It was found that the formulation led to 27-fold increase in drug solubility and upon addition of polyvinylpyrrolidone (PVP), the solubility increased upto to 55-fold. This ultimately led to increase in bioavailability of the same (Swaminathan et al. 2007). In another research vocation, Vyas and Sharma have developed cyclodextrin based nanosponges of poor water soluble, first generation cephalosporin anti-bacterial drug cefadroxil; used in skin, throat and urinary tract infections (Vyas and Sharma 2012). The complexes of cefadroxil with three types of β-cyclodextrin nanosponges having different cross-linking ratio were developed with a view to enhance cefadroxil solubility and phase solubility study was done with the rationale to evaluate the solubilisation efficiency of fabricated nanosponges. In presence of nanosponges enhanced solubility of cefadroxil (by fivefolds) was reported and has been categorized as AL-type, as evident from phase-solubility profiles.

Effect of cyclodextrin based nanosponges on doxorubicin hydrochloride, dexamethasone and flurbiprofen was explored by Trotta and Cavalli (2009) and Maeda et al. (2000). While flurbiprofen and dexamethasone are lipophilic (log P 4.1 and 1.9 respectively), doxorubicin is hydrophilic in nature (log P 0.25). Following loading into cyclodextrin based nanosponges, enhanced aqueous solubility for lipophilic drugs with respect to hydrophilic drugs was observed, which can be attributed to greater number of lipophilic sites present for complexation as compared to hydrophilic sites on

cyclodextrin (Bilensoy 2015). Potential to solubilize drug entity by nanosponges was also confirmed in case of tamoxifen, a non-steroidal anti-oestrogen molecule, used for prevention or treatment for breast cancer (Shete et al. 2014), with a very poor solubility of 5.9 mg/L. Encapsulation of tamoxifen into nanosponges resulted in loading efficiency of greater than 40% w/w and better solubilization (about 2.2 mg tamoxifen solubilisation per 5 mg nanosponges). Furthermore, developed formulation exhibited a pseudo zero order kinetics in vitro, with a drug release of 60% in pH 7.4 post 2 h (Torne et al. 2013).

A non-nucleoside reverse transcriptase inhibitor, efavirenz; exhibiting solubility-limited bioavailability, is persistently prescribed for patients infected by human immunodeficiency virus (HIV). An attempt has been made to enhance the dissolution and solubility of this BCS (Biopharmaceutical Classification System) Class II drug via β-cyclodextrin based nanosponges; owing to the high loading capability of nanosponges and proven effectiveness in enhancement of solubility. For fabricating nanosponges, β-cyclodextrin was crosslinked with carbonates in various ratios, and efavirenz was loaded in nanosponges via solvent evaporation technique. Nanosponges with high loading capacity were selected for further studies, followed by preparation of binary as well as ternary complexes with PVP K30, efavirenz, and nanosponges. These complexes were then characterized for saturation solubility, phase solubility, solution state interaction, in vitro dissolution, and in vivo pharmacokinetics. Furthermore, spectral characterization via FTIR, DSC, PXRD, and field emission SEM confirmed the inclusion complexation. Stability constant was found to be 1997 l/mole for ternary complex, thereby indicating the formation of stable complex. Moreover, saturation solubility with ternary complex was 17-fold and fourfold higher in distilled water and simulated gastric fluid, respectively, and also, in vitro dissolution was enhanced by threefold and oral bioavailability of efavirenz was found to be improved by twofold via ternary nanosponges complexes as compared to the plain drug (Rao and Shirsath 2017).

9.5.6 Protein Delivery

For protein delivery (BSA as model protein) via systemic route, swellable cyclodextrin-based poly(amidoamine) nanosponges, coded as nanosponges 10 and nanosponges 11 were prepared by cross-linking β-cyclodextrin with 2,2-bis (acrylamidoacetic acid), or with a short polyamido-amine chain derived from 2,2-bis(acrylamidoacetic acid) and 2-methylpiperazine, respectively (Swaminathan et al. 2009, 2010a). The prepared formulations were sensitive to the surrounding media and pH. Poly(amidoamine) were reduced in nanosuspension through high-pressure homogenization technique. The encapsulation efficiency of BSA was found to be more than 90%, and a high protein-complexation was successfully achieved. Prolonged release of albumin in vitro was observed from the two swellable β-cyclodextrin nanosponges over a period of 24 h. The same could be attained by encapsulation of albumin with carbonate nanosponges. Recently, these nanosponges 10 and nanosponges 11 were utilized for incorporating lysozyme, and an

encapsulation efficiency and loading percentage of 89%, 17% and 96%, 19.6% for nanosponges 10 and nanosponges 11 respectively was achieved. These enzyme loaded-nanosponges exhibited pH-dependent release of lysozyme with prolonged kinetics and with retention of lysozyme biological activity (Deshmukh et al. 2016).

9.5.7 Cancer Therapy

Minelli et al. have evaluated in vitro anti-tumor potentiality of nanosponge carriers against androgen sensitive (LNCaP cell line) and refractory (DU145 and PC-3 cell line) prostate cancer models. Camptothecin nanosponges displayed greater chemotherapeutic activity against both the above-mentioned models in contrast to free drug. Amongst the cells, LNCaP was less sensitive against both camptothecin and carbonate nanosponges, when compared to DU145 and PC-3 cells. Interestingly, drug loaded nanosponges showed superior anti-proliferative effect as well as DNA damaging capability when compared to free camptothecin. In vitro studies such as cell motility and tumor cell adhesion to human umbilical endothelial cells were utilized to assess the anti-metastatic activity. At lower doses, camptothecin nanosponges were effective in inhibiting the adhesion as well as motility, and through sprouting and tubulogenesis assay angiogenic activity inhibition of drug nanosponges was confirmed. Further, in vivo evaluation of drug nanosponges on PC3-xenografted mice revealed remarkable inhibition of PC-3 cell engrafted with absence of any toxicity. All these results established significant enhancement of antitumor activity of drug nanosponges as compared to plain drug (Minelli et al. 2012).

In another approach, Gigliotti et al. extended the previously reported work of Minelli et al. and evaluated camptothecin nanosponges for tumor cells adhesion, migration, and STAT3 phosphorylation. Reportedly, camptothecin nanosponges exerted anti-adhesive effect in human endothelial cells and moreover inhibited angiogenic activity as reflected by sprouting and tubulogenesis assays. In vivo studies using SCID mice showed delayed PC-3 cell engraft growth devoid of any toxic effects. Hence, researchers claimed potential applicability of fabricated nanocarrier in drug delivery for cancer therapeutics (Gigliotti et al. 2016). Thus, all these findings support probable use of nanosponge technology for camptothecin delivery in cancer therapy.

Evaluation of tamoxifen nanosponge cytotoxicity against MCF-7 cell line drew a similar inhibitory effect on cell proliferation as that of paclitaxel. In vivo evaluation in rats by oral administration of 2 mg/ml concentration of tamoxifen-loaded nanosponge aqueous suspension reported higher drug plasma concentration of tamoxifen as compared to that of plain tamoxifen (Torne et al. 2013).

Another important application of cyclodextrin based nanosponges is towards achieving sustained release of drug actives. Encapsulation of drug in crosslinked nanosponge structure can achieve sustained release manner for the drug which helps dose reduction, alters the kinetics and most importantly reduces the unwanted side effects. Taking this approach, doxorubicin, an established chemotherapeutic agent

but associated with severe side effects, was taken as a model drug. Doxil® liposomes, a nanotechnology based formulation, reduced the doxorubicin related side effects along with improving the drug therapeutic index. With a loading efficiency of 20% w/w of doxorubicin into carbonate nanosponges, the system showcased a prolonged in vitro release achieved over an extended period of time (Cavalli et al. 2006b; Zhao et al. 2013).

Reportedly, Jain et al. have fabricated temozolomide nanosponges as innovative delivery system for brain tumors therapy. Temozolomide loading in nanosponges was established via solution state interaction study; which reflected temozolomide wavelength shift with respect to increased nanosponge concentration, indicating hydrophobic group masking. Further, FT-IR, DSC, XRD and NMR studies results too confirmed drug-nanosponges complexation and reduction in temozolomide crystallinity post nanosponges loading. A sustained drug release was evident from in vitro release profile. Cell viability study (done using U-373 glioma cell line via SRB assay) outcomes indicated equal cytotoxic potential as that of pure temozolomide at similar dose with distortion of cells. Thus, fabricated nanosponges were claimed to be potent drug carrier in treatment of brain tumors (Jain et al. 2013).

Curcumin is a well-established and recognized polyphenolic antitumor agent obtained from rhizomes of *Curcuma longa* with enormously less water solubility (0.4 μg/ml) (Prasad et al. 2014). Cyclodextrin based nanosponges of curcumin were prepared with an aim to enhance curcumin solubility and subsequently the bioavailability (Darandale and Vavia 2013; Naksuriya et al. 2014). It has been previously established and reported that cyclodextrins and various cyclodextrin derivatives possess complexation ability with curcumin (Baglole et al. 2005; Naksuriya et al. 2014; Tonnesen et al. 2002). Cyclodextrin based nanosponges depicted enhanced solubilization of curcumin (20.9 μg/ml) with respect to native β-cyclodextrin (5.9 μg/ml). A biphasic in vitro release profile was depicted with a diminutive initial burst effect; which was corroborated to presence of uncomplexed drug in the cyclodextrin cavity. Curcumin release was reported to be slow and in controlled manner over long time period and only about 25% drug release has been traced after 48 h (Darandale and Vavia 2013).

Transresveratrol, a diphenyl stilbene derived from grapes, was complexed with β-cyclodextrin and 2-hydroxypropyl β-cyclodextrin based on the consideration of therapeutic application of transresveratrol in cancer chemotherapy (Amri et al. 2012; Berta et al. 2010; Lu et al. 2011; Sapino et al. 2009). Besides, Ansari et al. have tailored carbonate nanosponges of resveratrol, with a drug loading of 40% w/w and improvised photostability (Ansari et al. 2011b). When tested for cytotoxicity against HCPC-1 cells, it was seen that the cytotoxic potential of nanosponge formulation was much higher compared to the pure drug.

Hariri et al. have designed a sequential HVGGSSV peptide targeted nanosponges based delivery system of paclitaxel (microtubule inhibitor) and camptothecin (topoisomerase-I inhibitor) for lung cancer chemotherapy. Schedule-reliant combined therapy of paclitaxel nanoparticles and camptothecin nanoparticles was evaluated in vitro via confocal imaging and flow cytometry, for analyzing changes in microtubule morphology, cell cycle, apoptosis and proliferation. After exposure of

lung cancer cells to paclitaxel nanoparticles and camptothecin nanoparticles, results depicted significant G2 or M phase cell cycle arrest and changes in microtubule dynamics that led to reduced proliferation and enhanced apoptotic cell death. Binding of HVGGSSV-nanoparticles to tumor at 24 h was validated by TEM and in vivo molecular imaging studies; which also established nano-gold labelled HVGGSSV-nanoparticles presence in microvascular endothelial cells of tumor. Furthermore, efficacy studies carried out using paclitaxel and camptothecin nanoparticle exhibited higher tumor growth inhibition activity in combination compared to monotherapy (twofold increase) and untargeted group (fourfold increase). Significant levels of both drugs were quantified in tumors via HPLC-MS post 2 and 23 days of injection. Efficacy of fabricated nanosponges based delivery system in sequential treatments was established using both in vitro and in vivo lung cancer models; which reflected augmented microtubule disruption and G2 or M phase arrest, consequently ensuing reduced cell proliferation, vascularity and enhanced apoptotic cell death (Hariri et al. 2014).

Researches from Vanderbilt University reportedly developed anticancer drug encapsulated nanosponges carrier that could possibly inhibit the tumor growth upto fivefold more than that of the direct drug injection. The approach hypothesis was targeting the drug loaded nanosponge particles to tumor cells for binding with radiation induced receptors, followed by release of the loaded drug. In vivo studies to record tumor cell response (fast-acting glioma, slow-growing human breast cancer cells) suggested an efficient release of drug with a subsequent improvement in cancer cell death and no significant relapse (Osmani et al. 2016a; Swaminathan et al. 2016).

Choi et al. using the mucoadhesive polymer polyethylene oxide and thermosensitive polymer Pluronic F127 (PF127) have developed a buccal paclitaxel delivery system. Here, paclitaxel was incorporated into an inclusion complex with (2,6-di-O-methyl)-β-cyclodextrin (DM-β-CD) to improve paclitaxel aqueous solubility. Formation of the paclitaxel inclusion complex was confirmed using various techniques, such as PXRD, FT-IR spectroscopy, DSC and SEM. Hydrogels were prepared using cold method and the sol-gel transition temperatures of hydrogels were measured using tube-inversion method. Franz diffusion cell containing phosphate buffer solution (PBS, pH 7.4) at 37 °C was employed to measure drug release from the hydrogels. Cytotoxic potential of all formulations were assessed via MTT assay using a human oral cancer cell line (KB cell). As been reported, in presence of PF127, sol-gel transition temperature of hydrogels was decreased, and also varied in presence of mucoadhesive polymers. Moreover, the in vitro release was found to sustain on addition of polyethylene oxide and resulted in sluggish release rate. The cytotoxicity of blank formulation was low, although the drug-loaded hydrogel depicted acceptable cytotoxicity. Researchers on basis of these results concluded that the combination of PF127-based mucoadhesive hydrogel formulation and inclusion complexes improved the in vitro release and cytotoxic effect of paclitaxel (Choi et al. 2014).

Doxorubicin is one of the most used and efficient anticancer drug that acts through numerous mechanism, but toxicity and chemo-resistance limits doxorubicin use. Thus, to overcome these limitations, novel strategies for reducing dose and

overcoming chemo-resistance are required. As evident from several prior studies, chemo-resistant cancer cells become extremely adopted to inherent oxidative stress by escalating the antioxidant systems; which consequently led to higher intracellular glutathione content. Novel glutathione targeted doxorubicin nanosponges were prepared by Daga et al. for preferentially releasing doxorubicin in cancerous cells with higher glutathione content (Daga et al. 2016). It has been reported that glutathione targeted doxorubicin nanosponges significantly inhibited cell viability, clonogenic growth and topoisomerase II activity, and persuaded DNA damage more effectively than that of free doxorubicin. Furthermore, in vivo efficacy of fabricated nanosponges in reducing human tumor was also established in xenograft models.

In another research study, Xu et al. have synthesized and characterized γ-cyclodextrin based nanosponges carrier for molecular encapsulation of popular anticancer agent doxorubicin. The β-naphthyl alanine residue linked to primary face of γ-cyclodextrin derivative exhibited strong binding capacity with doxorubicin. Encapsulation efficiencies were assessed under various temperature and pH conditions, and it was reported that the carrier-doxorubicin inclusion complex was highly stable under wide range of acidic conditions (pH 1–7); however, encapsulated drug was slowly released under hyperthermic conditions (up to 50 °C). Cell culture studies showed that doxorubicin complexation with nanosponges protected cell uptake and also greatly reduced doxorubicin toxicity. Thermo-triggered doxorubicin release and increase in cellular uptake was further confirmed by in vitro experiments. In light of the findings, investigators concluded that the novel γ-cyclodextrin derivative effectively encapsulates doxorubicin and the inclusion was thermo responsive too; rendering efficient doxorubicin delivery in combination with hyperthermia treatment strategies (Xu et al. 2014).

Recently, Dora et al. have prepared erlotinib β-cyclodextrin nanosponges with rationale of assessing effect on solubility, dissolution, oral bioavailability and in vitro cytotoxicity of erlotinib (Dora et al. 2016). Stoichiometric concentrations of erlotinib and cyclodextrin nanosponges were optimized by conducting preliminary studies and finally erlotinib nanosponges (in optimized 1:4 ratio) were prepared by freeze drying technique. Obtained erlotinib nanosponges were noted to have average size of 372 ± 31 nm with least polydispersity index and high zeta potential. In vitro dissolution studies revealed improved dissolution efficiency of nanosponges compared to pure erlotinib, with a twofold enhancement in dissolution rate. Apoptosis assay carried out in PANC-1 and MIA PaCa-2 pancreatic cell lines indicated greater cytotoxic potential of erlotinib nanosponges with similar pattern (Fig. 9.7). Erlotinib depicted apoptotic index of 0.37 and 0.42, which has been elevated to 0.79 and 0.82 against MIA PaCa-2 and PANC-1 cell lines, respectively. Higher cellular uptake and uptake efficiency were unveiled via both qualitative and quantitative cell uptake studies. In addition, enhanced erlotinib oral bioavailability with higher Cmax (by 1.8-fold) and $AUC_{0\text{-}\infty}$ (by ~2 fold) was recorded with respect to pure erlotinib. Enhanced dissolution rate profile and oral bioavailability of erlotinib nanosponges compared to that of pure erlotinib. Taking into consideration all these observations,

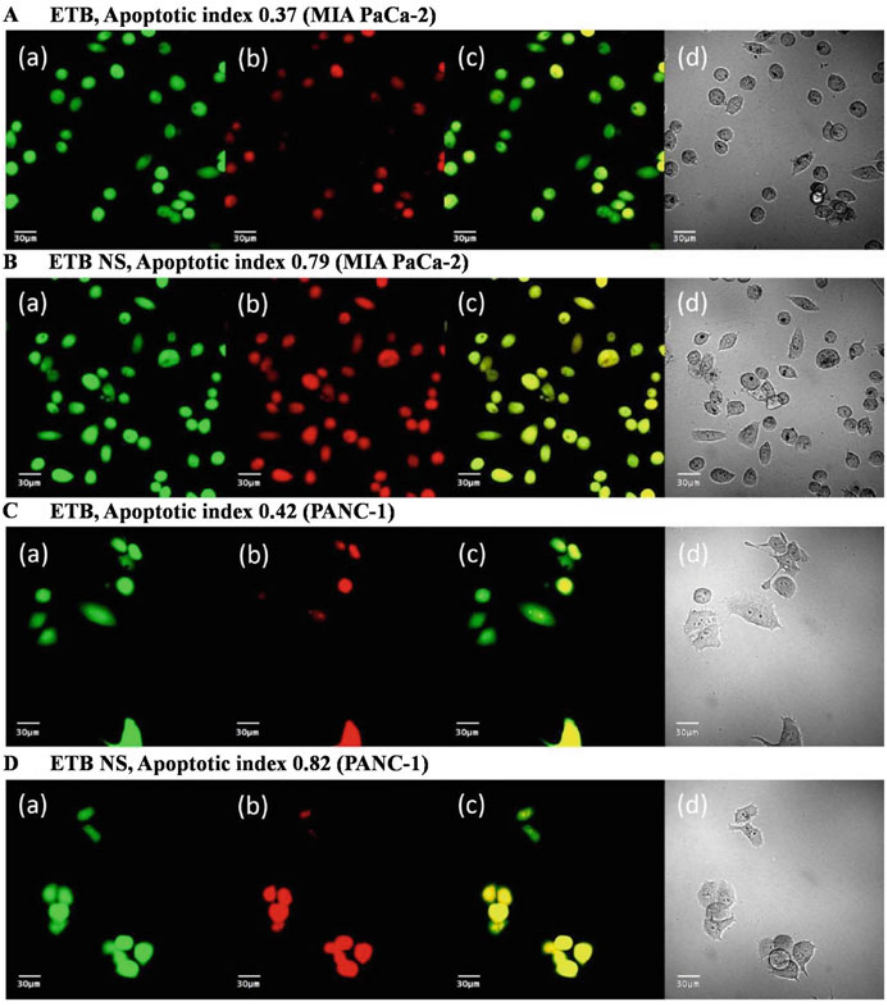

Fig. 9.7 Apoptosis assay of erlotinib nanosponges (ETB NS); (**a**) ETB (apoptotic index 0.37) and (**b**) ETB NS (apoptotic index 0.79) with MIA PaCa-2 cell line, and (**c**) ETB (apoptotic index 0.42) and (**d**) ETB NS (apoptotic index 0.82) with PANC-1 cell line. The assay results confirmed greater cytotoxic potential of ETB nanosponges with quite similar patterns in both PANC-1 and MIA PaCa-2 pancreatic cell lines. (Reproduced with permission from Dora et al. 2016, Copyright 2016 Elsevier B.V.)

researchers concluded nanosponge fabrication as an effective strategy to combat solubility issues and to reduce dose and dose allied side effects of erlotinib.

