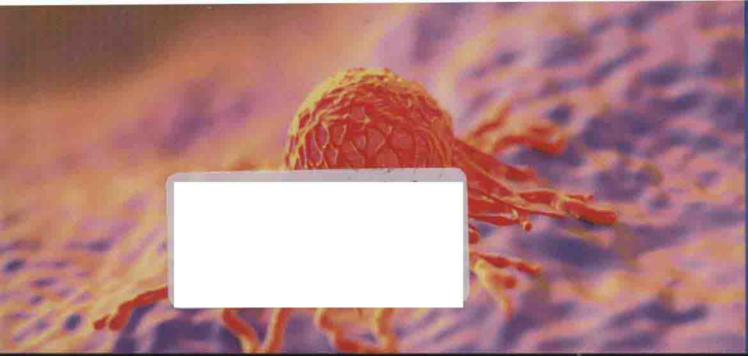
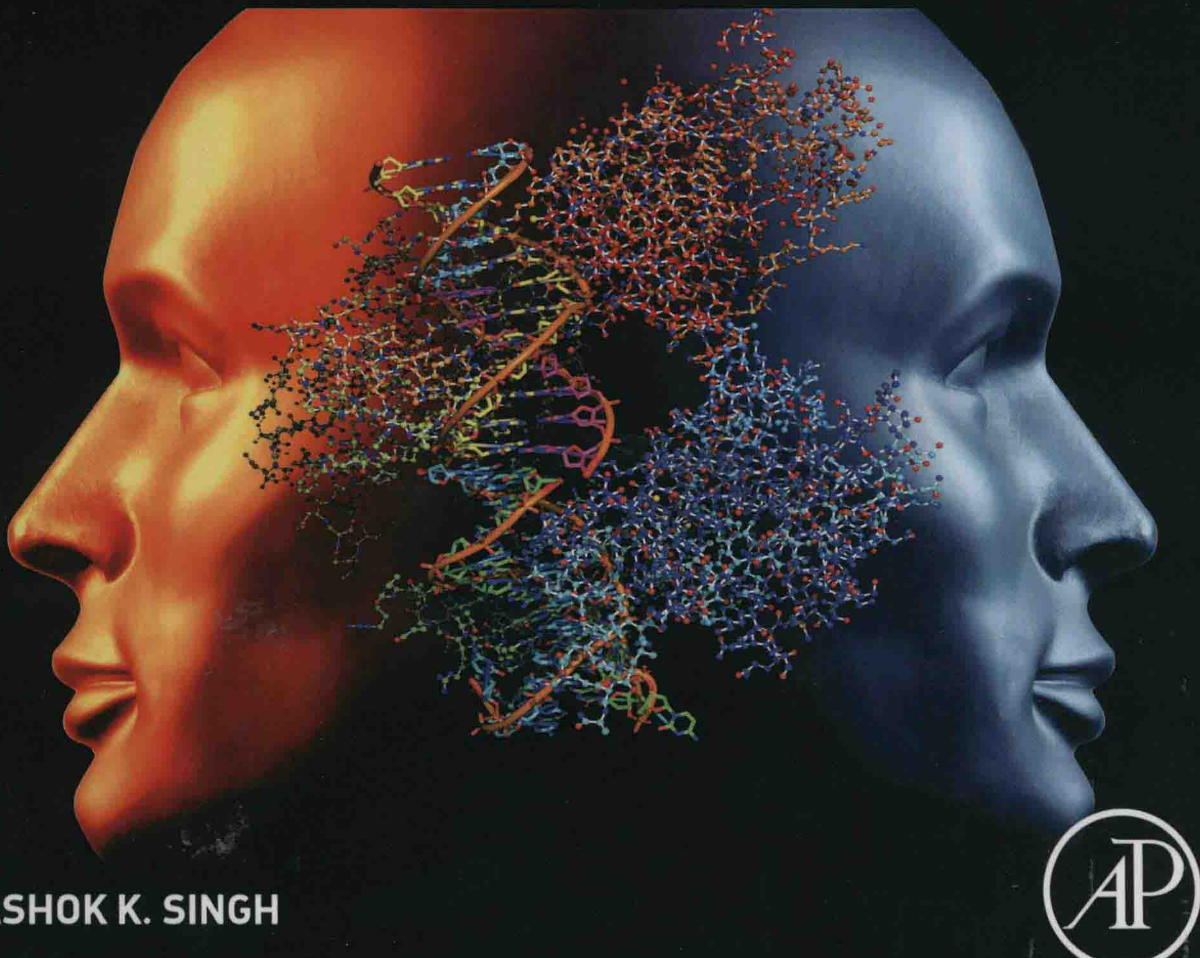