Preliminary studies on anti-tumoral potential of pyro-nanosponges showed promising results. Pyro-nanosponges possess significant encapsulation efficiency for both cisplatin and doxorubicin, which can be due to presence of an extra electrostatic interaction among protonated amine groups of both the above said drugs and the

carboxylic groups present in the pyro-nanosponge matrix. As a result, pyro-nanosponges achieve slower release profiles than carbonate nanosponges. Taking all the positive outcomes in consideration, in depth investigation in the direction of advance nanosponges formulation has been attracting interest.

9.5.8 Antimycotic Therapy

Cyclodextrin based nanosponges of itraconazole formulated by Swaminathan et al. in order to address the poor aqueous solubility at physiological pH (1 ng/ml) of the same (Swaminathan et al. 2007). Results showed a 27-fold increase in solubility, and in presence of PVP as a secondary component the solubility subsequently improved by 55-fold. On comparing the in vitro release profiles of prepared drug formulations with marketed products, the former exhibited much faster release dissolution profile. This further evidences the enhancement of bioavailability of poorly water soluble drugs via cyclodextrin-based nanosponges.

Inefficient absorption of econazole nitrate, an antifungal agent topically administered for superficial candidiasis requires higher drug concentration to be incorporated in the formulation for effective therapy. Therefore, econazole nitrate nanosponges prepared using emulsion solvent diffusion method, and further loaded in hydrogel as local depot for sustained drug release (Sharma et al. 2011).

In another research study, our group continued the quest by fabricating cyclodextrin nanosponges of a BCS Class II drug clotrimazole; therapeutic potential and widespread use of which is restrained by poor solubility, bioavailability and comparatively short half-life of clotrimazole. Varied molar ratios of hydroxypropyl-β-cyclodextrin (HP-β-CD) to dimethyl carbonate crosslinker were taken (1:2, 1:4 and 1:8) to synthesize clotrimazole nanosponges via hot melt method. Synthesis was followed by drug loading, and then characterization, interactions among clotrimazole and nanosponges were validated by FT-IR, DSC and PXRD analysis. FT-IR, DSC and PXRD results confirmed clotrimazole-nanosponge interaction, besides PXRD analysis revealed decreased crystallinity of clotrimazole following nanosponges loading. Moreover, the loaded nanosponges have shown more solubilization efficiency with respect to plain clotrimazole. Fabricated nanosponges particles depicted average size around 455.6 ± 11 nm and least polydispersity index (0.143), with quite high zeta potential (-21.32 ± 1.3 mV) to acquire a stable nanosuspension. The nanosponges size and surface morphology were further investigated using SEM and TEM analysis, observations of which revealed roughly spherical shape of nanosponges with spongy nature and uniform distribution. The TEM results showed that the regular size and shape of the blank HP-β-CD nanosponges were unaffected even after clotrimazole loading. A 3^2 full factorial design was implied to optimize Pluronic® based in situ intravaginal gel containing clotrimazole nanosponges for augmented vulvo-vaginal candidiasis therapy. Nine formulations were prepared as per the design using different Pluronic F-127: Pluronic F-68 ratios; evaluated for data collection and subjected to check point

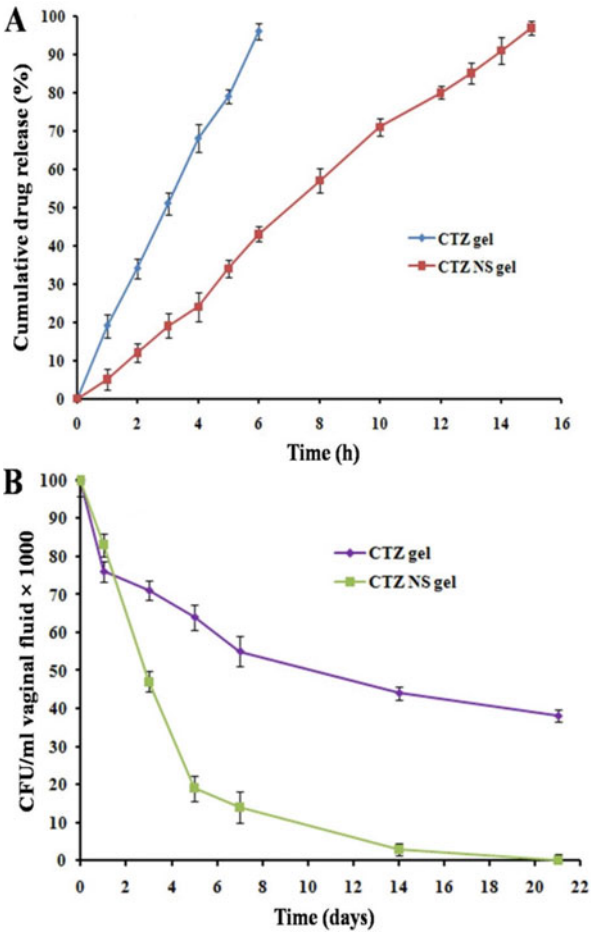

Fig. 9.8 (**a**) In vitro release profiles of plain clotrimazole (*CTZ*) and clotrimazole loaded hydroxypropyl beta-cyclodextrin nanosponges (*CTZ NS*) based in situ vaginal gels in simulated vaginal fluid. (mean±S.D, $n = 3$), (**b**) Fungal clearance kinetics of *C. albicans* infection in infected, oophorectomized rats; each curve represents the mean of six rats. Marked differences in the fungal clearance kinetics of clotrimazole hydroxypropyl beta-cyclodextrin nanosponge gel and plain clotrimazole gel have been noted (p smaller than 0.003)

analysis. Statistically optimized in situ gel was assessed for in vitro release, bioadhesion and in vivo antifungal, irritation study on female Wistar albino rats. Results showed that the optimized gel could prolong the drug release upto 15 h, which in contrast was higher than the drug release from the conventional in situ gel (6 h as depicted in Fig. 9.8a). Further, the in vivo antifungal and in vitro bioadhesion of prepared clotrimazole nanosponges gel formulation was found to be superior when compared to the conventional counter-part (Fig. 9.8b), and was non-irritant in nature. These findings signify the potential applicability of clotrimazole nanosponges gel as a novel delivery system for treating local vulvo-vaginal candidiasis and infections that are alike (Osmani et al. 2016b).

Lemongrass oil is a volatile principle derived from *Cymbopogon citratus* leaves; which has gained much importance in pharmaceutical industry owing to numerous clinical and pharmacological effects. However, poor aqueous solubility and instability issues limit prevalent use of lemongrass oil. Thus, to surmount aforementioned

problems, Aldawsari et al. have designed and fabricated lemongrass oil loaded ethyl cellulose nanosponges containing topical hydrogel with augmented antifungal effect. At first ethyl cellulose nanosponges were synthesized via quasi emulsion solvent diffusion technique and then nanosponge dispersions were integrated in carbopol hydrogels (0.4% w/v). Employing 3^2 full factorial design formulations were prepared considering ethyl cellulose: polyvinyl alcohol ratio and stirring rate as independent variables. Minimal inhibitory concentration and minimal fungicidal concentration of lemongrass oil estimated via broth macrodilution method against *Candida albicans* ATC 100231 strain were reported to be 2 and 8 μL/mL, respectively. All the nanosponge formulations had reasonable citral content and exhibited sustain release profiles. Statistical analysis depicted significant effect of both independent variables on responses (i.e. particle size and percent drug release) with more prominence of stirring rate. Design optimized nanosponges formulation subjected to morphological studies via SEM and TEM reflected uniform spherical shape with spongy nature that remained unaltered even after hydrogel integration. The optimized formulation was reported to be non-irritant with augmented antifungal efficacy (Aldawsari et al. 2015).

9.5.9 Antiviral Therapy

Nanosponges can serve as a versatile carrier to deliver the actives via ocular, nasal and pulmonary routes. Delivery of anti-viral drugs or small interfering RNA (siRNA) into the nasal epithelia and lungs can be augmented via these nanocarriers for specifically targeting viruses infecting the respiratory tract like rhinovirus, influenza virus and respiratory sinctial virus. Additionally, nanosponges can be utilized against Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV) and Hepatitis-B Virus (HBV). The drugs that can be incorporated to enact against the above-said viruses includes zidovudine, saquinavir, nelfavir and interferon-α (Ansari et al. 2011b). In a research vocation, Lembo et al. have fabricated carboxylated cyclodextrin based nanosponges carrying carboxylic groups within the structure, as novel acyclovir carriers. TEM measurements revealed spherical shape and an average size of about 400 nm. The behavior of carboxylated nanosponges with regard to the loading and delivery of acyclovir was compared to that of previously fabricated nanosponge carriers. DSC, XRPD and FT-IR analyses were implied to investigate the two nanosponge formulations; which confirmed the incorporation of acyclovir into the nanosponge structure and nanosponges-acyclovir interactions. The acyclovir loading into carboxylated nanosponges was found higher (70% w/w) than that of plain nanosponges. In vitro release studies showed prolonged release kinetics of acyclovir with no initial burst effect. The nanosponge uptake into cells was evaluated using fluorescent carboxylated nanosponges; which revealed the nanoparticle internalization. Superior antiviral activity of acyclovir loaded carboxylated nanosponges was reported against a clinical isolate of HSV-1 (Lembo et al. 2013).

9.5.10 Mammalian Cells Micropatterning

To mimic physiological-relevant situations in vivo, artificial scaffolding structures that can replicate the same in vitro becomes a critical criteria for various biological and medicinal areas like bone and cartilage generation, tissue engineering, biomaterials, small-scale biomedical devices, and developing nanofabrication methods. Based on simple techniques and principles like liquid vapour deposition and photolithography, a group of researchers developed non-cytotoxic scaffolds with a nanometer resolution using silicon substrates as backbone. The techniques comprise merging of optics-based approach along with chemical restructuring which can modify the surface properties. This nanofabrication-based approach enables the developing of hydrophobic oxidised silicon nanosponges, followed by probing cellular-responses examining cytoskeletal and morphological changes in living cells by combing fluorescence microscopy and scanning electron microscopy through culturing HIG-82 fibroblasts, Madin-Darby canine kidney cells and Chinese hamster ovary cells on these silicon nanosponges. The study shows the potential applicability of these silicon-based nanosponges on influencing cellular behaviours at desired locations (Yang et al. 2012).

9.5.11 Detoxification Treatments

Toxin-targeted anti-virulence therapy helps in detoxification of the body from virulence factors caused by bacterial infections, venomous infections and biological weaponry. However, the current available detoxification platforms like anti-sera and monoclonal antibodies act via targeting the molecular structure of toxins, and hence, a need for customised treatment for different diseases becomes mandate. A biomimetic toxin nanosponges were prepared by a group of researched from University of California, San Diego that could function as a toxin decoy in vivo. As reported, these nanosponges comprised of a polymeric nanoparticle core which is surrounded by RBCs membrane and absorbs the toxins capable of damaging the membranes, followed by diverting them away from the cellular targets (Fig. 9.9). This venture helps in combating drug-resistant infections like methicillin-resistant *Staphylococcus aureus* infections (MRSA). Each RBCs cell membrane can mask about 3000 nanosponges, thereby imparting a stealth nature. As tested on mouse model, reduction in toxicity of staphylococcal alpha-haemolysin (a toxin) by the prepared nanosponges was observed, which can be attributed to the safe disposition of toxin loaded nanosponges by liver, thereby improving the survival rate of toxin-challenged mice. Therefore, an alternative detoxification by using these toxin nanosponges can potentially treat a variety of injuries and diseases that are caused by pore forming toxins (Hu et al. 2013).

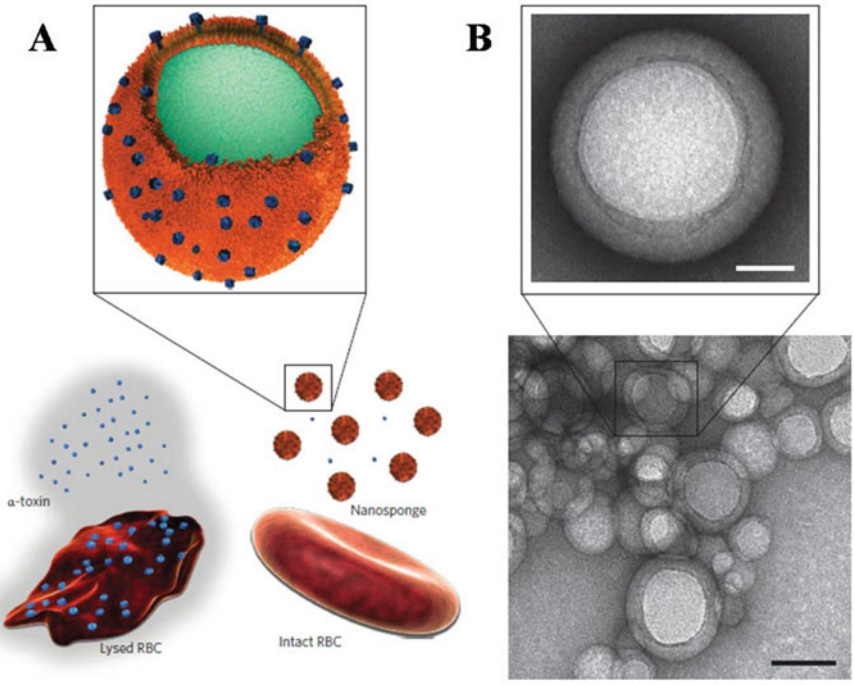

Fig. 9.9 Schematic and actual structures. (**a**) Schematic structure of toxin nanosponges and the mechanism of neutralizing pore-forming toxins (PFTs). The nanosponges consist of substrate-supported red blood cell (RBC) bilayer membranes into which PFTs can incorporate. After being absorbed and arrested by the nanosponges, the PFTs are diverted away from the cellular targets, thereby avoiding target cells and preventing toxin-mediated haemolysis. (**b**) TEM visualization of nanosponges mixed with α-toxin (scale bar, 80 nm) and the zoomed-in view of a single toxin-absorbed nanosponge (scale bar, 20 nm). The sample was negatively stained with uranyl acetate before TEM imaging. (Reproduced with permission from Hu et al. 2013, Copyright 2013 Macmillan Publishers Ltd)

9.5.12 Miscellaneous

The porous nature of nanosponges as a result of polymerization and the numerous cavities in cyclodextrin along with swelling behaviour upon absorption of water enables the nanosponges to either encapsulate or entrap a range of molecules (Liang et al. 2012). Molecular encapsulation of gases in cyclodextrin can play an important role in the field of biology, pharmaceuticals as well as cosmetics. β-cyclodextrin has been previously investigated for the ability to store large amounts of carbon dioxide, oxygen and 1-methylcyclopropene (Trotta et al. 2012). Different cyclodextrin nanosponges were synthesized by crosslinking α-, β-, γ-cyclodextrin with carbonyl diimidazole as oxygen-encapsulating formulations (Cavalli et al. 2010) with an ability to release oxygen with or without the influence of ultrasound. By a

combination of nanosponges and hydrogel, permeation of oxygen through a silicon membrane was successfully achieved. The synthesized nanosponges could encapsulate, store and achieve slower sustained release oxygen for prolonged durations, and in presence of ultrasound the in vitro release as well as permeation of the same was improvised. Thus, it could be said that nanosponges can serve as suitable carriers for topical delivery of oxygen, either in presence or absentia of ultrasound, and act as a reservoir for oxygen.

In the field of proteomics, three dimensional nanosponges have been proven useful in peptides fractionalization (Wong et al. 2009). Also, nanosponges serve as an important diagnostic tool for crucial disorders like cancer, as a result of the ability to soak up biomarkers and carry fluorescent dyes and reagents (Alongi et al. 2011). In a research approach, Deshmukh et al. have developed cyclodextrin based molecularly imprinted and non-molecularly imprinted polymer nanosponges for glucose estimation (Deshmukh et al. 2015). Molecularly imprinted nanosponges were prepared by first associating glucose phosphate to nanosponges via polymerization and then removal of glucose that contributes to higher glucose affinity of nanosponges. It has been noted that molecularly imprinted nanosponges retained more number of nano pores, whereas non-molecularly imprinted nanosponges were less porous with deprived aggregation propensity. Both nanosponges depicted varied binding specificities and capacities along with almost similar degree of swelling. FT-IR study results reflected possible entrance and selective binding of glucose molecules into cavities created by template extraction. The researchers concluded that molecularly imprinted nanosponges are superior to non-molecularly imprinted nanosponges owing to the binding specificity and high surface area.

For removal of organic pollutants, odours, flavours and oil spills, the ability of cyclodextrin based nanosponges to bind with these molecules can be utilized for eradicating the same from aqueous systems (Taka et al. 2017; Trotta and Wander 2005; Vasconcelos et al. 2016). Selective segregation of inorganic electrolytes using size exclusion chromatography can be achieved with hyper-crosslinked nanosponges (Donaldson 2012). Liang et al. have utilized carbonate nanosponges as supramolecular reaction media in order to sensitize the enantio-differentiating photoisomerization of cyclooctene and 1,3-cyclooctadiene compounds. The results showed nanosponges with exceptional photochirogenesis behavior with a considerable difference from that of conventional sensitizer-customized cyclodextrin based structure (Liang et al. 2012).

In a recently reported study, researchers have fabricated methyltrioctylammonium chloride (aliquat 336) tailored cellulose nanosponges as innovative absorbent for pre-concentration, determination and removal of tartrazine dye. Characterization of adsorbent was done implying FT-IR, XRD and SEM and dye pre-concentration and removal events were investigated via column and batches mode, respectively. Effects of diverse parameters like aqueous medium pH, adsorbent amount, methyltrioctylammounium chloride dose, interfering ions and desorption conditions on tartrazine adsorption were assessed and optimized. Tailored nanosponges depicted utmost tartrazine adsorption capacity (180 mg/g) and pursued Brunauer-Emmett-Teller

(BET) model as evident from experimental data fitted to conventional isotherm models. For UV spectrophotometric estimation, the noted linearity range was 2–300 ng/mL with a limit of detection 0.15 ng/mL. The proposed method was claimed to be applicable for pre-concentration and estimation of tartrazine dye in diverse water samples (Shiralipour and Larki 2017).

In addition to above covered approaches, it is worth to quote that by deeming unique beneficial assets of nanosponges (biocompatibility and versatility); one recent report by European Commission has recommended the utilization of cyclodextrin nanosponges for food technology, cosmeceutical, pharmaceutical and biomedical applications (Lu et al. 2011; Osmani et al. 2016a; Swaminathan et al. 2016). Hence, nanosponges hold many exigent advantages in the field of drug delivery and nanotherapeutics and are competent to overcome the few limitations allied with nano-delivery systems and conventional formulations. A tabulated summary of examples of β-cyclodextrin based nanosponges fabricated till date in the direction of facilitation of drug delivery and augmented therapy is given in Table 9.5.

9.6 Conclusions

Cyclodextrin based nanosponges constitutes atypical class of biocompatible delivery system that allows a smooth transformation from conventional delivery to a versatile delivery system due to presence of flexible crosslinked polymers, and fulfils the afore-mentioned required characteristics. The system offers encapsulation of hydrophilic as well as lipophilic drugs, and allows controlled-cum-predictable release of the drug at the target site, thereby improving the bioavailability and efficacy. The required particle size and release rate can be attained by controlling the polymer to crosslinker ratio. Further, nanosponges based delivery systems also addresses the solubility dilemma that are associated with newly developed drug entities, and protects the active moieties from degradation. Also, various dosage forms of the same can be formulated as desired, and the side effects associated with conventional formulations can be surmount by advanced approaches like stimuli sensitive nanosponges and tumor-targeting. Currently, extensive research has been focussed towards developing faster and simple techniques for developing nanosponges. Additionally, molecular imprinting of nanosponges with drugs is another area of research booming nowadays; wherein during synthesis the drug can be intercalated into the nanosponges reticulate complex to achieve slower drug release. At present, research is invested towards synthesis and characterization of PEGylated nanosponges, soluble nanosponges and cationic nanosponges for the umpteen numbers of applications. To conclude, cyclodextrin based nanosponges with multitude number of beneficial attributes can contribute as a promising tool for effective and efficient drug delivery, and can be endorsed as an advanced carrier in the field of drug delivery and nanotherapeutics.

Table 9.5 Detailed examples of β-cyclodextrin based nanosponges fabricated for the facilitated drug delivery and augmented therapy

Drug(s)	Indication	Study	In vitro or In vivo or mathematical model	Reference(s)
Antisense oligonucleotides	Cancer, viral infections and pathologic disorders	Pharmacokinetic studies	Mice	Aynie et al. (1999)
Itraconazole	Fungal infections	Saturation solubility study	Higuchi model	Swaminathan et al. (2007)
Bovine Serum Albumin (BSA)	Viral, malignant, autoimmune diseases	In vitro release	Dialysis bag	Swaminathan et al. (2010a)
Camptothecin	Cancer	In vitro release	Multicompartment rotating cells with dialysis membrane	Swaminathan et al. (2010b)
		Haemolytic activity	Diluted blood	
		Cytotoxicity	HT-29 cell line	
Oxygen gas (O_2)	Hypoxic conditions	Safety and oxygen delivery	Vero cells	Cavalli et al. (2010)
Paclitaxel	Cancer	Oral bioavailability	Sprague Dawley rats	Torne et al. (2010)
Paclitaxel	Cancer	Cytotoxicity	MCF-7 cell line	Ansari et al. (2011a)
Resveratrol	Inflammation, cardiovascular diseases, dermatitis, gonorrhoea, fever and hyperlipidemia	Cytotoxicity	HCPC-I cell line	Ansari et al. (2011b)
		Accumulation of drug in the buccal mucosa of rabbit	Rabbit buccal mucosa	
		Ex vivo permeation study	Pig skin	
Paclitaxel	Cancer	In vitro drug release	Dialysis bag technique	Mognetti et al. (2012)
		Haemolytic activity	Red blood cells	
		Cytotoxicity	AT84 cell line	
1-methylcyclopropene, oxygen and carbon dioxide	Diverse biomedical conditions	CO_2 and O_2 encapsulation	Gravimetric analysis and oxymeter	Cavalli et al. (2010) and Trotta et al. (2012)

(continued)

Table 9.5 (continued)

Drug(s)	Indication	Study	In vitro or In vivo or mathematical model	Reference(s)
Cefadroxil	Skin, throat and urinary tract infections	Phase solubility	Mechanical shaker	Vyas and Sharma (2012)
Camptothecin	Prostate cancer	In vitro anti-tumor efficacy	Androgen refractory DU145 and PC-3 model, and androgen sensitive LNCaP model	Minelli et al. (2012)
Acetyl salicylic acid	Fever and pain conditions	In vitro drug release	Membrane dialysis	Shende et al. (2012)
		Analgesic and anti-inflammatory activity	Albino Wistar rats	
Telmisartan	Hypertension	In vitro drug release	USP type-I apparatus	Rao et al. (2013)
		Bioavailability	Albino Wistar rats	
Dexamethasone	Brain tumours	In vitro drug release	Dialysis bag technique	Swaminathan et al. (2013)
		Ex vivo safety study	Excised bovine cornea	
Tamoxifen	Breast cancer	Cytotoxicity	MCF-7 cell line	Torne et al. (2013)
Acyclovir	Viral infections	In vitro release	Multicompartment rotating cells with dialysis membrane	Lembo et al. (2013)
		Cellular uptake	Vero cells	
		Cytotoxicity	Vero cells	
		Antiviral activity	HSV-1 MRC	
Calcium carbonate ($CaCO_3$)	Hyperphosphatemia	In vitro release study	USP type-I dissolution apparatus	Shende et al. (2013)
		Accelerated stability study	Stability chamber	
Temozolamide	Brain tumours	In vitro release study	Membrane dialysis	Jain et al. (2013)
		Cytotoxicity	SRB assay using U-373 glioma cell line	
Curcumin	Cancer	In vitro drug release	Dialysis bag technique	Darandale and Vavia (2013)
		Haemolytic activity	Red blood cells	
		Cytotoxicity	MCF-7 cell line	

Minoxidil	Alopecia	In vitro drug release	Franz diffusion cell	Ansari et al. (2014)
Paclitaxel	Cancer	In vitro drug release in PBS (pH 7.4) and gastrointestinal fluid	Franz diffusion cell	Stevens et al. (2014)
Ibuprofen sodium	Inflammatory and painful conditions	Molecular environment and transport properties of drug	High resolution magic angle spinning (HRMAS) NMR spectroscopy	Ferro et al. (2014)
		Mean square displacement (MSD) of drug in gel	Pulsed field gradient spin echo (PGSE) NMR spectroscopy	
Quercetin	Cancer	In vitro dissolution	Multicompartment rotating cell with dialysis membrane	Anandam and Selvamuthukumar (2014)
		Stability study	Photostability using UVA lamp,	
			Simulated intestinal fluid (SIF) stability assay	
		In vitro antioxidant activity	DPPH assay, antisuperoxide formation assay, superoxide anion-scavenging activity assays and metal chelating activity	
Atorvastatin	Dyslipidemia	In vitro drug release	USP type-II dissolution apparatus	Deshpande and Patel (2014)
		Accelerated stability study	Stability chamber	
Paclitaxel and camptothecin combination	Lung cancer	In vitro study	Flow cytometry and confocal imaging	Hariri et al. (2014)
		In vivo study	Molecular imaging and TEM	
Paclitaxel	Cancer	In vitro drug release study	Franz diffusion cell	Choi et al. (2014)
		Cytotoxicity	MTT assay using KB cell	
Doxorubicin	Cancer	Cytotoxicity	MTT assay using KB cell	Xu et al. (2014)
		Cellular uptake	BCA assay using KB cell	
Neuroprotective drug	Glaucoma	Drug release and pharmacokinetic studies	Animal model, ex vivo human tissue	Galloway et al. (2014)

(continued)

Table 9.5 (continued)

Drug(s)	Indication	Study	In vitro or In vivo or mathematical model	Reference(s)
Brimonidine travoprost and bimatoprost	Occular hypertension, glaucoma	Intraoccular pressure, retinal deposition and retinal ganglion cell (RGC) uptake of neuro-DiO,	Mice	Lambert et al. (2015)
		Confocal microscopy		
Lemongrass oil	Fungal infections	Particle size	DLS technique	Aldawsari et al. (2015)
		Citral content	HPLC quantitative analysis	
		In vitro release	Dialysis bag technique	
		Statistical analysis	Design of Experiment (DoE)	
		Surface morphology	SEM, TEM	
		Minimal inhibitory concentration and minimal fungicidal concentration	*Candida albicans* strain ATC 100231	
		Skin irritation	Draize patch test on Albino Wistar rats	
		Antifungal activity	Albino Wistar rats	
Nanosponges synthesized with different cross-linking agents	–	Acute and repeated dose toxicity studies, necropsy, haematological and biochemical parameters	Albino Wistar rats (both sex)	Shende et al. (2015a)
Gabapentin	Epilepsy, neuropathic pain and hot flashes	Taste	Threshold bitterness concentration and in vitro taste evaluation	Rao and Bhingole (2015)
		Saturation solubility	Flask method	
		In vitro dissolution	USP type II (paddle type) dissolution apparatus	
		Sedimentation volume	Measuring cylinder method	
		Leaching	Orbital shaker method	
		Pharmacokinetics	Male Wistar rats	

Tamoxifen and quercetin	Cancer	In vitro release	Modified method using magnetic stirrer	Lockhart et al. (2015)
		In vitro metabolism	Eppendorf tubes	
Meloxicam	Inflammatory and painful conditions	Solubility study	Flask method	Shende et al. (2015b)
		In vitro drug release	Membrane dialysis technique	
		Analgesic activity	Swiss albino mice	
		Anti-inflammatory activity	Albino Wistar rats	
Erlotinib	Pancreatic cancer	In vitro drug release	USP type-II dissolution apparatus	Dora et al. (2016)
		In vitro cytotoxicity study and apoptosis assay	Pancreatic cell lines (MIA PaCa-2 and PANC-1)	
Melatonin	Sleep diseases, sleep regulation and cancer	In vitro drug release	Franz diffusion cell	Mihailiasa et al. (2016)
Camptothecin	Prostate cancer	Angiogenic activity	Tubulogenesis and sprouting assays	Gigliotti et al. (2016)
		In vivo PC-3 cell growth	SCID mice model	
Doxorubicin	Cancer	Glutathione nanosponge internalization	PC-3, DU145, HT-29 and HCT116 cell lines	Daga et al. (2016)
		Cytotoxicity	MTT assay	
		DNA damage	Comet assay	
		In vivo DU145 cell growth	Mice xenograft model	

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Chapter 10
Gold Nanoparticles for Tissue Engineering

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Contents

Abstract Regenerative medicine is currently recognized as an emerging field of nano-medicine with promising opportunities to fully heal tissues damaged by disease, trauma or congenital issues. Within this field, tissue engineering aims at the combination of cells, new bio-materials, and biochemical factors to regenerate biological tissues. The societal impact of this research is significant due to the possibility of implanting natural, synthetic, or semi-synthetic tissues and organs that are fully functional from the start, or can grow into the required functionality. Recently advances of nanotechnology provided wide possibilities to fabricate

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nanostructured scaffolds that mimic the tissue-specific microenvironment. The unique properties of a variety of nanomaterials allow to prepare scaffolds with improved biochemical, mechanical, and electrical properties and capable also to cell adhesion, proliferation, differentiation and to foster the cell growth. Within many types of nanoparticles, gold nanoparticles nowadays are widely used in biology and medicine due to the wide range of valuable chemical and physical properties. However, efficient application of gold nanoparticles for tissue engineering purposes is still at incipience stage.

Here we review the current advances of application of gold nanoparticles for tissue engineering. We will summarize (1) properties of gold nanoparticles relevant to tissue engineering, (2) interaction of gold nanoparticles with cell and toxicity, (3) the current advances in tissue engineering, focusing on cardiac, bone, neural and skin tissue engineering, recognized as the most significant fields of regenerative medicine. In addition, other fields of tissue engineering, where gold nanoparticles have been also applied, are also highlighted. The major point of this review is to highlight the relevance of gold nanoparticles as co-factor, that impart to the scaffolds properties valuable for tissue engineering. According to the reviewed publications the main function of gold nanoparticles in tissue engineering is aimed on enhancing scaffolds properties and delivery efficiency. Moreover, the examples of direct impact of gold nanoparticles on cells differentiation are also provided.

Abbreviation

LSPR Localized surface plasmon resonance

10.1 Introduction

Tissue Engineering has gained enormous interest as a means to restore, maintain and improve tissue function, capable to meet the increasing demand for replacement tissues and organs (Nerem et al. 2000). Such approach is a valuable alternative to replace a damaged tissue or organ instead of applying transplants. Tissue engineering lies at the interface of several disciplines and combines cell technology, materials development and fabrication, and creation of suitable biochemical factors to create artificial organs and tissues, or to regenerate damaged tissues (Liu et al. 2007; Langer and Vacanti 1993). One of the major strategy of tissue engineering encompasses the in vitro growing of cells onto a scaffold with subsequent implantation into the body (Liu et al. 2007). Therefore, the engineering of scaffolds with the proper architecture, high cyto-and tissue compatibility, bioactivity, and good mechanical properties is an important task in tissue engineering (Chan and Leong 2008). A number of scientific publications have already highlighted the advances in bone tissue engineering, cardiac tissue engineering, tissue engineering for the skin regeneration and wound

healing, and other areas, and many of corresponding publications have also discussed the future prospects of tissue engineering (Huu et al. 2013; Amini 2012a, b; Gong et al. 2016; Langer and Vacanti 2016; Dong and Lv 2016; Boccaccini and Harding 2012; Boccaccini and Ma 2014; Liverani et al. 2016; Skobot et al. 2015).

Nanotechnology is continuously being applied in the field of tissue engineering with increasing success since biomaterials to be engineered (extracellular fluids, bone marrow, cardiac tissue etc.) are of nanometer size. The application of nanotechnology to the tissue engineering field comprises the fabrication of nanofibers, 2D and 3D nano-structures and of nanoparticles for controlled-release approaches. These can be employed for building and functionalization of the scaffolds, aimed to enhance the repopulation of the scaffold by cells of the hosting organism (Kingsley et al. 2013; Chung et al. 2007). In addition, the optical and conductive properties of specific nanoparticles can significantly increase of cells growth (Tiwari and Siväjärvi 2016). Indeed, based on achieved results, nanotechnology showed the superiority in tissue engineering and in regenerative medicine in general, in comparison of conventional techniques (Kingsley et al. 2013; Kim et al. 2014). Beside the direct use in the fabrication of nanostructured scaffolds, other important properties of nanoparticles, such as surface chemistry and ability to deliver bioactive agents, play also an important role in enhancing the tissue engineering capabilities. Thus, tissue engineering strategies based on the combination of bioactive agent-loaded nanoparticles and scaffolds have significant increased in recent years, and biomaterial scaffolds can be combined with bioactive agents loaded into nanoparticles to improve tissue regeneration (Monteiro et al. 2015).