ENGINEERED NANOPARTICLES

Structure, Properties and Mechanisms of Toxicity



ASHOK K. SINGH

ENGINEERED NANOPARTICLES

STRUCTURE, PROPERTIES AND MECHANISMS OF TOXICITY

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ENGINEERED NANOPARTICLES

Dedication

This book is dedicated to the memory of my niece Sony, who left us at a young age.

Ashok K. Singh

Foreword

A rare Roman cage cup at the British Museum in London has been a source of delight to the eyes and wonderment to the mind for nearly 17 centuries. When viewed *en face*, its jade green glass depicts the scene of a Thracian king ensnared by vines. However, when backlit, the dichroic glass of the eponymous Lycurgus cup assumes a ruby red coloration. An explanation for this dazzling effect can be found roughly a mile away at the Faraday Museum, where a container of ruby red liquid containing minute colloidal gold particles sits on display. Colloidal gold and silver are embedded in the glass of the Lycurgus cup. Michael Faraday and his scientific successors in the nineteenth and twentieth centuries discovered that these gold nanoparticles in solution possess intriguing optical properties. They are capable of altering the wavelength of transmitted light in a size-dependent fashion. The precise mechanism underlying this phenomenon is clearly described in this excellent monograph authored by my colleague, Professor Ashok Singh, who is a distinguished chemist, toxicologist, and educator.

The growing field of nanoengineering was sparked by the advent of the electron microscope in the 1930s and inspired by physicist Richard Feynman's 1959 Caltech lecture entitled "There's Plenty of Room at the Bottom". Numerous materials have since been created, which possess distinctive properties at nanometric sizes (i.e., ranging from 1 to 100 nanometers in any single dimension). These novel materials, manufactured in all shapes and nanometric dimensions, have already made a significant, overarching impact on many essential aspects of our daily lives. Nanoscale materials have become incorporated into the processed foods that we consume, cosmetic and clothing products we wear, medications we take, vehicles that move us daily from place to place, and the computational devices to which we are constantly and intimately tethered in the early twenty-first century—and we are just at the beginning stages of this new technology. There is more to come, and the fruits of this endeavor are destined to transform humankind.

The few examples that follow represent only a small fraction of efforts in this area of inquiry and design. In the medical arena alone, oncologists have long been anticipating the development of a biocompatible nanoscale platform that will detect and then chemically treat localized tumors within the body, a so-called theranostics strategy. Virus-like nanoparticles and nanoengineered formulations of drugs are being designed to achieve high drug concentrations in localized body regions while reducing the risk of systemic adverse effects. Finally, the engineering of controlled biomolecular motors that can shuttle cargo around inside cells offer promise as a key step in the development of nanomachines, which can improve human health and wellness.

The first chapters of this book provide the reader with a fundamental understanding of the physicochemical properties of nanoparticles and their current and potential applications.

Professor Singh writes in a simple, direct prose style that will satisfy an expert, yet not entangle a casual reader with a basic scientific background in unexplained technical jargon and complexities.

Where there is great promise, there may be also pitfalls and even perils. Since the beginning of the twenty-first century, there has been increasing interest and concern about the safety of nanoparticles. As Professor Singh emphasizes throughout this book, nanomaterials with a large surface area to volume ratio may possess chemical reactivity and toxic properties that are not observed when they are present in larger sizes. Because they are very small, nanoparticles may become readily airborne and capable of being inhaled into the lungs. A fraction of an inhaled amount of nanoparticulate material may reach the lowest level of the lungs, the alveoli, and after traversing a single layer of alveolar epithelial cells, enter the bloodstream.

As nanotoxicology was becoming a recognized discipline, the toxic effects of airborne engineered nanoparticles in the respiratory system were found to be analogous those of known "incidental" ultrafine particles from polluted air. Since then, the toxicological properties of nanomaterials entering by other routes have been examined, including ingestion and skin contact. Regardless of how they enter the body, these materials are in general eliminated quite slowly and can persist in the body. Indeed, multiple exposures to nanoparticles may result in their accumulation within a host organism, augmenting the potential for adverse effects. Moreover, engineered nanoparticles are raising environmental concerns as they have been detected in soil, water and air, although the fates, behaviors, and ecological impacts of many nanomaterials in these settings are not yet fully understood.