Various types of nanoparticles are applied nowadays in tissue engineering approaches. Nanocomposite scaffolds provide structural support for the cells. The nanoscale details of the scaffold may have significant effects on cell-scaffold adhesion, integrin-triggered signaling pathways and cellular function (Gong et al. 2015). For example, polymeric nanoscaffolds capable of continued release of bioactive growth factors, with different release profiles and surface hydrophilicity have been fabricated (Sahoo et al. 2010; Kim et al. 2014). "Functional" magnetite nanoparticles were developed for cell manipulation using magnetic force, and magnetic nanoparticles were applied to assemble more complex tissue structures than structures that are achieved by conventional scaffold-based tissue engineering strategies (Ito and Kamihira 2011; Lee et al. 2014; Zhang 2015a, b). Improved biocompatibility of carbon nanotubes, led to the possibility to apply carbon nanotubes as tissue scaffolding materials to enhance the organ regeneration (Veetil and Ye 2009; Haniu et al. 2012; Bosi et al. 2014). Mesoporous silica nanoparticles provide a flexible platform for controlled delivery of drugs and imaging agents in tissue engineering and stem cell therapy (Rosenholm et al. 2016; Li 2015b). Indeed, nowadays there are many reviews highlighting in details the application of different nanomaterials for tissue engineering approaches, for example nanomaterials in bone tissue engineering (Vieira et al. 2017); applications of magnetic nanoparticles for controlled tissue engineering (Lee et al. 2014); nanomaterials for tissue engineering in dentristy (Chieruzzi et al. 2016); nanomaterials for cardiac tissue engineering

(Zhang et al. 2011); application of carbon-based nanomaterials for tissue engineering (Ku et al. 2013). Summarized and detailed information regarding fabrication and application in tissue engineering of broad range of nanoparticles, for example polymeric nanomaterials, nanoporous biomaterials, carbon-based nanomaterials, nanofibrous scaffolds was published in 2013 (Gaharwar et al. 2013).

Nanoparticles of noble metals have been studied with growing interest, since they exhibit significantly distinct physical, chemical and biological properties from nanoparticles bulk counterparts (Armentano et al. 2010; Rosarin and Mirunalini 2011; Pandey and Pandey 2016). Within these types of nanoparticles, silver and gold nanoparticles are the most frequently used due to valuable optical, electronic, catalytic, biocompatible properties and potentially high surface reactivity (Rosarin and Mirunalini 2011). The nanoscale size of gold nanoparticles, wide range of easy preparation techniques, high surface area, and broad opportunities of surface functionalization make these nanoparticles attractive to fit the requirements of tissue engineering (Vial et al. 2016). Moreover, the unique optical properties of gold nanoparticles, e.g. Localized Surface Plasmon Resonances (LSPR), located in the Visible and Near-Infrared range, can be used to enhance scaffold properties and correspondingly improve cells adhesion, growth or differentiation.

However, despite the advances of gold nanoparticles application in cancer therapy, imaging and sensing agents, delivery platforms, the potential of gold nanoparticles in the tissue engineering field has not been sufficiently explored. Nevertheless, this interest is growing rapidly, and this is the main focus of current work. Therefore, firstly the properties of gold nanoparticles relevant to tissue engineering will be briefly highlighted. Then the recent advantages of gold nanoparticles application in most important fields of tissue engineering will be summarized and discussed. Moreover, current problems and restrictions to gold nanoparticles applications, together with possible solutions, will be also provided.

10.2 Properties of Gold Nanoparticles

Gold nanoparticles are among the most extensively studied nanoparticles, due to the high stability and facile synthetic preparation techniques (Chirico et al. 2015; Tateno et al. 2014). Moreover, gold nanoparticles have a range of unique properties (Yeh et al. 2011), that include tunable optical resonances, electronic properties and easy surface functionalization approaches. All these factors make gold nanoparticles versatile platforms for different nano-biological application (Yeh et al. 2011; Han et al. 2007; Chirico et al. 2015). Gold nanoparticles are also very attractive due to the well-controlled size and due to the possibility to fine tuning optical properties by shape and size (Herizchi et al. 2016). Based on these properties, nowadays gold nanoparticles are explored in diverse biomedical application e.g. genomics, biosensors, immunoassays, clinical chemistry, laser phototherapy of cancer cells and tumors, the targeted delivery of drugs, DNA and antigens, optical bioimaging and

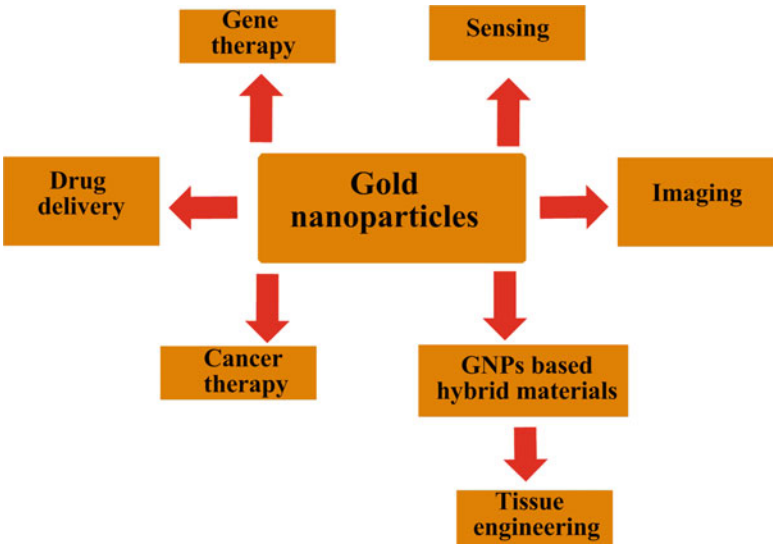

Fig. 10.1 Application of gold nanoparticles in biomedical fields

monitoring of cells and tissues (Dykman and Khlebstov 2011). The major possible applications fields of gold nanoparticles in biomedical field are shown in Fig. 10.1.

Therefore, it is useful to revise briefly the most essential properties of gold nanoparticles including the interaction of nanoparticles with cells before discussing the promising possibility of application in tissue engineering.

10.2.1 Synthesis of Gold Nanoparticles

Generally, gold nanoparticles are synthesized in a liquid phase by reduction of chloroauric acid ($HAuCl_4$) (Yeh et al. 2011; Chirico et al. 2015). This process usually contains two steps: (1) reduction using agents such as borohydrides, aminoboranes, hydrazine, formaldehyde, hydroxylamine, saturated and unsaturated alcohols, citric and oxalic acids, polyols, sugars, hydrogen peroxide, sulfites, carbon monoxide, hydrogen, acetylene, and monoelectronic reducing agents including electron-rich transition-metal sandwich complexes; (2) stabilization by agents such as trisodium citrate dihydrate, sulfur ligands (in particular thiolates), phosphorus ligands, nitrogen-based ligands (including heterocycles), oxygen-based ligands, dendrimers, polymers and surfactants (Zhao et al. 2013). Stable gold nanoparticles can be also synthesized by laser ablation without the addition of any external chemical reagent (Wender et al. 2011). The particle shape and size depend on a large numbers of parameters, for example, it can be controlled by the initial reagent concentrations (Zhou et al. 2009; Hostetler et al. 1998) and also on the nature of

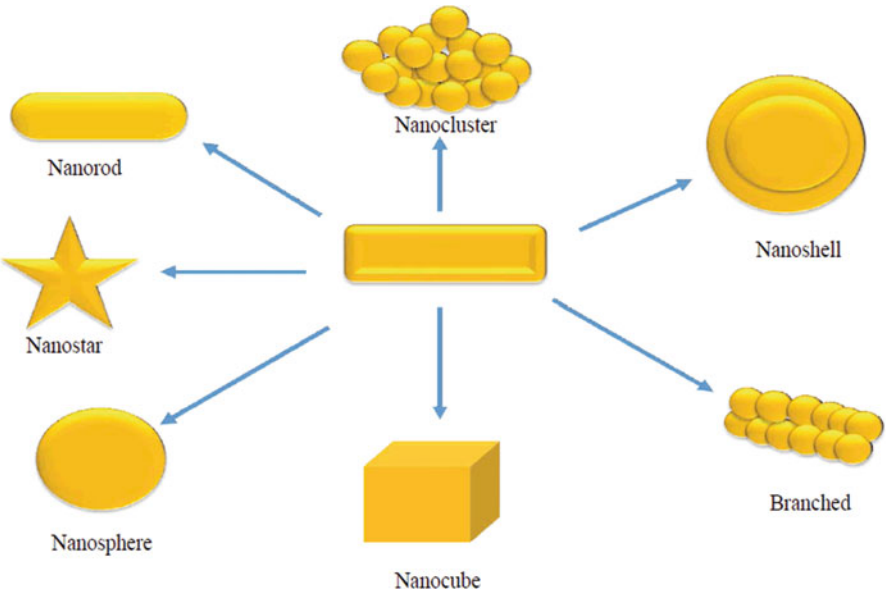

Fig. 10.2 Examples of different shapes of existing gold nanoparticles. (Modified after Alaqad and Saleh 2016)

surfactant (Pallavicini et al. 2013). Some of the various shapes of gold nanoparticles that can be prepared by the existing synthetic techniques are summarized in Fig. 10.2:

One of the simplest approach to produce gold nanoparticles is based on reduction of $HAuCl_4$ pioneered by *J. Turkevich* and refined by *G. Frens* in 1970s (Frens 1973). This method is used in general to obtain monodisperese spherical gold nanoparticles suspended in water with an average size 10–20 nm. Nowadays the *"in situ" Turkevich-Frens* method has been further improved for reproducible preparation of citrate-stabilized gold nanoparticles (Kimling et al. 2006; Polte et al. 2010). The two-phase *Brust-Schiffrin* method, published in 1994, was the first method for the *in-situ* synthesis of thiolate-stabilized gold nanoparticles, based *on* $NaBH_4$ as reduction agent (Brust et al. 1994). This method is performed in ambient conditions with relative high stability of the resulting gold nanoparticles with diameter located in the 2–5 nm range (Templeton et al. 2000; Sardar and Shumaker-Parry 2009).

Compared with the in situ synthesis, the recent widely used *seed-growth* technique enlarges the particles step by step, and it is much easier to control the sizes and shapes of resulted gold nanoparticles (Nikoobakht and El-Sayed 2003; Ziegler and Eychmüller 2011; Leng et al. 2015). This powerful strategy involves two main steps: small-size gold nanoparticles seeds preparation and adding of resulted seeds to a "growth" solution containing $HAuCl_4$ and the stabilizing and reducing agents

(Bastus et al. 2011; Casu et al. 2012; Pallavicini et al. 2013). Among other techniques *Martin method* discovered in 2010 allows to obtain stable "naked" gold nanoparticles in water by reducing $HAuCl_4$ with sodium borohidride (Martin et al. 2010). The resulted gold nanoparticles are easily functionalized with hydrophilic species or hydrophobic ligands in non-polar solvents.

The sonolysis synthetic approach based on ultrasound was introduced by Baigent and Müller (1980). Later, the ultrasound was applied to form gold nanoparticles during reaction of $HAuCl_4$ aqueous solution with glucose (Zhang et al. 2006). In this case, the reducing agents are hydroxyl radicals and sugar pyrolysis radicals that form at interface of collapsing cavities and the bulk water. The resulted gold nanoparticles have a shape of nanoribbons with width 30–50 nm and length of several micrometers.

10.2.1.1 "Green" Synthesis of Gold Nanoparticles

Common methods of gold nanoparticles synthesis usually lead to the adsorption of some toxic chemical species e.g. surfactants on the nanoparticles surface that can cause a problem for effective application in the medical field, such as tissue engineering (Singh and Scrivastava 2015). This drawback forced researchers to utilize biofriendly and eco-compatible natural compounds for the reduction of Au-containing salts needed for the synthesis of gold nanoparticles (Mandal et al. 2006). These new approaches also improve substantially the production efficiency, being based on a one-step process, with no need of supplementary surfactants or polymers, capping agents etc. In addition, these synthetic techniques can significantly improved the biocompatibility of gold nanoparticles. Recently, the following natural sources have been successfully utilized in gold nanoparticles "green" synthesis: *plant extracts* (Sujitha and Kannan 2013; Bhau et al. 2015; Sett et al. 2016; Patra and Baek 2015), *aglae* (Ramakrishna et al. 2016; Rajeshkumar et al. 2013; Parial et al. 2012), *bacteria and fungi* (Kitching et al. 2015; Mukherjee et al. 2002), *polysaccharides* (Huang and Yang 2004; Potara et al. 2009; Pandey et al. 2013), and *proteins* (Leng et al. 2016). Another one-step "green" approach is based on thermal evaporation of gold from surfaces to obtain gold nanoparticles (Anantha et al. 2012).

This subchapter provided very brief review of classical and recently developed techniques of gold nanoparticles preparation. The importance of "green approaches" of gold nanoparticles synthesis for tissue engineering should be highlighted. All previously mentioned "green" methods are being actively investigated since, beside the economical benefits that comes from the use of cheap compounds, absence of toxic compounds, the antibacterial, antifungal and antioxidative properties of gold nanoparticles prepared by these "green" techniques, could also bring additional valuable properties of gold nanoparticles based scaffolds.

10.2.2 Surface Decoration of Gold Nanoparticles

Surface functionalization of the nanoparticles with suitable ligands is essential to ensure the stability of nanoparticles against aggregation or to enhance the targeting efficiency for cells (Park et al. 2013; Tiwari et al. 2011). Indeed, finely tuned surface decoration of the nanoparticles, which determines the interaction of nanoparticles with the environment and provides biocompatibility, is strongly required for an efficient application of gold nanoparticles in nanomedicine in general and in particular for tissue engineering (Sperling and Parak 2010). Briefly, the proper surface decoration of gold nanoparticles brings following advantages: makes them biocompatible, stable in physiological media, provides the possibility to carry and deliver, drugs and target molecules, reduces the non-specific binding, and enhances accumulation of gold nanoparticles. Moreover, proper tuning of surface chemistry promotes effective cells adhesion proliferation, and growth. Therefore, surface functionalization of gold nanoparticles is an important condition for efficient application in tissue engineering. For this purpose, the most common strategies of functionalization of gold nanoparticles are reviewed.

Gold nanoparticles can be easily functionalized using different kind of ligands, synthetic and nature origin polymers, biomolecules, etc. depending on the final application (Spampinato et al. 2016). The most widely applied approaches are following:

(a) functionalization of gold nanoparticles with thiol and disulfide containing molecules;
(b) embedding of gold nanoparticles into inorganic/polymer shell;
(c) non-covalent functionalization of gold nanoparticles.

These methods are pictorially summarized in Fig. 10.3:

The direct interaction of the gold surface with thiols (-SH) and disulfides (-S-S-), forming self-assembled monolayers, is the most widely employed method for grafting a coating onto the gold nanoparticles (Borzenkov et al. 2015). This may be either a small molecule or a polymer or a combination of both (Daniel and Astruc 2004; Gronbeck et al. 2000). Biocompatible polyethylene glycols (PEGs), with terminal –SH groups, are very frequently used as coatings for gold nanoparticles, due to many advantages in bio-medical applications (Borzenkov et al. 2015; Chirico et al. 2015). PEG coating is also used for nanoparticle specific functionalization, as many commercial PEGs feature, in addition to the thiol function for grafting on gold, terminal functional groups (e.g. -OH, -COOH, $-NH_2$) suitable for further chemical modification (Manson et al. 2011; Shenoi et al. 2013). The corresponding bifunctional linkers allow also to conjugate gold nanoparticles with biomolecules e.g. DNA, peptides, antibodies and proteins (Ojea-Jimenez and Puntes 2009; Li et al. 2013; Jazayeri et al. 2016).

Embedding gold nanoparticles into inorganic/polymer shell allows to enhance several properties of the nanoconstructs. The shell structure usually bears functional groups for further modification or for recognition of and binding with bio-molecules,

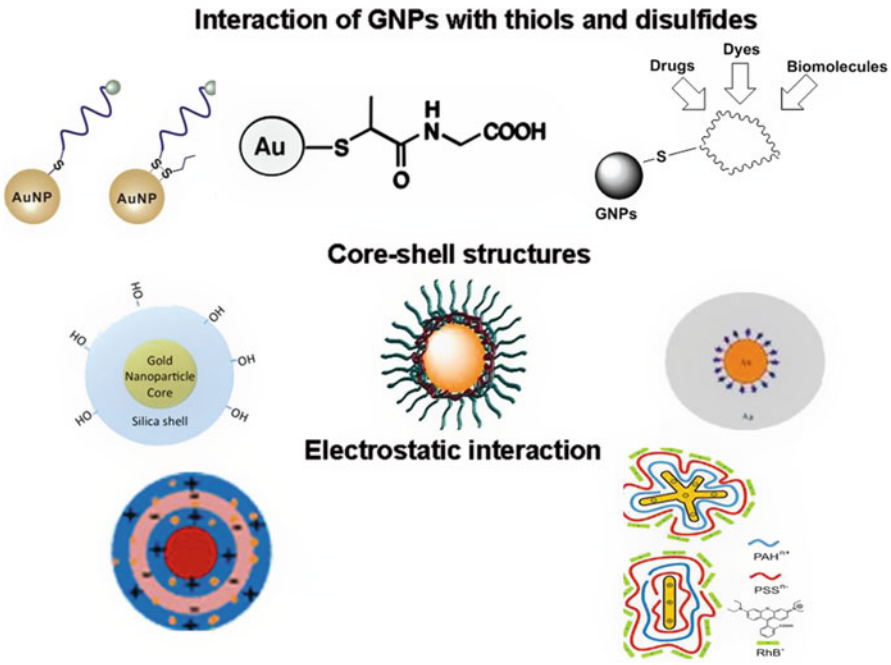

Fig. 10.3 Common functionalization methods of gold nanoparticles: covalent functionalization, preparation of core-shell structures, and electrostatic interaction

such as cellular receptors (Vial et al. 2016). For example, incorporating of gold nanoparticles into polymer nanospheres is attractive for developing biocompatible nanomaterials and plasmonic photonic crystals (Khan and MacLachlan 2015). Such structures exhibit high biocompatibility, biodegradability and high cell uptake (Vial et al. 2016; Jokerst et al. 2012). A broad range of gold nanoparticles core-shell structures were studied, with various shell nature such as iron oxide (Liang et al. 2009), silica (Kandpal et al. 2007; Liz-Marzan et al. 1996; Fales et al. 2011), silver (Lu et al. 2013; Pustovalov et al. 2012), polymers like poly(N-isopropylacrylamide), chitosan, amino-terminated polystyrene (Kanahara et al. 2014; Dong et al. 2014; Wu et al. 2016).

The non-covalent functionalization strategy is based on a combination of electrostatic and hydrophobic interactions of the molecules and the gold surface (Rayavarpu et al. 2007). One of the most frequently used technique of non-covalent coating is the so-called layer-by-layer method that provides multilayer structures (Vial et al. 2016). Charged target molecules can be electrostatically bound onto the outer layer, or better incorporated within alternate layers. The multiply layers were formed using different charged compounds such as polyelectrolytes (Mayya et al. 2003; Toccoli et al. 2012; Dorris et al. 2008), proteins (Brewer et al. 2005; Takahashi et al. 2008), oligonucleotides (Elbakry et al. 2009; Bishop et al. 2015), antibodies (Jazayeri et al. 2016).

10.2.3 Conductive Properties of Gold Nanoparticles

Electrical stimulation was shown to enhance cardiac, muscle and nerve tissues growth therefore raising the interest of researchers for diverse conductive polymers that could be used for scaffolds fabrication (Ghasemi-Mobarakeh et al. 2011; Amezcua et al. 2016). In this line of research, the incorporation of conductive nanoparticles (e.g. metal, carbon nanotubes) in scaffolds was also applied (Martins et al. 2014; You et al. 2011). The electrical conduction properties of gold nanoparticles have been intensively exploited for the development of gold nanoparticles based devices and sensors including also nanoelectronic devices for biomedical applications (Tateno et al. 2014; Wuelfing et al. 2010; Zotti et al. 2008; Homberger and Simon 2010; Edwardson et al. 2016).

Therefore, the electrical properties of gold nanoparticles can be advantageously used to fulfill the needs of tissue engineering, particularly of cardiac and nerve tissues growth. For example, the intercellular electrical communications can be enhanced presence of gold nanoparticles in hybrid fibrous scaffolds (Shevach et al. 2013). In addition, engineering of gold nanoparticles based hybrid scaffolds can promote superior electrical signal conductivity (Fleischer et al. 2014).

10.2.4 Optical Properties of Gold Nanoparticles

Unique optical properties of gold nanoparticles provide additional advantages to be applied in tissue engineering. For example, they assist to monitor cells differentiation process, cells uptake and migration (Vial et al. 2016). Therefore, the whole tissue regeneration process can be easily studied. In addition, their photo-thermal properties can promote cells growth and differentiation as will be discussed below. For this reason the brief discussion of Localalized Surface Plasmon Resonance of gold nanoparticles as a key-factor of their photo-thermal properties is provided. Gold nanoparticles absorb and scatter light with extraordinary efficiency with respect to organic compounds. Such impressive interaction with lights is explained by the fact that the conduction electrons on the gold surface undergo a collective oscillation when they are excited by light at certain wavelengths (Huang and El-Sayed 2010; Freddi et al. 2013). This interaction produces coherent localized plasmon oscillations with a resonant frequency that strongly depends on the composition, size, geometry, dielectric environment and particle–particle distance of nanoparticles (Chirico et al. 2015).

The Localized Surface Plasmon Resonance (LSPR) response arises from the electric field of the incident light driving surface conduction electrons collectively away from the metal nanoparticle lattice (Messersmith et al. 2013). As a result of corresponding collective factors, the absorption and scattering cross-sections of gold nanoparticles are much higher than non-plasmonic nanoparticles. Apart of particle size and local surface refractive index, the shape of the LSPR spectra can be widely tuned also by varying of gold nanoparticles shape (Chirico et al. 2015; Nehl and

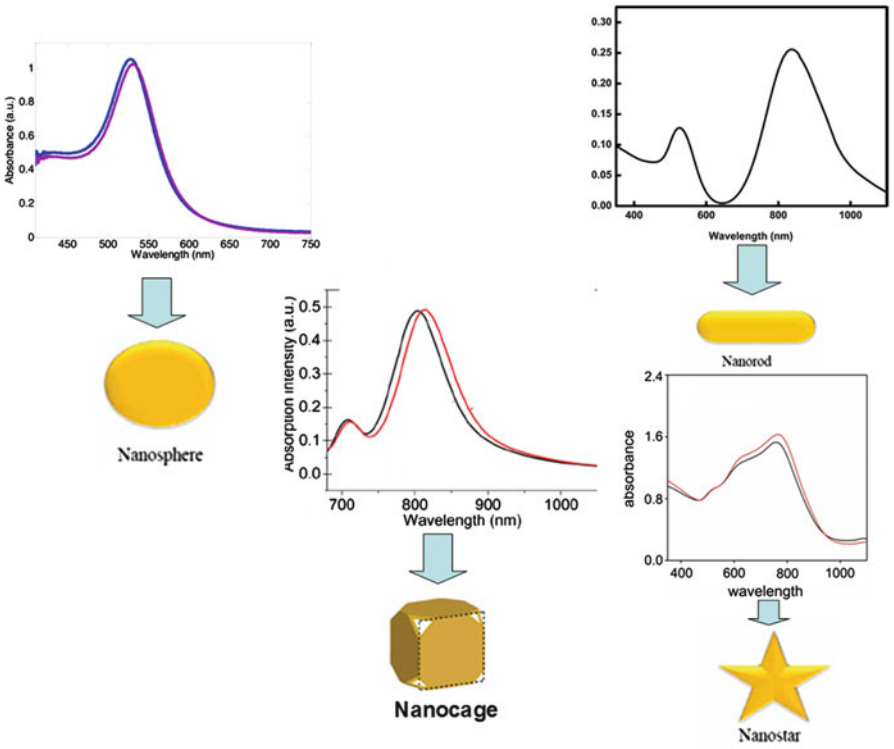

Fig. 10.4 Localized Surface Plasmon Resonance (LSPR) positions of different types of gold nanoparticles

Hafner 2008; Noguez 2007). The LSPR positions of spherical and some types of nonspherical gold nanoparticles are schematically shown in Fig. 10.4:

Precise tuning of LSPR position can be also achieved by regulating concentrations of reagents during preparation stage (Casu et al. 2012; Pallavicini et al. 2013). The sensitivity of LSPR to environment changes and surface modification of gold nanoparticles have led to development gold nanoparticles based biosensors (Messersmith et al. 2013). In addition to wavelength-selective photon absorption and scattering, an important consequence of LSPR excitation is the local electromagnetic field enhancement that lies at the heart of surface-enhanced spectroscopy (Butler et al. 2015; Vo-Dinh et al. 2010).

The capability of gold nanoparticles to locally release heat upon irradiation with wavelength that matches $LSPR_{max}$ of nanoparticles is promising and valuable property, that has been already applied in cancer hyperthemal treatments (Huff et al. 2007; Faheem and Banu 2014). In addition it provides a prospective opportunity also for tissue engineering, as suggested recently for optical stimulation of cells growth (Paviolo et al. 2013; Gentemann et al. 2017). Therefore, this phenomenon should be discussed more in details.

10.2.4.1 Photo-Thermal Effect of Gold Nanoparticles

The possibility to trigger by Near-Infrared irradiation a localized heat release from metal nanoparticles, is an attractive approach to provide spatial and temporal control of heat both in vivo and in vitro (Kabb et al. 2015; Avvakumova et al. 2016). The application of gold nanoparticles in local hyper-thermal treatment exploits high absorption cross-sections of gold nanoparticles in the Near-Infrared (700–1200 nm) which is the range of the so called biological transparent window (Borzenkov et al. 2016). The absorption cross-section has a large dependence on the gold nanoparticles shapes and the corresponding LSPR band can be tuned by changing the shape parameters (Richardson et al. 2006). Beside the direct hyperthermal effect, gold nanoparticles can be used also as smart drug delivery vehicles, in which the release of the bound compounds can be triggered by the localized heating obtained by Near-Infrared irradiation (Bakhtiari et al. 2009; Borzenkov et al. 2015). Closely related to the medical field, also the possibility to exploit the local photo-thermal effect for controlled deformations of macroscopic shape-memory polymeric nanocomposites was reported (Zhang et al. 2014).

The group of El-Sayed has pioneered the use of gold nanoparticles induced hyperthermia for cellular treatments. Spherical gold nanoparticles with a peak absorption at 530 nm have been initially exploited. They were irradiated at 514 nm to kill cancer cells in vitro (El-Sayed et al. 2006). However, spherical gold nanoparticles absorb only visible light, being generally poor prospects for tissue heating since the penetration of ultraviolet and visible light in tissues is limited. Non-spherical gold nanoparticles can instead be used to locally release heat in the tissues, when irradiated in Near-Infrared region where tissues are transparent (Huang et al. 2006). For example, gold nanostars with LSPR finely tuned by synthetic conditions in the range 700–1100 nm, displayed a pronounced photo-thermal effect under Near-Infrared irradiation in solutions, as monolayers grafted on the dry glass surface, and when printed on coated flexible paper substrates, showing higher temperature increase in the latter case (Casu et al. 2012; Borzenkov et al. 2015, 2016; Pallavicini et al. 2014, 2015). In addition, it was shown that the photo-thermal action of the gold nanostars monolayer on glass efficiently induces cell death in *S. aureus* biofilms upon Near-Infrared irradiation (Pallavicini et al. 2014).

The direct monitoring of the temperature around gold nanoparticles is also essential to test therapeutic efficiency of nanoparticles (Shao et al. 2013; Zharov et al. 2006). Freddi et al. proposed an all-optical method to measure the temperature of nonspherical gold (nanorods and nanostars) and magnetite nanoparticles under Near-Infrared and radiofrequency excitation, based on the temperature dependence of the excited state lifetime of Rhodamine B, bound at ≈20 nm from the nanoparticles surface (Freddi et al. 2013). It was shown that gold nanostars are ≈3 and ≈100 times more efficient that than gold nanorods and magnetite nanoparticles in inducing localized hyperthermia as it shown in Fig. 10.5:

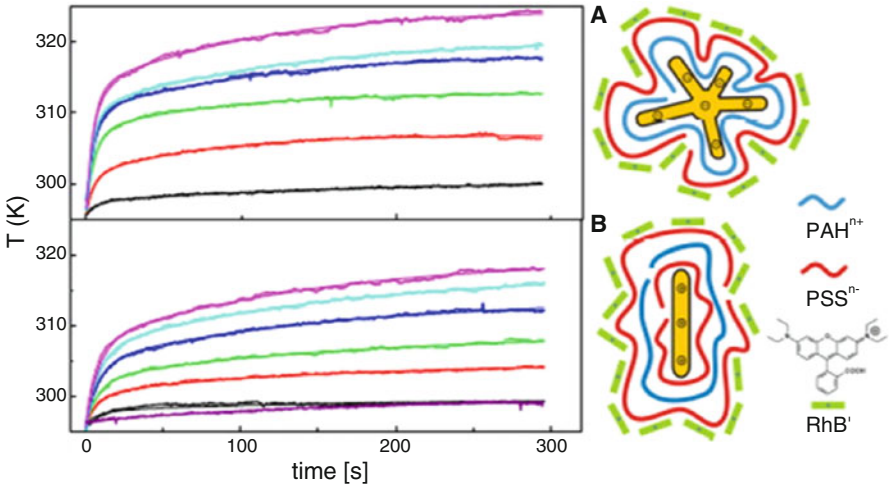

Fig. 10.5 The temperature increased profile of gold nanostars and gold nanorods coated with polyelectrolytes and decorated with Rhodamine B (Reprinted with permission from Freddi et al. 2013)

10.2.4.2 Gold Nanoparticles as Tracking and Contrast Agents

Nanoparticles are also widely used as contrast agents for molecular targeting imaging by exploiting various types of interactions. Single particle tracking is an important tool to investigate dynamic biological processes by following the movement of individual labeled molecules with high spatial and temporal resolution using various microscopic techniques (Rong et al. 2008). Regarding to tissue engineering field an accurate imaging of cells, differentiation process and subsequent tissue regeneration process is crucial for in vitro and in vivo studying of the scaffold performance (Vial et al. 2016; Appel et al. 2013). Four major imaging techniques employing gold nanoparticles as contrast agents have been developed: *optical fluorescence imaging*, *X-ray imaging*, *photoacoustic imaging*, and *dark field optical microscopy*.

In addition to chemical stability and wide opportunities of surface functionalization, the strong two-photon luminescence of gold nanoparticles coupled to a specific targeting makes these nanoparticles ideal candidates as contrast agents for optical microscopy, which is the most adequate to investigate in vivo samples (Chirico et al. 2015). Major advantages of the use of gold nanoparticles, compared to the organic dyes, are the large absorption cross-section of the gold nanoparticles and extreme photophysical stability. Gold nanoparticles do not blink or bleach unlike many fluorescent dyes or quantum dots (Rong et al. 2008). Indeed, different types of gold nanoparticles have recently been successfully examined as contrast agents for biomedical imaging because of brightness of gold nanoparticles at near-infrared wavelengths, which can penetrate through tissue better than visible light (Chirico et al. 2015).

Gold induces also a strong X-ray attenuation making gold nanoparticles attractive for in vivo computer tomography molecular imaging (Popovtzer et al. 2008). Hybrid nanoparticles such as antibiofouling polymer-coated gold nanoparticles, gadolinium coated gold nanoparticles, PEG coated gold nanoparticles were developed as computer tomography contrast agents (Kattumuri et al. 2007; Alric et al. 2008; Cai et al. 2007). It was demonstrated that the assembly of gold nanoparticles that form exclusively on the targeted cancer cells yield a strong selective X-ray attenuation that is distinct from the attenuation obtained by identical but untargeted cancer cells or by normal cells (Popovtzer et al. 2008).

Gold nanoparticles as exogenous contrast agents have also great potential for photoacoustic imaging due to inherent and geometrically induced optical absorption (Li and Chen 2015). In addition, at the LSPR wavelengths gold nanoparticles have higher extinction coefficients than conventional organic dyes (Song et al. 2016). The most widely utilized gold nanoparticles for photoacoustic imaging are spheres, rods, shells, prisms, cages, stars and vesicles (Li 2015). Dark field optical microscopy is another commonly applied technique to monitor cellular uptake, cell migration and molecular affinity (Nenasheva et al. 2012; Ahijado-Guzman et al. 2014). It should be noted that upon light excitation only frequencies matching the LSPR are strongly scattered resulting to visualization of gold nanoparticles as bright spots (Vial et al. 2016). Recently super-resolution imaging of fluorescence-free plasmonic gold nanoparticles was achieved using enhanced dark-field illumination based on wavelength-modulation (Zhang 2015).

10.2.5 Interaction of Gold Nanoparticles with Cells and Toxicity of Gold Nanoparticles

The information about long-term and short-term biological effects of gold nanoparticles nanotoxicity is crucial for safe application in tissue engineering (Yen et al. 2009). Potential risks and possible biomedical effects of gold nanoparticles on human organism must be assessed firstly, as utilization of non-toxic or biodegradble components is important requirement in the tissue engineering field (Wang 2015a, b; Vial et al. 2016). In physiological conditions, gold nanoparticles can be internalized, trafficked, stored, or secreted by cells (Wang 2015; Wang et al. 2011). However, the interaction of gold nanoparticles with cells is rather complicated interfacial process in space and time (Wang 2015).

Gold nanoparticles can be internalized by cells along at least two major pathways: receptor-mediated endocytosis and phagocytosis (Wang 2015). The impact of the gold nanoparticles size and surface effects on cell interactions has been widely investigated (Chirico et al. 2015; Liu et al. 2013). For example, it was demonstrated that, for spherical gold nanoparticles stabilized by citric acid ligands, 50-nm diameter is an optimal size to maximize the rate of uptake and intracellular concentration in mammalian HeLa cells (Chithrani et al. 2006). Once internalized, nanoparticles

may affect the cellular activity at different levels, by interacting with vital cell components such as the membrane, mitochondria, or nucleus (Alkilany and Murphy 2010). Star-shaped gold nanoparticles with average size 180 nm increased firing rate of hippocampal neurons modifying excitability of neurons (Salinas et al. 2014). Gold nanoparticles can also induce cell differentiation as it was demonstrated in case of mesenchymal stem cells and NG108-15 neuronal cells (Yi et al. 2010; Paviolo et al. 2013).

However, the nanotoxicological screening studies done in vitro could not predict accurately in vivo toxicity (Griffith and Swartz 2006). Gold nanoparticles are found to be non toxic due to numerous reports (Connor et al. 2005; Alkilany 2010; Villiers et al. 2009). On the other hand, other reports claimed some toxicity of gold nanoparticles (Goodman et al. 2004; Pan et al. 2009). Such contradictory results may rise from the variability of the used toxicity assays, cell lines, and nanoparticles chemical/physical properties. The strong need to systematize all collected data suggests employing an appropriate metric, e.g. the particle concentration, that could help in comparing and organizing the available data in a more accurate way (Fratoddi et al. 2015). In fact, it was demonstrated that at constant numerical particle concentration (number of particles per unit volume of cell culture), at least in the case of HeLa cells, no effect of diverse functionalization could be observed (Fratoddi et al. 2015). At least for this cell line, the particle concentration was the single parameter that triggered toxicity. Therefore, it is mandatory to define the therapeutic window together with synthetic and coating protocols where gold nanoparticles can be employed without side effects (Fratoddi et al. 2015). In addition, the important issue is also to understand the long term effect of gold nanoparticles on organism, clearly defining the difference between toxicity and cell damage. From this short discussion is evident that there is a strong need or reliable models for detailed in vivo investigations (Rushton et al. 2010; Fratoddi et al. 2015).