Similar to other exciting and rapidly emerging technologies, the processes of design, creation, and production of new materials often precede those concerned with hazard protection and containment. In the latter half of this book, Professor Singh provides guidance on how to deploy the steadily growing knowledge base of toxicokinetic and toxicodynamic information on nanoparticles to formulate thoughtful risk assessments and effective containment strategies for safeguarding people, other organisms, and the environment.

The Roman admiral and natural philosopher Pliny the Elder perished in the eruption of Mount Vesuvius in 79 AD, presumably after inhaling nanoparticles of volcanic ash. To him is the following quote attributed: "In these matters, the only certainty is that nothing is certain." This adage could be applied to the current, early phase of nanotechnology. Compilations of existing knowledge presented with precision and clarity, as represented in this monograph, will support future developments in this exciting area, which lies at the intersection of materials science, bioengineering, and chemical biology.

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CHAPTER

1

Introduction to Nanoparticles and Nanotoxicology

OUTLINE

1. INTRODUCTION TO NANOPARTICLES

In 1966, the science-fiction film *Fantastic Voyage*, directed by Richard Fleischer and produced by 20th Century Fox, was released. In the movie, agent Charles Grant, pilot Captain Bill Owens, Dr Michaels, surgeon Dr Peter Duval, and his assistant Cora Peterson are placed aboard a submarine that is then miniaturized and injected into a patient suffering from a life-threatening brain clot. Their goal was to travel to and then fix the clot. After an amazing journey across various organs, they reach their destination and achieve the goal.

Engineered Nanoparticles
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How did the scientists shrink the submarine and its inhabitants? By reducing Plank's constant (you will read about Plank's constant in Chapter 3) that increased the speed of light and reduced the graininess of the universe. According to the movie, the submarine was reduced to the size of a bacterium (1 μm in diameter); therefore, its inhabitants may have been reduced to smaller size, probably in the nanometer range. I viewed this movie in the early 1970s and was amazed by the special effects, especially the scenes depicting the submarine attacked by the immune cells (Figure 1(B)). I never expected the plot to become a reality. However, 50 years after the movie's release, although nanosized humans are still a fantasy, nanosized drug-loaded submarines that travel within the body may become a reality. Scientists have developed devices that can travel into the body and fix diseased cells (Sailor and Park, 2012; Peer et al., 2007). The submarine in *Fantastic Voyage* may become a reality when nanomotors are controlled inside a living cell and literally fight the disease. This is the miracle of nanotechnology.

In 2002, Michael Crichton published his novel *Prey*, which tells the story of a mechanical plague that occurred when a cloud of self-sustaining and self-reproducing nanoparticles with collective intelligence (remember the "Borg" of *Star Trek*, Figure 1(C)) escaped from the laboratory. The nanocloud (*cloud*—Does this word sound familiar?) learns from its experiences and becomes more deadly with each passing hour. The novel describes the desperate efforts of a

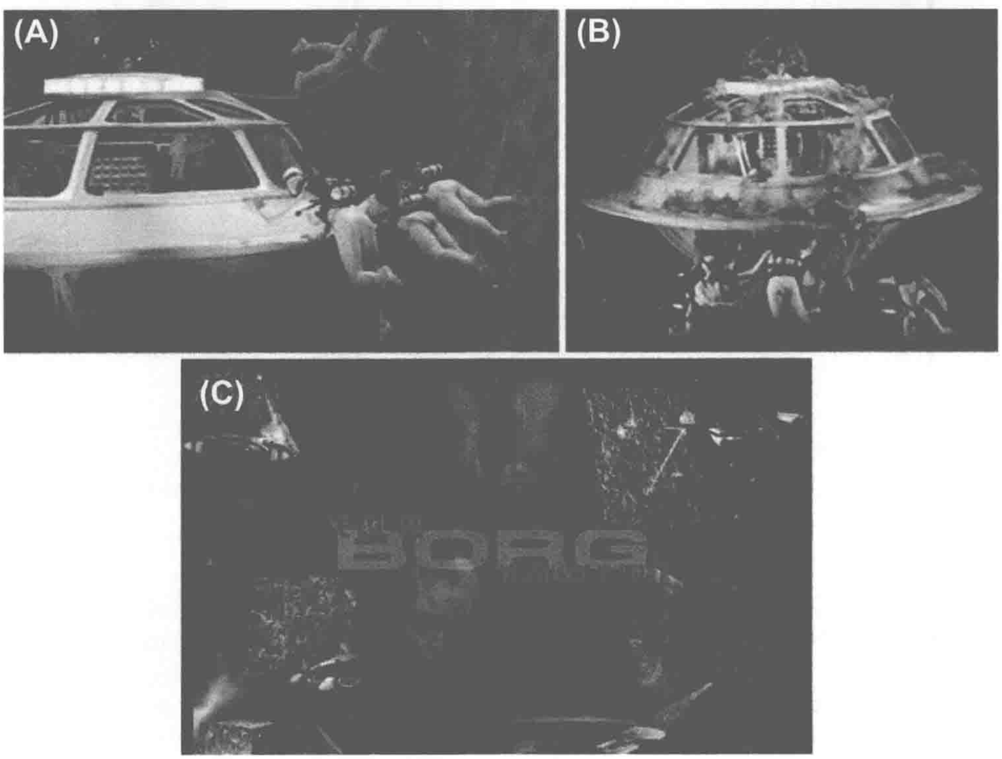


FIGURE 1 (A) In the movie *Fantastic Voyage*, the miniaturized submarine and its occupants are injected into the scientist's body. (B) The body's defense cells attach the submarine. (C) The "Borg" of *Star Trek*—a collection of species that turned into a cyberorganism functioning collectively.

handful of scientists to stop the cloud as time is running out for the entire humanity. Although *Prey* is fiction, it brings up many of the issues relevant to this topic, especially the conflict between commerce and public safety.

How much risk can we, as humans, take to make our life better? Many earlier technologies, such as use of fossil fuel for energy (the first industrial revolution), the development of pharmaceutical drugs and insect eradicators (the chemical revolution), and/or the construction of nuclear power plants (the nuclear revolution), were incorporated in household and commercial products because of the perception that these technologies were safe to society and the environment without addressing safety concerns or developing regulations. We all are aware of the extensive pollution and ensuing health and environmental consequences that these "revolutions" created—and we are still dealing with their effects. Is nanotechnology heading in the same direction? The technology has been extensively integrated in our daily lives (food, cosmetics, medicine, electronics, and energy) despite the lack of adequate safety information and regulations. Therefore, the overall aim of this book is to present basic information regarding the structure, beneficial effects, and toxicity of nanoparticles, which can be used to make regulatory decisions.

1.1 Historical Aspects

Nanotechnology, although considered to be a recent phenomenon, is also evident in ancient civilizations. The Celtic-red enamels dating from 400 to 100 BC contain copper and cuprous oxide (cuprite Cu_2O) nanoparticles (Brun et al., 1991), while most of the red-tesserae used in Roman mosaics were made of glass containing copper nanocrystals (Brun et al., 1991; Colomban et al., 2003; Ricciardi et al., 2009). The Roman artisans achieved unusual color changes by adding noble metal-bearing material to glass prior to being molten. The middle age (1066–1485 AD) saw an emergence of glazed ceramics with striking optical effects obtained from metallic nanoparticles (Caiger-Smith, 1991). Ancient Indian (Ayurveda) and Chinese medicines used gold bhasma (Yadav et al., 2012) and soluble gold (http://www.zhengjian.org/sci/sci/home/newscontent.asp?ID=11330), respectively, for therapeutic purposes; these substances have been shown to contain gold nanoparticles mixed with larger particles. Ancient civilizations, however, did not understand the unique properties and potential of their preparations as we understand them now. Recent technological advancements have revolutionized the synthesis, characterization, and applications of nanoparticles, which are gradually becoming an integral part of society.

In 1959, Richard Feynman (http://metamodern.com/2009/12/29/theres-plenty-of-room-at-the-bottom%E2%80%9D-feynman-1959/) suggested the possibility of building machines small enough to manufacture objects with atomic precision. He also predicted that information could be stored with amazing density. The term *nanotechnology* was coined by Norio Taniguchi (1974), but it was used unknowingly by Eric Drexler in his 1986 book *Engines of Creation: The Coming Era of Nanotechnology*. The technology is growing and diversifying rapidly, as shown in Table 1.