10.3 Gold Nanoparticles in Cardiac Tissue Engineering

The main goal of cardiac tissue engineering is the development of functional tissue constructs that can reestablish the structure and function of injured myocardium (Vunjak-Novakovic et al. 2010). In cardiac tissue engineering contracting cells are seeded within supporting biomaterial scaffolds that provide cells with the microenvironment which is essential for the assembly of functional cardiac tissue (Shapira et al. 2016). A wide range of approaches and methods for cardiac tissue engineering scaffolds creation have been proposed and investigated up to now. In addition to bulk synthetic and natural materials, nanomaterials are being actively investigated. They are considered particularly promising as they are able to significantly improve mechanical, electrical, optical and magnetic properties due to large surface-area-to-volume ratio and surface roughness of nanomaterials (Amezcua et al. 2016). The limiting factor of most engineered scaffolds for cardiac tissue engineering is that they are electrically insulating (Suuronen and Ruel 2015). Cardiac muscle is a type

of tissue that would benefit from an electrically conductive scaffold to regenerate lost or lower functional areas (Mckeon-Fischer and Freeman 2012). The native myocardium displays a direct current conductivity of 0.1 S/m and the conduction is facilitated by electrically conducting Purkinje fibers (Shin et al. 2013; Suuronen and Ruel 2015). Therefore, one of the main conditions of successful application of scaffolds for cardiac tissue engineering is the ability to reduce electrical impedance of the cellular environment.

Incorporation of gold nanoparticles into scaffold structure can improve the cardiac excitability and the cellular attachment. Microporous thiol-hydroxyethyl methacrylate scaffolds with immobilized gold nanoparticles for cardiac tissue engineering were fabricated and tested (You et al. 2011). Cardiac muscle tissues cultured on such scaffolds demonstrated improved levels of connexin 43. However, the sophisticated preparation technique and absence of cell adhesive functions limited the application. The application and limitation of conductive polyaniline and gold nanoparticles for fabrication conductive scaffolds for cardiac and muscle tissues growth was discussed by Mckeon-Fischer and Freeman (2012). Gold nanoparticles incorporated into PET polymer structure enhanced the cellularity of the reconstituted tissue, reduced ROS, and reduced bacteria adhesion to PET (Whelove et al. 2011). Significantly enhanced biocompatibility of the polyurethane – gold nanoparticles composites over the original polyurethane was also achieved by extensive modification of the surface morphology and by increasing the free radical scavenging ability (Hsu et al. 2008).

With particular regard to cardiac tissue engineering, electrospinning is considered to be most effective fabrication technique. These structures mimic extracellular matrix fibrous structure and enhance the cell adhesion (Tallawi et al. 2015). For example, peptide-functionalized gold nanoparticles were also successfully incorporated within polymethylglutarimide nanofibers through electrospinning (Jung et al. 2012). Grafting functionalized gold nanoparticles led to high-density localization of the cell-adhesive peptides on the nanofiber and to the enhancement of HeLa cell adhesion that potentiated cardio-myocyte differentiation of human pluripotent stem cells.

Cohen-Karni et al. combined controlled cell-biomaterial interactions and improved cell proliferation and differentiation by fabricating silk nanofibers containing gold nanoparticles that were subsequently decorated with peptides (Cohen-Karni et al. 2012). Silk fibroin mixed with gold seed nanoparticles was electrospun to form nanofibers doped with gold seed nanoparticles. Following gold reduction, there was a twofold increase in particle diameter confirmed by the appearance of a strong absorption peak at 525 nm. The resulted scaffolds displayed improved Young's modulus and were then modified with RGD peptide due to the interaction with gold nanoparticles. It was shown that Human mesenchymal stem cells cultured on such scaffold had a more than twofold larger cell area compared to the cells cultured on bare silk fibroin scaffold.

With a similar approach the research group led by *Tal Dvir* demonstrated that gold nanoclusters can be incorporated into macroporous scaffolds to increase the matrix conductivity and enhance the electrical signal transfer between cardiac cells

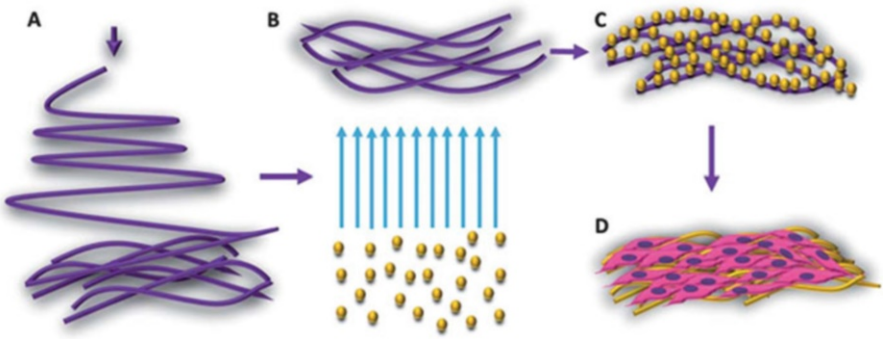

Fig. 10.6 Fabrication of gold nanoparticles based hybrid scaffold for cardiac tissue regeneration. (**a**) Fabrication of polycaprolactone–gelatin fiber scaffolds by electrospinning. (**b**) Evaporation of gold nanoparticles onto the fibers to create nanocomposite scaffolds. (**c**) Cardiac cells are seeded in the nanocomposite scaffolds for engineering a functional cardiac tissue. (Reprinted with permission from Shevach et al. 2013)

(Shevach et al. 2013). For this purposes gold nanoparticles were evaporated on the surface of polycaprolactone–gelatin fibrous scaffolds fabricated by means of electrospinning creating nanocomposites with a nominal gold thickness between 2 and 14 nm. The scaffold fabrication strategy is shown in Fig. 10.6.

The authors showed that cardiac cells seeded on the nano-gold scaffolds assembled into more elongated and aligned tissues. Also, the presence of gold nanoparticles in scaffold structure promoted the growth of cardio-myocytes with significantly higher aspect ratio and promoted massive cardiac sarcomeric actinin expression. In general, cardiac cells grown on gold nanoparticles decorated scaffolds exhibited significantly higher contraction amplitudes and rates, as compared to those grown on scaffolds without gold.

It is worth mentioning that in a previous work Tal Dvir et al. showed that incorporation of gold nanowires within alginate scaffolds can bridge the electrically resistant pore walls of alginate and improve electrical communication between adjacent cardiac cells (Dvir et al. 2011). Gold nanowires were grown by anisotropic elongation of the seeds (Kim et al. 2008). Tissues grown on these composite matrices were thicker and better aligned than those grown on pristine alginate and it was expected that the integration of conducting gold nanowires improve the therapeutic value due to enhanced electrical properties. These works laid the basis for the more recent development of composite nanofibrous structures incorporating gold nanoparticles. As briefly outlined below, two major approaches are related to the use of fibrous synthetic compounds or hydrogels, or to the use of decellularized matrices.

Regarding the employment of synthetic matrices, most of the applications appeared on polymeric nanofibers. Coiled electrospun fibers with gold nanoparticles were presented as a new promising nanocomposite scaffold for cardiac tissue engineering (Fleischer et al. 2014) since the natural heart matrix contains a unique subpopulation of coiled perimysial fibers that provide the mechanical properties

crucial for efficient and continuous contractions (Robinson et al. 1988; Fleischer et al. 2014). Gold nanoparticles were obtained by evaporation of gold on polycaprolactone fibers. It was shown that integrated gold nanoparticles provided anisotropic transfer of the electrical signals throughout engineered cardiac tissues. Cultivation of cardiac cells within the fabricated hybrid scaffolds led to cell organization into elongated and aligned tissues generating a strong contraction force, high contraction rate and low excitation threshold.

Nanocomposite scaffold based on gold nanotubes/nanowires incorporated into biodegradable castor oil based polyurethane was fabricated to be applied in cardiac tissue engineering (Ganji et al. 2016). H9C2 cardiomyocyte cells were cultured on the scaffolds for one day, and electrical stimulation was applied to improve cell communication and interaction in neighboring pores. Gold nanotubes/nanowires were fabricated by using template-assisted electrodeposition and gold in the form of nanowires allowed the formation of conductive bridges between pores and enhanced cell communication. Also, the addition of gold nanoparticles caused the formation of hydrogen bonding with the polyurethane matrix and improved the thermomechanical properties of nanocomposites. It was demonstrated that gene expression level was up-regulated by the incorporation of gold nanotubes/nanowires into the polyurethane scaffolds, in particular after electrical stimulation. Moreover, hybrid scaffolds displayed more native morphology and enhanced proliferation compared to gold-free scaffolds.

Gold nanoparticles with the size of 16 nm were embedded into nanofibrous polycaprolactone together with vitamin B12, *aloe vera* and silk fibroin to fabricate novel scaffolds to differentiate mesenchymal stem cells into cardiac lineage (Sridhar et al. 2015). Nanoparticle loaded nanofibrous scaffold displayed a mechanical strength of 2.56 MPa matching that of the native myocardium. The most important conclusion is that phenotype and cardiac marker expression in differentiated cells were highly resonated in gold nanoparticle loaded nanofibrous scaffolds.

Regarding the use of hydrogels, the use of chitosan based thermosensitive conductive hydrogel with a highly porous network of interconnected pores, as scaffold for cardiac tissue engineering was reported (Baei et al. 2016). Chitosan stabilized gold nanoparticles were evenly dispersed throughout the polymer matrix in order to provide electrical cues. The fabricated scaffolds supported viability, metabolism, migration and proliferation of mesenchymal stem cells. Therefore, it was confirmed that incorporation of electro-conductive gold nanoparticles into hydrogel structure enhances the properties of myocardial constructs. Hybrid material based on a natural collagen scaffold with incorporated gold nanoparticles was also reported recently (Li et al. 2016). Gold nanoparticles, namely gold nanorods were immersed in collagen matrix uniformly providing easier adhesion and better matching of the cell on substrate. The presence of gold nanoparticles improved mechanical properties of scaffolds, increased protein expression and Ca^{2+} fluctuation. The authors demonstrated that such hybrid scaffolds with suitable stiffness distribution properties could efficiently regulate ID assembly and formation in

cultured cardiac myocytes. Previously it was shown, that nanocomposites based on I type collagen containing a small amount (17.4, 43.5, and 174 ppm) of gold nanoparticles (approximately 5 nm) displayed improved biocompatibility and promoted proliferation and migration of mesenchymal stem cells (Hung et al. 2014). Gold-coated collagen nanofibers produced by a single-step reduction process were found to be biocompatible and to improve the myocardial and neuronal differentiation process of the mesenchymal stem cells (Orza et al. 2011).

Ultraviolet-crosslinkable gold nanorod-incorporated gelatin methacrylate hybrid hydrogels with enhanced material and biological properties for cardiac tissue engineering were fabricated (Navaei et al. 2016). Embedded nanorods promoted electrical conductivity and mechanical stiffness of the hydrogel matrix. Later, gelatin methacrylate hydrogel constructs comprised of surface micro-topographies incorporated with electrically conductive gold nanorods were developed to provide simultaneous electrical and topographical cues that mimic physiological relevant myocardium function (Navaei et al. 2017). Notably, that only electrically conductive cardiac tissues showed a consistent response in changing beat rate as a result of external stimulation.

Along similar research lines, a novel therapeutic hybrid scaffold that can couple electrical, mechanical, and biological properties suitable for cardiac tissue engineering was developed (Ravichandran et al. 2013). The electrospun scaffold was based on BSA/PVA and embedded gold nanoparticles in the ratios BSA/PVA/Au of 2:1:0.1. The structure of fabricated gold nanoparticles based scaffold is shown in Fig. 10.7. Results indicated that obtained gold nanoparticles based scaffolds could

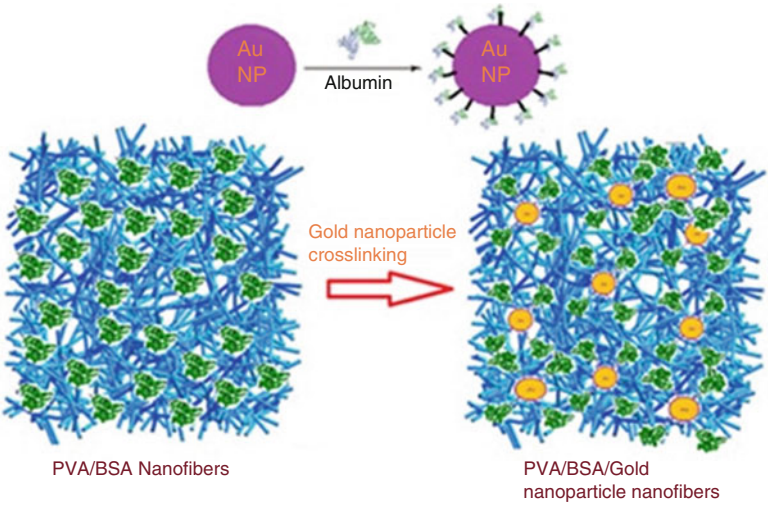

Fig. 10.7 Fabrication of PVA/BSA/Gold nanoparticles scaffolds for cardiac tissue engineering. (Reprinted with permission from Ravichandran et al. 2013)

lead to enhanced cardiomyogenic differentiation and result in superior biological and functional effects on infarcted myocardium regeneration.

Decellularized matrices have been considered since long times as promising and valuable scaffolds for engineering functional cardiac patches but the lack of quick and efficient electrical coupling between adjacent cells may jeopardize the success of the treatment (Shevach et al. 2014). To overcome this drawback gold nanoparticles were deposited on fibrous decellularized matrices and morphology, conductivity, and degradation of scaffolds was studied (Shevach et al. 2014). Gold nanoparticles were deposited on the scaffold's fibers using an e-beam evaporator. The authors showed that cardiac cells engineered within the hybrid scaffolds exhibited elongated and aligned morphology, massive striation, and organized connexin 43 electrical coupling proteins. In addition it was demonstrated that the hybrid patches display superior function as compared to pristine patches, including a stronger contraction force, lower excitation threshold, and faster calcium transients.

Interesting results have been reported very recently by utilizing photothermal properties of gold nanoparticles for cells simulation. Gentemann et al. applied a 532 nm picosecond laser to heat gold nanoparticles on cardiomyocytes leading to calcium oscillations in the HL-1 cardiomyocyte cell line (Gentemann et al. 2017). The authors observed a contraction rate increase in calcium containing buffer with neonatal rat cardiomyocytes. Notably, that in all tested cells these reactions were observed only in presence of gold nanoparticles. Therefore, this finding can provide novel approaches for a light based, nanoparticle mediated stimulation systems.

Indeed, incorporation of gold nanoparticles into scaffold structure can significantly improve mechanical, electrical properties, cell attachment on surface due to decoration of gold nanoparticles surface with proper ligands – all factors essential for successful application of designed scaffolds in cardiac tissue engineering. However, the important aspect is related to gold nanoparticles toxicity and impact on cardiac tissues in living organism. For example, the treatment of rat's heart tissue with 100 μl of 10 and 20 nm gold particles for 3 days or 7 days induced congestion in the heart muscle with prominent dilated blood vessels and extravasations of red blood cells. On the other hand, the treatment with 100 μl of 50 nm particles for 3 or 7 days demonstrated normal looking heart muscle with normal muscle direction and fascicles (Abdelhalim 2011). To have a comprehensive evaluation of the chronic cardiac toxicity of gold nanoparticles to the heart, PEGylated gold nanoparticles at three different sizes (10, 30 and 50 nm) were administrated to mice via tail vein for 14 consecutive days (Yang et al. 2016). Gold nanoparticles with smaller size displayed higher accumulation in mouse heart and faster elimination. It was shown, that none of the three sizes of gold nanoparticles affected cardiac systolic function. However, results indicated that the accumulation of small size gold nanoparticles can induce reversible cardiac hypertrophy. Therefore, the apart of numerous benefits of gold nanoparticles based scaffolds for cardiac tissue engineering, the toxicity of employed gold nanoparticles and impact on heart should be studied more precisely.

10.4 Gold Nanoparticles in Neural Tissue Engineering

Nerve regeneration process is a complex biological activity. In the peripheral nervous system, nerves can regenerate if injuries are tenuous (Schmidt and Leach 2003). However, larger injuries and spinal cord injuries are complicated processes, where self nerve regeneration is inhibited by numerous factors and neural tissue engineering can be a valuable help in the treatment of these injuries. For the peripheral nervous system the traditional treatment is based on nerve grafting. However, for spinal cord injury not much can be done without exogenous implants. Therefore, neural tissue engineering is also focused on the development of suitable environments for regeneration of neural tissue (Schmidt and Leach 2003). One of the first examples of the use of nanotechnology for neural tissue engineering was the effect of the surface nano-structure on the neuronal pattern of growth (Baranes et al. 2012, 2016). Indeed, nanotechnology can provide microstructured scaffolds to promote regeneration and direct repair by reconnecting axons (Limongi et al. 2017). Moreover, metal nanoparticles that act as anchoring sites for the small filopodial projections on 2D surfaces, allowed significant improvement of neurite–substrate interactions, leading to controlled growth of the neuronal processes (Baranes et al. 2016; Alon et al. 2014).

Park et al. evaluated the potential of gold nanoparticles (20 nm) to deliver electrical stimulation to nerve cell cultures in vitro to induce nerve regeneration (Park et al. 2008). For this puprpose authors introduced a novel method for the fabrication of a nanostructured 2D substrate in which gold nanoparticles were attached to the surface of cover glass via an adsorption system. By the electrical stimulation (250 mV for 1 h) through the network the authors observed an increase of the PC12 cells showing outgrowth length of neutrite, with a mean length of 98.5 μm. For comparison, the neutrite outgrowth length without electrical stimulation was approximately 10–20 μm. Interesting, that the alternating current stimulation showed good viability (<90%) of cells, while a high percentage of dead cells (more than 30%) was observed under constant current stimulation.