1.2 Nanotechnology

In general, nanotechnology deals with the fabrication and control of nanoparticles less than 100 nm in at least one dimension. Nanoparticles exhibit unique physicochemical properties that are absent in their bulk (>500 nm) counterparts. An exception to the 100-nm rule is solid-lipid nanoparticles that exhibit the unique nanoparticle-related properties at diameters greater than 100 nm (Carla et al., 2011). Because of their unique properties, nanoparticles are being used in diverse applications such as the following.

TABLE 1 History of Nanotechnology

Year	Items
1981	Scanning tunneling electron microscope that could process single atoms.
1985	Discovery of fullerene, 60 carbon atoms in a circle (C60).
1992	Discovery of carbon nanotubes that are stronger than steel; can be used in drug delivery, energy storage, and power transmission.
1993	Discovery of quantum dots.
2000	Construction of passive nanoparticles for applications as nano fuel cells and in products of daily use, including cosmetics.
2005	Construction of active nanoparticles for target-directed drugs and other adaptive structures.
Future	Nanosystems, hierarchical nanoarchitectures, atomic devices, nano DNA-based computers, diagnostic robots, etc.

- Medical (targeted drug delivery, imaging, and personalized medicine) and cosmetic (makeup and sunscreens) applications (Patel et al., 2011; Pathak and Thassu, 2011; Raj et al., 2012; Smijs and Pavel, 2011; Wen-Tso, 2006; West and Halas, 2000)
- Efficient energy-storage devices using hybrids of carbon nanotubes and oxide nanoparticles (Gruner et al., 2006), as the development of high-temperature, heat-transfer nanofluids may allow storage of thermal energy (Wong and DeLeon, 2010)
- Efficient removal of pollutants such as metals (cadmium, copper, lead, mercury, nickel, zinc), nutrients (phosphate, ammonia, nitrate, and nitrite), cyanide, organics, algae (cyanobacterial toxins), viruses, bacteria, parasites, and antibiotics from water in waste treatment plants (Tiwari et al., 2008)
- Construction of implantable devices to treat neural disorders using carbon-nanotube-protein hybrids (Andersen et al., 2004; Green and Hersam, 2011)
- Clothing, sporting equipment, food packaging, dietary supplements, etc.

These developments may represent the next revolution—the nano-industrial revolution—which will significantly alter society. However, the pace of nanotechnology commercialization is much faster than the assessment of their safety, thus posing a significant health risk to the general population. A key hurdle in determining the health risk of nanoparticles is their structural heterogeneity.

1.3 Atoms, Nanoparticles, and Bulk Materials

Atoms (less than 0.1 nm) are the smallest unit taking part in chemical reactions. They are transformed into bulk materials (greater than 500 nm) through formation of clusters (approximately 1 nm) followed by small nanoparticles (1−100 nm) and large nanoparticles (greater than 100 nm), as shown below:

Atoms ⟶ Clusters ⟶ Nanoparticles* ⟶ Large Nanoparticles ⟶ Bulk particles
<0.1 nm 0.1 – 1 nm >1 – 100 nm >100 – 500 nm >500 nm

Elemental properties ***Distinct properties*** ***Elemental/Chemical properties***

Clusters ranging from 0.1 to 1.0 nm in diameter possess elemental characteristics. As the clusters grow from 1 to 100 nm, they get transformed into nanoparticles possessing distinct physicochemical properties (described earlier) that are absent in their bulk counterparts. The relationship between the number of atoms in a nanoparticle and the percentage of atoms at the

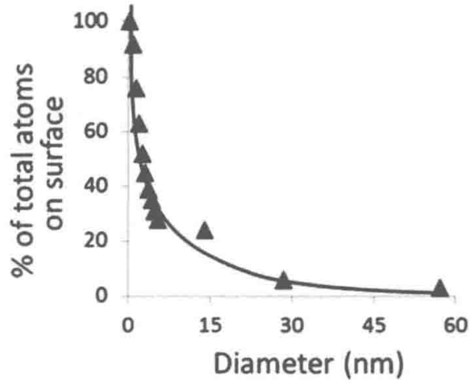


FIGURE 2 Relationship between diameter and percentage of atoms present at the surface. There is an inverse relationship between the two indices. An increase in nanoparticle size is associated with a decrease in the percentage of total atoms at the surface. All of the atoms were surface atoms in nanoparticles having 1 nm (12–25 atoms) diameter, while only 5% of atoms were surface atoms in nanoparticles having 5 nm (about 2000 atoms) diameter. In bulk particles, the share of the surface atom is <0.1%.

surface is shown in Figure 2 and Table 2. There is a direct relationship between the total number of atoms in a nanoparticle and the number of surface atoms or the particles' diameter (Table 2). There is an inverse relationship between the diameter (nm) and the percentage of atoms at the surface (Figure 2).

As nanoparticles become smaller, the proportion of atoms on the surface increases. In the nanometer range, a size reduction results in a drop in melting temperature and an increase in reactivity, as well as the dominance of surface atoms over the core atoms (Gupta et al., 2014; Lia et al., 2013). A transition from classical mechanics to quantum mechanics occurs when free electrons in nanoparticles start to behave like a wave (described in Chapter 3).

1.4 Classification of Nanoparticles

As shown in Figure 3, nanoparticles can be classified according to their dimensions, origin, application, chemistry, and counterpart types and applications.

TABLE 2 Mathematical Relationship between Total Atoms, Diameter, Surface Atoms, and Percentage of Surface Atoms in Gold Nanoparticles

Shell	Diameter (nm)	Total Atoms	Surface Atoms	Surface Atoms (%)
1	0.288	1	1	100
2	0.864	13	12	92
3	1.44	55	42	76
4	2.01	147	92	63
5	2.59	309	162	52
6	3.16	561	252	45
7	3.74	923	362	39
8	4.32	1415	492	35
9	4.89	2057	642	31
10	5.47	2869	812	28
25	14.1	4.9×10^4	5083	24
50	28.5	4.04×10^5	2.40×10^4	6
100	57.3	3.28×10^6	8.80×10^4	3

1.4.1 *Dimension-Based Classification*

Nanoparticles exist as zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) particles. The 0D nanoparticles, such as nanospheres and nanoclusters, are less than 100 nm in all dimensions (Figure 4). The 1D nanomaterials, such as nanotubes, nanorods, and nanofibers, are less than 100 nm in at least one dimension. The 2D nanomaterials are films (graphene, molybdenum disulfide, and germanane (a single-layer crystal composed of germanium)) with less than 100 nm thickness. The 3D nanomaterials are more than 100 nm in all dimensions (Figure 4).

1.4.2 *Natural or Anthropogenic Nanoparticles*

Natural nanoparticles originate from forest fires, volcanic eruptions, lightning, etc. (Angelucci

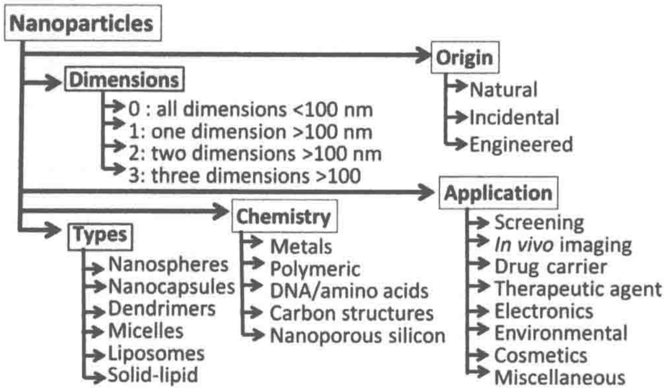


FIGURE 3 Nanoparticle classification.

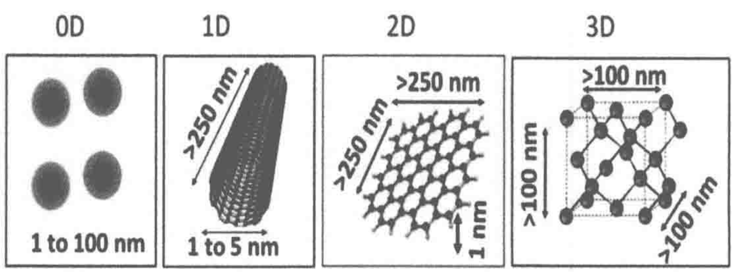
et al., 2010; Buzea et al., 2007). They have been an integral part of the environment since the origin of the planet (http://sustainablenano.com/2013/03/25/nanoparticles-are-all-around-us/). Anthropogenic nanoparticles fall into two general categories: incidental and engineered nanoparticles. Incidental nanoparticles are heterogeneous in size and shape; they are generated by burning fossil fuel (gasoline, diesel, coal, and propane), large-scale mining, incinerating forests for agriculture, etc. (Buzea et al., 2007; Kittelson, 1998). Engineered nanoparticles are specifically designed particles having precisely controlled sizes, shapes, and compositions. They may even contain multiple layers (e.g., a gold nanoparticle covered in drug-loaded porous silica nanoparticles coated with specifically chosen antibodies). Engineered nanoparticles are becoming more complex with each passing year.