2D surfaces were therefore largely developed for neural tissue engineering purposes. On the other hand, 3D neuronal networks seem to give promising opportunities for repairing damaged spinal cord (Baranes et al. 2016). 3D composite scaffolds based on polycaptolactone/gelatin electrospun nonofibers decorated with gold nanoparticles (≈10 nm) encouraged a longer outgrowth of the neurites, as judged by the total length of the branching trees and the length and total distance of neurites (Baranes et al. 2016). The authors demonstrated that decorated nonofibers with gold nanoparticles provided additional topographical and anchoring sites for superior morphogenesis leading to more complex neuronal networks as shown in Fig. 10.8.

The authors suggested that future works must focus on determining the exact role of the gold nanoparticles in neuronal tissue engineering, e.g. investigating whether these nanoparticles promote axon elongation and higher expression of neuronal markers because of topographical cues or due to the conductivity of

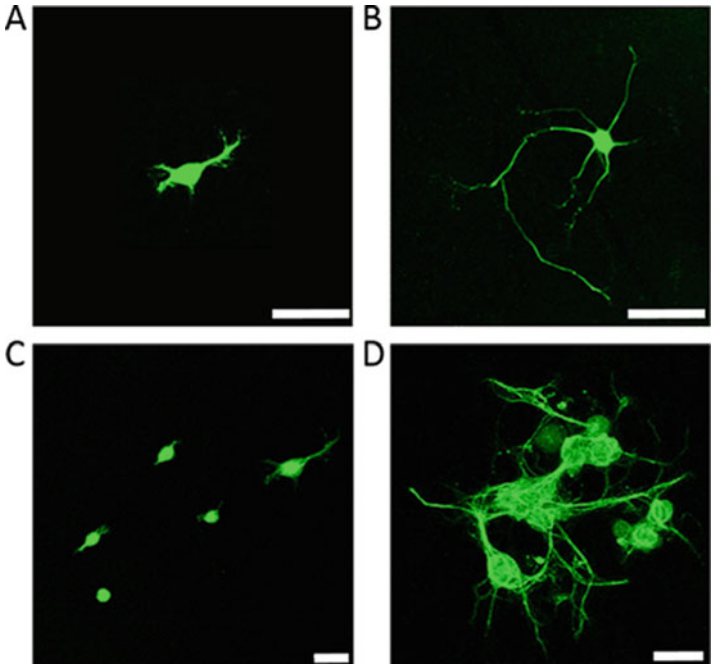

Fig. 10.8 Confocal microscopy images of single neurons cultivated on pristine (**a**) and gold nanoparticles (**b**) decorated 3D electrospun scaffolds. Neural network resulted on pristine (**c**) and gold nanoparticles based (**d**) scaffolds. (Reprinted with permission from Baranes et al. 2016)

corresponding nanoparticles. In addition, the effect of nanoparticle size and shape on neuronal tissue assembly must be also taken into account.

As demonstrated in opto-genetics, light absorption can modulate or trigger neural stimulation due to the action of light-activated membrane channels. Recently, the interest in extrinsic absorbers to assist neural stimulation in an aspecific way (typically through temperature) has grown. Gold nanoparticles have attracted some interest in this field due to the ability to efficiently absorb laser light at the plasmonic peak and to dissipate it into surrounding environment in form of heat (Chirico et al. 2015; Borzenkov et al. 2016; Freddi et al. 2013). Indeed, neuronal guiding and stimulation of neurons treated with gold nanoparticles can be achieved by applying Near-Infrared light at corresponding plasmonic resonance. In one of the first examples NG108-15 neuronal cells were treated with gold nanorods and then treated with low laser power (Paviolo et al. 2013). Bare, PSS and SiO_2 coated nanorods with LSPRs in range 750–810 nm were synthesized for this purpose. When the cells were irradiated with a 780 nm laser, the average number of neurons with neurites increased. Furthermore, when the NG108-15 cells were cultured with both bare and coated gold nanorods and then irradiated with 1.2–7.5 W/cm^2, they showed a neurite length increase up to 25 μm with respect to the control. Although the detailed mechanism of such

stimulation was not clear, the author connected this effect to the absorption of light by gold nanorods. This behavior was not specific to the gold nanoparticles surface chemistry.

The same authors demonstrated that intracellular calcium transients (Ca^{2+}) can be induced after Near-Infrared optical exposure of NG108-15 cells cultured with gold nanorods (Paviolo et al. 2014). The underlying mechanism was partially clarified in a subsequent detailed study and it is based on the transient heating associated with the optical absorption of gold nanoparticles, which can trigger neuronal cell differentiation and increase the level of intracellular calcium activity (Paviolo et al. 2015). The results indicated that nanoparticle absorbers can enhance and/or replace the process of infrared neural stimulation based on water absorption, with high potential for future applications in neural prostheses and cell therapies.

This phenomenon was confirmed also in other publications, though no definitive consensus has been found. Thus, the thermal transduction mediated by gold nanoparticles is particularly promising and can be a versatile tool to affect neuronal growth and to trigger the membrane depolarization from 0.025 to 25 ms illumination pulses (Colombo et al. 2016; Yong et al. 2014). Eom et al. reported that the neuronal stimulation could be activated by triggering temperature-sensitive channels in the rat sciatic nerve in vivo upon Near-Infrared illumination of gold nanoparticles (Eom et al. 2014). The authors demonstrated that temperature increase of 6 °C resulted in 5.7 times higher neuronal responsivity. From the other hand, PEGylated gold nanorods were shown to be effective in driving photothermal inhibition of the electrical activity of cultured neurons exposed to prolonged 785 nm laser pulses (Yoo et al. 2014).

Neurons can be directly stimulated with light to produce action potentials, particularly through the action of the opsins. In such approaches one does not rely on the localization of the absorbed light energy as it can be done by exploiting the high gold nanoparticles absorption. Recently it has been shown that gold nanoparticles can be conjugated to high-avidity ligands for a variety of cellular targets (Carvalho-de-Souza et al. 2015). Once bound to a neural membrane proteins, these particles transduce millisecond pulses of light into heat, which changes membrane capacitance, depolarizing the cell and eliciting the action potentials (Carvalho-de-Souza et al. 2015). The authors conjugated gold nanorods with LSPR ≈800 nm to molecules that bind neural membrane proteins with high avidity without damaging the cells. These findings indicate a possible promising alternative to optogenetics and potential applications for a variety of therapies involving neuronal photostimulation.

The light-assisted manipulation of cells can be exploited to control membrane activity or intracellular signaling (Lavoie-Cardinal et al. 2016). Lavoie-Cardinal et al. tested an optical method for the stimulation and the monitoring of localized Ca^{2+} signaling in neurons that exploits the plasmonic excitation of gold nanoparticles. They showed by means of confocal microscopy that the application of 800 nm laser pulses to neurons decorated with a few functionalized gold nanoparticles, triggers a transient increase in free Ca^{2+}. It is believed, that such gold nanoparticles-Assisted

Localized Optical Stimulation (NALOS) may bring a new complement to light-dependent methods for controlling neuronal activity and cell signaling.

The use of gold nanoparticles for neural tissue engineering has been tightly related also to development of hybrid polymeric matrices. In fact, nerve conduits derived from chitosan have favorable mechanical properties and slow biodegradability. Chitosan based scaffolds for neural tissue engineering, modified with other biodegradable polymers, were reported in publications (Shirosaki et al. 2014). Chitosan-gold nanocomposite materials were also investigated for similar purposes (Lin et al. 2008). The authors showed that gold nanoparticles improved the mechanical strength of the chitosan and also affected the behavior of neural stem cells in vitro. It was found that that 50 ppm of gold nanoparticles stimulated cell proliferation and gene expression. The analyses revealed that the number of myelinated axons in the regenerated nerve fibers was higher in animals where the nerve was reconstructed with the chitosan-gold nanocomposite (Lin et al. 2008).

A novel silk-gold nanocomposite based nerve conduit was tested on a model for a neurotmesis grade sciatic nerve injury in rats over a period of 18 months (Das et al. 2015). This conduit was fabricated by adsorbing gold nanoparticles onto silk fibers and transforming fibers into a nanocomposite sheet by electrospinning. The authors demonstrated that these implants are safe, stable and remain functional in vivo for a long duration. The use of gold nanoparticles synthesized by a "green technique" in the conduits was probably the key factor that inhibited the inflammatory response both in the host and in situ at the site of implantation. In addition, the strong interaction between the nanoparticles and nanofibers kept the gold nanoparticles embedded in the nanofibers, therefore limiting the migration of nanoparticles into the surrounding tissue. Based on these results it is likely that fabricated nanocomposites would enable chemical modifications of biomaterial and can potentially act as platforms for delivery of nerve growth factors providing chemical cues for cellular proliferation and directing neurite outgrowth.

Nevertheless, the effect of gold nanoparticles on central nervous system has still to be investigated accurately, since contradictory results are reported. For example, Söderstjerna et al. studied the size effect on the growth of human embryonic neural precursor cells with well-characterized commercial spherical 20 and 80 nm gold nanoparticles (Söderstjerna et al. 2013). It was demonstrated that only the highest dose of 20 nm gold nanoparticles significantly affected proliferation, whereas no effect was seen on apoptotic cell death. In another multi-parametric study, the exposure to gold nanoparticles affected cellular proliferation and differentiation in an immortalized neural cell line (Soenen et al. 2012). The effect of Gold/Fe_3O_4 nanoparticles on biocompatibility and differentiated properties of rat olfactory bulb stem cells was studied (Wang et al. 2013). The obtained results indicated that Gold/Fe_3O_4 nanoparticles at the concentrations of 40 μg/10^4 cells enhanced cell viability and decreased the cell death rate. The authors suggested the application of such nanoparticles as new nanotechnologies in stem-cell-based transplantation therapies for the treatment of central nervous system diseases. In terms of electrical activity, it was observed that intracellular nanoparticles might alter neuronal functions and

cause hyper-excitability in pathological conditions (Jung et al. 2014; Paviolo and Stoddart 2015). Indeed, for a successful application of gold nanoparticles as stimuli for neural cells growth, detailed studies on the adverse effects of gold nanoparticles on the developing central nervous system are mandatory.

10.5 Gold Nanoparticles in Bone Tissue Engineering

Bone defect repair using the tissue engineering approach is becoming a promising and highly effective method because the repair process may proceed with the patient's own tissue by the time the regeneration is complete (Laurencin et al. 1999; Amini 2012). Bone tissue engineering is considered as a complex process that starts with migration and recruitment of osteoprogenitor cells followed by cells proliferation and differentiation and by the matrix formation along with remodeling of the bone (Bose et al. 2012). Nowadays nanotechnology is integrated in the bone tissue engineering field to overcome some of the current limitations associated with bone regeneration methods including insufficient mechanical strength of scaffold materials, ineffective cell growth and osteogenic differentiation at the defect site, and stimulate bone cell growth (Kim and Fisher 2007). Nanomaterials can also act as carriers for bioactive molecules necessary for bone tissue formation. They stabilize the bioactive molecules through encapsulation or surface attachment and provide controlled release at the designated target (Walmsley et al. 2015). Based on a range of scientific reports, the following functions of gold nanoparticles applied to bone tissue engineering can be highlighted:

(a) act as osteogenetic agents;
(b) have antibacterial effect;
(c) enhance grafting of bone implants.

Gold nanoparticles are promising osteogenic agents for bone tissue regeneration, promoting osteogenic differentiation of mesenchymal stem cells (Liu et al. 2010; Yi et al. 2010). Gold nanoparticles with sizes 20 and 40 nm induce the increase of the osteogenic differentiation rate of MC3T3-E1 osteoblast-like cells (Liu et al. 2010). Furthermore, gold nanoparticles synthesized by citrate reduction of $HAuCl_4$, can affect osteoclast formation (Sul et al. 2010). In this direction a biodegradable hydrogel loaded with gold nanoparticles has been more recently developed as a new approach for bone tissue regeneration (Heo et al. 2014). The authors used photo-curable gelatin hydrogels in order to provide a proof of principle of gold nanoparticles loaded hydrogels in regeneration strategies for bone tissue engineering as shown in Fig. 10.9. The in vitro results revealed that the hydrogels loaded with gold nanoparticles promote proliferation, differentiation, and alkaline phosphate activities of human adipose-derived stem cells as they differentiate towards osteoblast cells in a dose-dependent manner. The in vivo results demonstrated that these hydrogels loaded with high concentrations of gold nanoparticles had a significant influence on new bone formation.

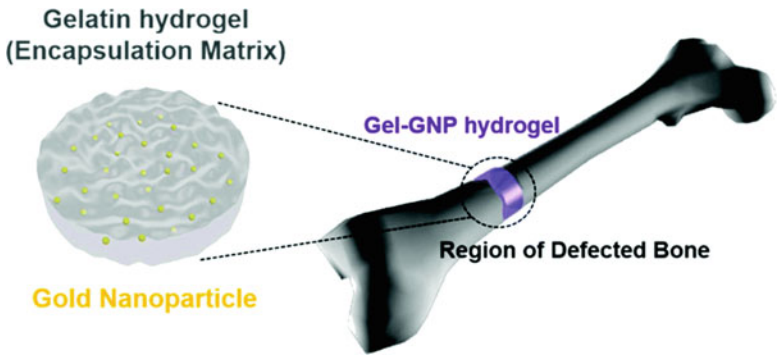

Fig. 10.9 Photo-cured gelatin hydrogel-gold nanoparticles network developed for bone tissue repair. (Reprinted with permission from Heo et al. 2014)

More recently, Choi et al. studied the effect of chitosan conjugated gold nanoparticles on the osteogenic differentiation (Choi et al. 2015). Positively charged gold nanoparticles with hydrodynamic diameter ≈40 nm were prepared using the chitosan reduction method. The results indicated that chitosan-conjugated gold nanoparticles increase the deposition of calcium content and the expression of marker genes related to osteogenic differentiation in human adipose-derived mesenchymal stem cells at nontoxic concentrations. The authors showed that such nanoconstructs can promote osteogenesis through the Wnt/β-catenin signaling pathway and can be applied as agents for bone formation.

The osteoinductive nature and the good bio-compatibility of hydroxyapatite makes it an optimal candidate as a graft material for bone repair, augmentation, and substitution (Chang et al. 2001). Moreover, gold nanoparticles with collagen form an efficient matrix for the growth of hydroxyapatite (Aryal et al. 2006). Such growth on gelatin–chitosan composite capped gold nanoparticles by means of wet precipitation was studied (Sobhana et al. 2009). These authors proved that gelatin–chitosan capped gold nanoparticles can act as a matrix for the growth of crystals, thus introducing low cost and effective approach.

Interesting results, appeared in *Nano Letters* in 2015, describing the fabrication of substrates with precisely spaced and tunable gold nanoparticles arrays (Schwab et al. 2015). Moreover these gold nanoparticles carried single bone morphogenetic proteins belonging to the transforming growth factor-β. In this work, glass cover slips were decorated with a regular arrangement of gold nanoparticles by using diblock copolymer micellar nanolithography, and gold nanoparticles 5–8 nm in size were functionalized with the morphogenetic proteins via bifunctional linker (11-mercaptoundecanoyl-*N*-hydroxysuccinimide ester). With such nanoconstructs, one can achieve controlled and sustained local delivery of different growth factors. Employing this set up it would be possible to assess, at unprecedented level, the minimum concentration (ranging from <0.5 to >3 ng/cm^2) of surface-bound growth factor needed to initiate individual signal pathways.

Too many orthopaedic implants undergo undesired bacterial infection. The subsequent inflammation leads to implant failure and second surgery. To overcome this drawback nanoparticle treatment of the prostheses has been applied. Beside silver, with known antimicrobial activity, also gold nanoparticles have been more recently used to load ceramic scaffolds and induce endogenous antimicrobial and anti-inflammatory activity that increase the success of bone implantation and tissue regeneration (Farag et al. 2012). The authors evaluated the effect of gold nanoparticles on the scaffold's mechanical properties, porosity and cell growth. Resulted scaffolds with incorporated gold nanoparticles displayed enhanced porosity, degradability and mechanical properties compared with the ceramic scaffolds. In a very recent publication the problem of rapid emergence of antibiotic resistance of bone tissue implants is also discussed (Ribeiro et al. 2017). The authors claimed that biomaterials must be modified to promote the tissue integration before bacterial adhesion. For this purpose, they fabricated silk fibroin/nanohydroxyapatite hydrogel modified with in situ synthesized silver and gold nanoparticles. In vitro antimicrobial studies revealed that hydrogels with both types of nanoparticles exhibited significant inhibition ability against both gram-positive and gram-negative bacteria. Cytocompatibility studies performed by using osteoblastic cells indicated that up to 0.5 wt% of silver nanoparticles, and for all concentrations of gold nanoparticles, the hydrogels can be effectively used as antimicrobial materials, without compromising cell behavior.

Gold nanoparticles can enhance grafting of bone implants. Ross and Roeder showed that bisphosphonate (alendronate)-functionalized gold nanoparticles exhibited more rapid binding kinetics and greater binding affinity to hydroxyapatite compared to carboxylate (L-glutamic acid) and phosphonate (2-aminoethylphosphonic acid) functional groups (Ross and Roeder 2011). However, it must be considered that the results for binding to synthetic crystals may not reflect real binding to tissue. Therefore, in following publication, the authors suggested that damaged bone tissue can be targeted by functionalizing gold nanoparticles with molecules exhibiting affinity for calcium (Ross et al. 2012). They studied the binding affinity of gold nanoparticles surface functionalized with carboxylate (L-glutamic acid), phosphonate (2-aminoethylphosphonic acid), or bisphosphonate (alendronate) in vitro (Ross et al. 2012). Based on obtained results, the authors suggested that bisphosphonate-functionalized gold nanoparticles have potential for targeted delivery to damaged bone tissue as shown in Fig. 10.10.