1.4.3 Classification of Nanoparticles According to Their Chemistry

Chemically, nanoparticles consist of metals/metal oxides, DNA and other biological materials, carbon, polymers, and clays. In addition to the common size-related properties, nanoparticles retain their chemical characteristics, which may be helpful in the selection of appropriate nanoparticles for a particular use. Some important groups of nanoparticles include the following:

- *Metal nanoparticles* (gold, copper, silicon, iron, etc.) are widely used in catalysis, electronics, sensors, photonics, environmental remedies, and medicine. Because of surface plasmon resonance and paramagnetic properties, metal nanoparticles find unique applications in medical and electronic technology

FIGURE 4 Types of nanoparticles determined by the size of their structural elements. 0D, zero-dimensional; 1D, one-dimensional; 2D, two-dimensional; 3D, three-dimensional.



(http://www.mpikg.mpg.de/886767/MetalNanoparticles.pdf). Porous silicon nanoparticles contain microscopic reservoirs that can hold and protect sensitive drugs in a pH-sensitive manner. Acidic pH disrupts the drug-nanoparticle binding, thus releasing the drug load. Functionalizing the surface with target molecules provides target-selective delivery of the nanoparticles.

- *Polymeric nanoparticles* are prepared from either synthetic polymers such as poly(2-hydroxy ethyl methacrylate), poly(*N*-vinyl pyrrolidone), poly(methyl methacrylate), poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, or natural polymers such as gums (e.g., acacia, guar, etc.), chitosan, gelatin, and sodium alginate. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices.
- *Biochemical nanoparticles* such as DNA, proteins, and poly-amino acids such as poly-L-lysine and poly-L-serine are synthetized from biological precursors. DNA nanoparticles are three strands of DNA with a lipid and functional molecule attached to its ends. In water solutions, the combination of hydrophilic DNA and lipophilic lipids causes the units to self-assemble into hollow spheres consisting of multiple layers of DNA, lipids, and cargo.
- *Carbon nanotubes* (*CNTs*) are formed from rolled-up graphite sheets. Depending on the direction of hexagons, carbon nanotubes can exhibit metallic or semiconductor properties. CNTs are twice as strong as steel but weigh many times less. In 1996, a new form of carbon—the Buckminster fullerene—was discovered; it looks like a nanometer-sized soccer ball made from 60 carbon atoms (Thess et al., 1996).
- *Nanoclays* are layers of mineral silicate nanoparticles. Organically modified or hybrid organic-inorganic nanomaterials have potential uses in polymer nanocomposites and as rheological modifiers, gas absorbents, and drug delivery carriers.

1.4.4 Isotropic and Anisotropic Nanoparticles

Isotropic nanoparticles include nanocapsules (Figure 5(1)), nanospheres (Figure 5(2)), dendrimers (Figure 5(3)), liposomes (Figure 5(4)), spheres (solid), capsules, and liposomes, whose physical and chemical properties are not dimensional. Nanospheres (solid) and nanocapsules (hollow) are polymeric nanoparticles consisting of a shell and a space, in which desired substances may be loaded and protected from the environment. Dendrimers are artificially manufactured branched nanoparticles comprised of many smaller ones linked together, built up from branched units called monomers. Liposomes consist of an outer single or multilamellar membrane and an inner liquid core. Liposomes consisting of natural or synthetic phospholipids are similar to those in cellular plasma membranes. Because of this similarity, liposomes are utilized by the cells. Micelles are similar to liposomes but they do not have an inner liquid

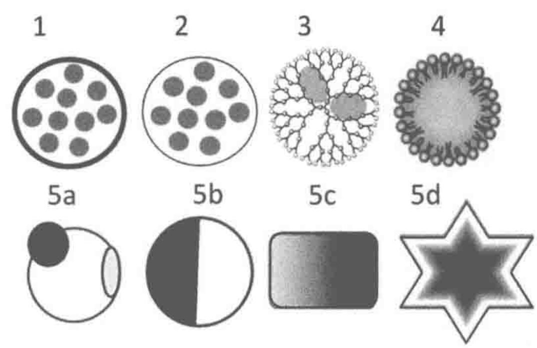


FIGURE 5 Examples of different forms of nanoparticles. (1) capsules, (2) sphere, (3) dendrimers, (4) liposomes, and (5) noble-metal anisotropic nanoparticles. (5a) Patchy particles that have one or more patches and exhibit strong surface anisotropy. (5b) A Janus particle defined as a particle with two faces or a particle with one patch covering half of the particle surface (Wurm and Kilbinger, 2009). (5c) Nanorods Janus particle. (5d) Nanoclusters as an example of patch particles.

compartment (Yang et al., 2004). A solid-lipid nanoparticle is typically spherical with an average diameter of 50–1000 nm. Solid-lipid nanoparticles possess a solid lipid core matrix.

Anisotropic nanomaterials, shown in Figure 5(5a–5d), were first described by Banholzer (2011) and Casagrande and Veyssie (1988). They exhibited direction- and dimension-dependent physicochemical properties (dendrimers can be constructed to be anisotropic). Multifunctional anisotropic nanoparticles have attracted increasing attention because of their promising properties for applications in biotechnology, nanotechnology, electronics, and clean/reusable energy (Grosse and Delgado, 2010; Perro et al., 2005; Rhodes et al., 2009; Walther and Muller, 2008; Wood et al., 2010).

1.4.5 Nanoparticle Classification Based on Application

Nanoparticles are currently being applied in medicine, environmental remediation, cosmetics, electronics, and energy-storage industries. Medicinal uses include screening, in vivo imaging, drug carriers, and treatment (Dykman and Khlebtsov, 2011; Salata, 2004). Nanoparticle applications in environmental remediation (Henn and Waddill, 2006; Masciangioli and Zhang, 2003; Wang and Zhang, 1997) include the clean up of oil spills (photocatalytic copper tungsten oxide nanoparticles), the destruction of volatile organic pollutants in air (gold nanoparticles embedded in a porous manganese oxide), and the removal of metals from water samples. Iron nanoparticles remove carbon tetrachloride from ground water. Iron oxide nanoparticles are used to clean up arsenic from water wells (Zhang, 2003). Nanoparticle applications in energy and electronics include low-cost electrodes for fuel cells, energy storage (http://www.understandingnano.com/nanoparticles.html, Lianga and Zhi, 2009), and catalysts such as a platinum-cobalt hybrid for fuel cells that produce 12 times more catalytic activity than pure platinum. Construction of a memory field-effect transistor (combining gold nanoparticles with organic molecules) can function in a way similar to synapses in the nervous system. Silicon nanoparticle-coated anodes of lithium-ion batteries can increase battery power and reduce recharge time. Nanoparticles are used in cosmetic products (Bertrand et al., 2013; Patel et al., 2011; Raj et al., 2012) including deodorant, soap, toothpaste, shampoo, hair conditioner, antiwrinkle cream, moisturizer, foundation, face powder, lipstick, blush, eye shadow, nail polish, perfume, and after-shave lotion.

2. INTRODUCTION TO NANOTOXICOLOGY

Toxicology is study of the nature, effects, and detection of toxins and the treatment of toxicosis. Toxins are natural or synthetic chemicals capable of causing harm or disease when introduced into the body. In general, there are three basic laws of toxicology:

- *The dose makes the poison* (Paracelsus theory). In general, dose is defined as the mass of a chemical per unit of body weight, such as g/kg body weight. From Paracelsus's time to the present, the mass-based dose has been used to determine a chemical's beneficial effects and toxicity. However, as we will see later, the mass-based definition of dose may not be entirely applicable to nanoparticles. This is because, in addition to the mass, the size, shape, and surface functionality may also play a significant role in determining a nanoparticle's beneficial effects and toxicity. Therefore, the concept of a dose based on size, surface area, or surface reactivity will be introduced later.
- *The biological actions of chemicals are specific to each chemical.* In the sixteenth century, Ambriose Paré recognized that the toxic effects of a chemical are specific to the chemical's structure. He postulated that each