The effect of gold nanoparticles functionalization on grafting was also reported in paper published in *Biomaterials* in 2015 (Li 2015). In this study human bone marrow-derived mesenchymal stem cells were treated with amine (-NH2), carboxyl (-COOH) and hydroxyl (-OH) functionalized gold nanoparticles possessing different surface charges. These functionalized nanoparticles showed no acute toxicity and positively charged nanoparticles exhibited higher cellular uptake. All types of gold nanoparticles did not inhibit osteogenesis, though calcium deposition was markedly

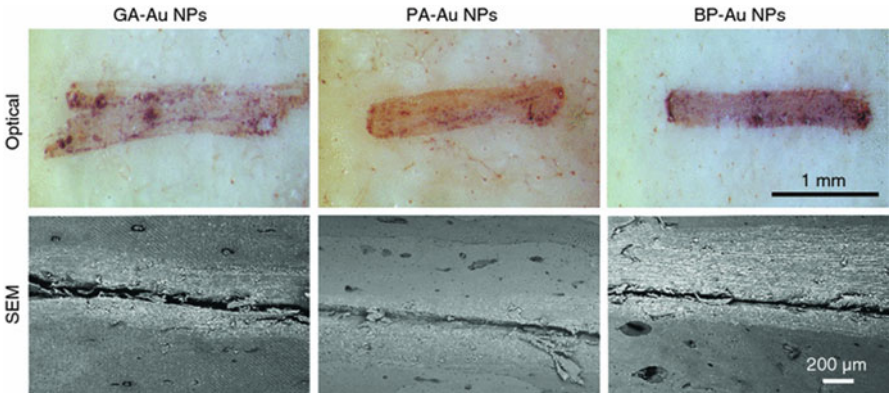

Fig. 10.10 Optical and backscattered electron micrographs showing surface damage (scratch) on bovine cortical bone specimens labeled with glutamic acid (GA)-, phosphonic acid (PA)-, and bisphosphonate (BP)-functionalized gold nanoparticles. The relative depth of the color or contrast observed in optical and backscattered electron micrographs, respectively, for damaged bone tissue inside the scratch versus undamaged tissue outside the scratch qualitatively suggested that BP-gold nanoparticles exhibited the greatest binding affinity for damaged bone tissue. (Reprinted with permission from Ross et al. 2012)

reduced during gold nanoparticles-COOH treatment. These results provided additional confirmation that functionalization of gold nanoparticles can play an important role during materials engineering.

Small non-coding RNAs, microRNAs (miRNAs) play an important role in stem cell differentiation through regulating target-mRNA expression. They are therefore important effectors in tissue engineering. In a very recent paper novel, surface-engineered, ultra-small gold nanoparticles (<10 nm) have been used as highly efficient miR-5106-delivery systems that enable the regulation of bone mesenchymal stromal cells differentiation (Yu et al. 2017). The authors exploited the effect of gold nanoparticles coated layer-by-layer with polyethylenimine and liposomes to enhance miR-5106-delivery activity and subsequent cells differentiation capacity. Coated gold nanoparticles showed negligible cytotoxicity, good miRNA-5106-binding affinity, highly efficient delivery of miRNAs to cells, and long-term miRNA expression. These finding can open a promising strategy for the rational design of ultra-small inorganic nanoparticles as highly efficient miRNA-delivery platforms for tissue regeneration. Another interesting delivery approach was developed on the basis of alginate made capsule systems capable of rapidly releasing multiple polyloads in response to ultrasonic signals (Kennedy et al. 2016). As a proof of concept, gold nanoparticles were decorated with bone morphogenetic protein-2 to demonstrate the potential bioactivity of the nanoparticle payloads. These nanoparticles were not cytotoxic and induced an osteogenic response in mouse mesenchymal stem cells.

Due to increasing interest of researchers to apply gold nanoparticles for bone tissue engineering, a few recent works have appeared on the effect of various sizes of

gold nanoparticles on the differentiation of human adipose-derived stem cells (ADSCs) into osteoblasts (Ko et al. 2015). Spherical gold nanoparticles with different sizes (15, 30, 50, 75 and 100 nm), at a single concentration of 1 μM, were used for this purpose. The results showed that independently of the size of the gold nanoparticles, no significant toxicity on cells was observed over 1 week of incubation. The authors found by means of dark field assays and optical microscope of the treated cells, that 30 nm and 50 nm gold nanoparticles were preferentially up taken. Moreover, it was also shown that all sized of gold nanoparticles promoted the differentiation of cells more than control. Nevertheless, 30 nm and 50 nm gold nanoparticles displayed the highest differentiation rates providing the most effective osteogenic differentiation.

Despite of promising results achieved recently by incorporation gold nanoparticles in bone tissue engineering, there are a few issues that still remain unclear and have to be solved in future. Indeed, the employment of gold nanoparticles brought relevant improvement of scaffolds properties. The ability to use gold nanoparticles as delivery vectors of biomolecules has been also explored. The study of the tissue growth and the scaffolds behavior in-vivo can be easily done exploiting the gold nanoparticles scattering or luminescence. However, the precise answer how gold nanoparticles promote bone formation still remains unclear (Vial et al. 2016). Primary goals for future studies are the development of protocols to reveal these mechanisms together with more detailed studies regarding the impact of nanoparticles sizes, shapes and surface properties on the bone tissue engineering. Further efforts should also be done towards the application of localized photothermal effect of gold nanoparticles in bone tissue engineering, similarly to what was done in the case of neural cells.

10.6 Gold Nanoparticles in Skin Tissue Engineering and Wound Healing

The skin is the largest organ of the body and engineered skin substitutes have a critical medical application to patients with a variety of injuries, for example with burn wounds (Wong and Chang 2009). Tissue-engineered skin includes endogenous cells implants, cells implanted within two- or three-dimensional biomaterials, biomaterials for replacement of the skin's dermal layer (both with and without cells), and biomaterials to support the replacement of both the epidermis and dermis (MacNeil 2008).

The ideal and primary goal of skin tissue engineering is to enable the rapid formation of a construct that will support and enable the complete regeneration of functional skin with all the skin appendages, the various layers (epidermis, dermit, fatty subcutis), and a fully functioning and scar free integration of the vascular and nerve network within the host tissue (Mohamed and Xing 2012). Skin regeneration and wound healing approaches that exploit the achievement of nanotechnology is the

topic treated in studies and investigations worldwide (Chaudhury et al. 2014; Parani et al. 2016). The current approaches of nanotechnology based methods for skin tissue engineering are:

1. Antimicrobial effect;
2. Anti-oxidative stress effect;
3. Growth factors in scaffolds for skin regeneration;
4. Nanofibrous scaffolds and nanoparticles loaded hydrogels with improved properties

Metal nanoparticles exhibit a range of useful properties for skin tissue engineering, such as enhancing mechanical strength, controlled release, and antibacterial activity against both bacteria and fungi, which make such nanoparticles excellent candidates for topical use in wound healing (Parani et al. 2016). For example, gold nanoparticles functionalized with antibiotics, antioxidants, and ROS scavengers can improve wound healing process. In addition, they can directly be applied in tissue welding and also act as vehicles for gene delivery (Parani et al. 2016).

Bacterial infections are severe problems in skin treatments. The impact of surface chemistry of gold nanoparticles antimicrobic activity was then studied in detail by means of gold nanoparticles carrying different cationic functionalities varying in chain length and nonaromatic and aromatic characteristics (Li et al. 2014). The authors demonstrated that gold nanoparticles with cationic and hydrophobic functional groups were the most effective against Gram-negative and Gram-positive bacteria. The light-absorbing capability of gold nanoparticles for tissue welding to facilitate healing of cut wounds was also studied (Gobin et al. 2005). In this work synthesized gold nanoshells with Near-Infrared LSPR were used as exogenous chromophores to absorb the near-infrared energy while the histological examination revealed good wound-healing response. It was also shown that antibiotics display enhanced activity when conjugated to gold nanoparticles (Parani et al. 2016). As an example, it was demonstrated that vancomycin capped gold nanoparticles acted as a rigid polyvalent inhibitor of vancomycin resistant enterococci (Gu et al. 2003). Moreover, it was shown that gold nanoparticles had unexpected direct activity against E coli strain. A prospective application for gold nanoparticles in wound healing was also demonstrated by a study on the fibroblast cell detachment, patterning, and regrowth on artificially engineered gold nanoparticle-based surfaces that were triggered by laser irradiation (Kolesnikova et al. 2012). The antimicrobial activity can be obtained also by decorating the gold nanoparticles with short peptides. Chen et al. reported the use of gold nanorods functionalized with the antimicrobial peptide surfactin (Chen et al. 2015). These decorated nanorods showed high antimicrobial activity likely related to bacterial membrane disruption. In addition, in vivo wound healing studies on rats demonstrated good biocompatibility, faster healing and better epithelialization.

Wound healing is also largely hindered by the inflammation due to oxidative stress (Parani et al. 2016; Chen et al. 2012). Also in this case, it has been shown that

the combination of antioxidants, such as epigallocatechin gallate and α-lipoic acid, with gold nanoparticles displayed significant antioxidation effect and enhanced the action of the growth factor of endothelial cells (Chen et al. 2012; Leu et al. 2012). Despite the fact that such combination accelerates the wound healing process, the combined effect of all components requires more accurate studies. Gold nanoparticles can also be used in gene therapy for wound healing. Anti-miR-378a RNA fragments were conjugated to methoxy PEG thiol and coated on the surface of gold nanoparticles (Gaharwar et al. 2014). The RNA decorated gold nanoparticles showed better wound closure compared to the wounds treated with gold nanoparticles carrying blank vector.

Regarding the use of gold nanoparticles in scaffolds for skin regenerations, there are a few studies on the growth of epithelial cells. Rosman et al. first studied the growth of these cells on substrates decorated with gold nanorods (Rosman et al. 2014). These nanoparticles were coated either with a positively charged (cytotoxic) surfactant or with a biocompatible polymer exhibiting one of two different terminal groups, resulting in a neutral or negative surface charge. It was found that all particles supported cell adhesion with no evidence of directed cell migration or particle internalization. The authors found an impaired cell growth correlated to the cytotoxicity of the surface bound surfactant. However, in the case of the presence of a biocompatible polymer on the nanoparticles, they observed no effect on cell growth for the functional terminated –COOH group, whereas the $–NH_2$ group reduced adherence and proliferation compared to cells growing on a bare glass substrate. It was concluded that the impact of basolateral exposure of gold nanorods on epithelial cells depends critically on the exposed chemical moiety in contact with the cell membrane. Along this line of studies, negatively charged and positively charged gold nanoparticles were incorporated into a decellularized porcine diaphragm to produce a biocompatible scaffold suitable for wound healing (Cozad et al. 2011). The incorporation of gold nanoparticles led in this case to enhanced cell proliferation and free radical generation, suggesting that also the shape and concentration of the gold nanoparticles may affect the growth of epithelial cells.

Volkova et al. have recently explored the possibility of using cryopreserved human of fibroblasts cultured with gold nanoparticles to treat experimental burns (Volkova et al. 2016). The immunofluorescent analysis emphasized that the use of these fibroblasts accelerated the skin synthetic processes and was helpful in recovering type I and III collagen content on day 21 after therapy. The authors ascribed the observed phenomenon to the unique structure and antimicrobial properties of gold nanoparticles. Interestingly, in an earlier work, gold nanoparticles immobilized on a silica substrate forming 500 nm SiO_2/gold nanoparticles core-shell structure promoted proliferation of mouse embryonic fibroblast cells (Li 2015). This observation was explained by the fact that the silica substrate kept gold nanoparticles outside the cells and the nano-size concavo-convex gold shell facilitated to cell adhesion, resulting in the proliferation. It was also shown that resulted core-shell nanomaterials can promote wound healing also due to anti-inflammatory and antioxidation properties of gold nanoparticles.

Incorporation of gold nanoparticles into polymeric network can bring advances in wound dressing fabrication. Gold nanoparticles-chitosan composites showed enhanced proliferation of human fibroblasts in vitro in comparison with pure chitosan (Hsu et al. 2011). In recent study nanocomposite collagen scaffolds incorporating gold nanoparticles were fabricated for wound healing applications (Akturk 2016a, b). It was shown that intercalation of gold nanoparticles into cross-linked scaffolds enhanced the stability against enzymatic degradation and increased the tensile strength. These nanocomposites displayed also inhibition of the inflammatory response and had a pronounced effect on skin tissue formation. Nevertheless, the authors noted that further studies are needed to investigate if and how higher loading of gold nanoparticles affects positively these results in a statistically meaningful manner (Akturk 2016). Citrate-capped gold nanoparticles were also incorporated in different concentrations into collagen/poly(ethylene oxide) nanofibrous matrixes for novel skin tissue engineering approaches (Aktürk and Keskin 2016). Nanocomposites with 14.27 ppm of gold nanoparticles showed the best morphology. The cell attachement and proliferation onto these scaffolds were similar to commercially available Matriderm substrate. In another paper published by the same authors 3D silk fibroin matrices loaded with citrate-capped gold nanoparticles (d = 24 nm) were used for skin tissue engineering applications (Akturk 2016). Also in this case, gold nanoparticles incorporation improved degradation profiles and mechanical properties significantly. Though, bare and gold nanoparticles based scaffolds showed similar cells attachment and layer by layer proliferation, more flattened and spread cells morphology was observed on gold nanoparticles based nanocomposite. Therefore, incorporation of gold nanoparticles into fibroin matrix at 14.27 ppm led to enhancement of matrix properties and did not cause toxicity both in vitro and vivo conditions.

In a paper published in 2015 Kim et al. studied the therapeutic effect of phytochemically stabilized gold nanoparticles grafted on hydrocolloid membrane, as shown in Fig. 10.11, for curing cutaneous wounds (Kim et al. 2015). Phytochemically stabilized gold nanoparticles are synthesized under non-toxic conditions suitable for medical applications.

The authors demonstrated that topical application of gold nanoparticle coated membranes for 15 days induced the acceleration of wound healing including tissue regeneration, connective tissue formation, and angiogenesis. It was also shown that such membranes did not induce toxicity.

10.7 Other Examples of Gold Nanoparticles Application in Tissue Engineering

Having discussed the application of gold nanoparticles in the most emerging fields of tissue engineering, it is also worth to mention very briefly other fields of tissue engineering, where corresponding nanoparticles have been already applied. An

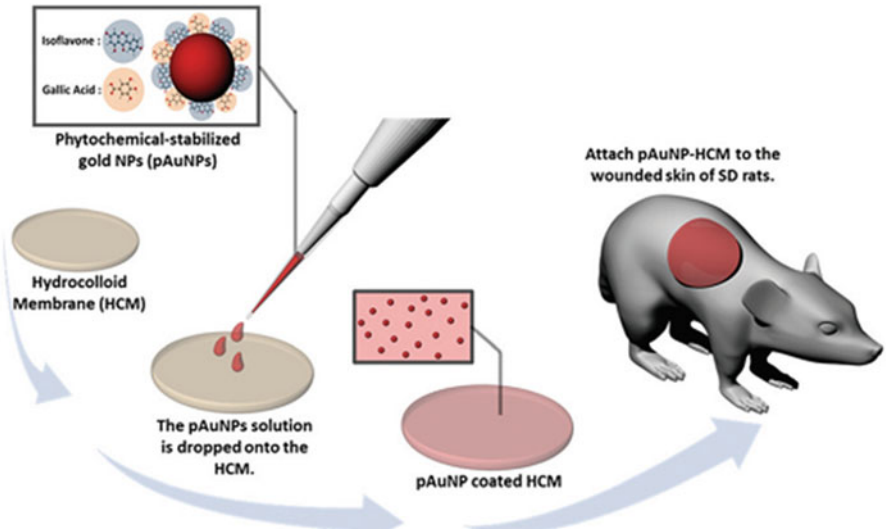

Fig. 10.11 Preparation of phyto-chemically stabilized gold nanoparticle coated membranes for skin damage treatment. (Reprinted with permissions from Kim et al. 2015)

active patch composed from decellularized tissue conjugated to 100 nm gold nanoparticles was shown to be efficient biomaterial for vascular repair (Ostdiek et al. 2015). Recently, it was demonstrated that systemically administered collagen-targeted gold nanoparticles were capable to bind to arterial injury following vascular interventions, therefore providing new opportunities in vascular injury treatments (Meyers et al. 2017). Gold nanoparticles were applied also to improve materials for hernia repair. Thus, it was demonstrated, that gold nanoparticles covalently linked to polypropylene mesh displayed improved biocompatibility as compared to pristine mesh (Grant et al. 2011). Also, a couple of examples regarding the application of gold nanoparticles for muscle tissue engineering are provided. Poly(L-lactic acid) and gold nanoparticles were used to prepare electrospun scaffolds with improved biodegradable, biocompatible and conductive scaffolds for skeletal muscle tissue regeneration (Mckeon-Fischer and Freeman 2011). The photo-thermal properties of gold nanoparticles can be also successfully applied in muscle tissue engineering. In the recent paper published in 2017 mild heat stimulation of muscle cells induced by Near-Infrared irradiation of gold nanoshels efficiently induced myotube contraction (Marino et al. 2017). The reported "wireless" activation can bring advances in tissue engineering and bionics, where large cell population can be simultaneously activated.

10.8 Conclusions

Without much doubts recent advances of nanotechnology brought significant advances in tissue engineering field. Among different types of nanomaterials, gold nanoparticles allowed significantly improvement the scaffold properties together with direct effect on the growth of different types of cells. The origin of gold nanoparticles efficacy lies likely in their multifunctional nature. Therefore, as it has been shown in this review, gold nanoparticles can be successfully applied for cardiac, neural, bone and skin tissues regeneration. The future trends are detailed studies of all observed challenging results in all mentioned fields providing summarized protocols. However, beside these promising results, many questions still remain unsolved, e.g. the formulation of clear models of their effect on cells growth. Long-term studies of the prolonged treatment of cells with gold nanoparticles, while growing on scaffolds, are required. Therefore, these factors have to be investigated in future opening an opportunity for further clinical trials.

Again, most studies still need more details on protocols to achieve best results in tissue engineering assisted by gold nanoparticles. Moreover, many studies still remain at in vitro level. Therefore, more investigations performed in vivo conditions are required. Finally, detailed protocols regarding the toxicity and side effects of gold nanoparticles in tissue engineering are important topics to be addressed for any efficient clinical application.

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