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Introduction

Nanotechnology can be conceived as the customized synthesis, design, and application of materials whose morphology has been tailored at the nanoscale. It exploits the remarkable physicochemical, optoelectrical, and thermomechanical properties that emerge when matter is intelligently assembled at the nanoscale. Figure 1.1 illustrates the relative dimensions of few commonly observed items one is familiar with in our day-to-day life.

“Nanoscience is the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale.” This constitutes the consensual definition of nanoscience adopted in the July 2004 Royal Society of London report *Nanoscience, and Nanotechnology: Opportunities and Uncertainties* (Royal Society, 2004).

However, this definition is too vague and ambiguous that adds to the confusion pertaining to the term “nano.” “Nanoscience should be reserved solely for the study of a single atom or a single molecule, that is, of one entity at a time, and not for groups of such entities where statistics or interactions between them come into play” as per Joachim (2005).

Nanoparticles are characterized by their low dimensionality, high surface energy, spatial confinement, and reduced imperfections. Due to their size, nanoparticles exhibit unusual properties quite different from the bulk material. Physical properties like melting point, mechanical strength, optical and magnetic properties, and electrical conductivity can be very different for nanoparticles compared with their bulk material. The following are some examples that show the properties of nanoparticles. The melting point of a metal or semiconductor reduces with decrease in particle size below 100 nm. This can be seen for the case of gold nanoparticles shown in Figure 1.2. The melting point decreases rapidly for particles below 5 nm (Buffat and Borel, 1976). Similar observations have been made in the case of lead (Peters, Cohen, and Chung, 1998) and other metals. The lowering of melting point is because of the profound influence of surface atoms as the ratio of surface to bulk atoms increases. The electronic structure of a material is also modified with the size of the particle. When the size of the particle is smaller than a critical value, the electron’s de Broglie wavelength, “quantum size effect” becomes important. This effect leads to the spatial confinement of electrons and holes, formation of electric dipoles, and formation of discrete energy

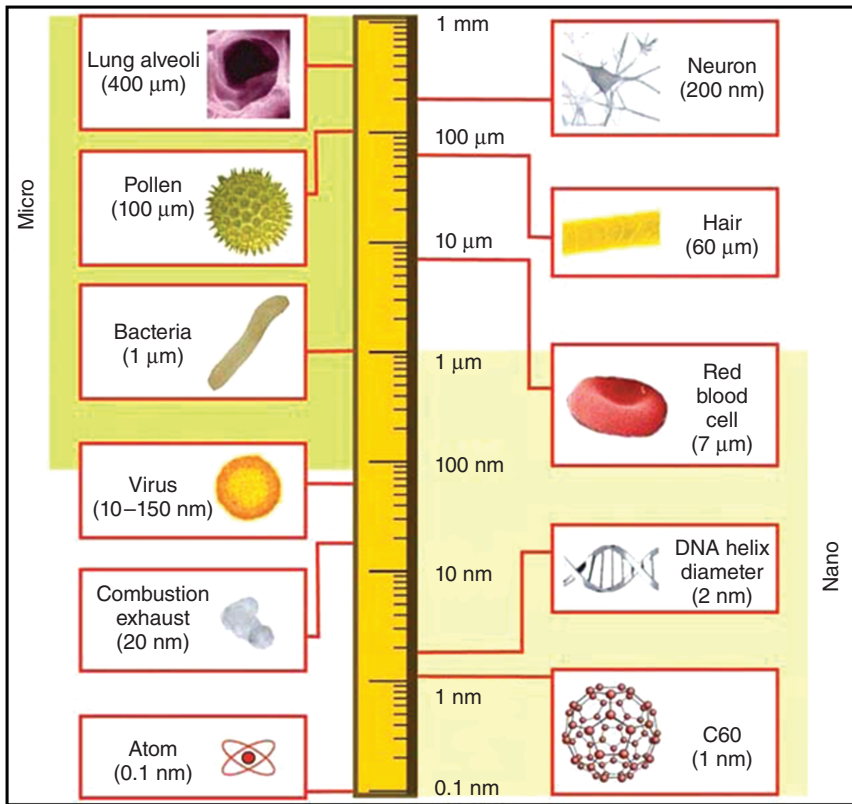


Figure 1.1 Representative picture showing the size of nanostructures compared with biological objects. (Buzea *et al.*, 2007. Reproduced with permission of American institute of Physics.)

levels in the material. Consequently, electric properties of nanosize objects can be very different from their bulk counterpart. As an interesting example, it was shown that bismuth nanowires of 50 nm width have semiconductor properties rather than being metallic (Choi *et al.*, 2000). Quantum size effect influences both electric and optical properties (Rossetti, Nakahara, and Brus, 1983).

Joachim, Gimzewski, and Aviram (2000) argued that it is more appropriate to use the term “nano” for objects of a few nanometers and the term “nanno” for the intermediate scale. This allows the definition to be size independent, allowing the distinction between the *statistical* and the *individual* approach to the system to be more relevant. For instance, the optoelectronic and spintronic devices reveal quantum phenomena but are analyzed and discussed statistically to constitute mesoscopic physics. Similarly machines in molecular biology like myosin, kinesin, ATP synthase, and so on are typically understood under appropriate stochastic signal-to-noise conditions. Joachim’s definition of nanotechnology excludes the following: nanoscale microelectronic devices whose individual components are refined to the precision of a few nanometers, nanomaterials whose properties are regulated at the nanoscale, and nanoparticles. In biological

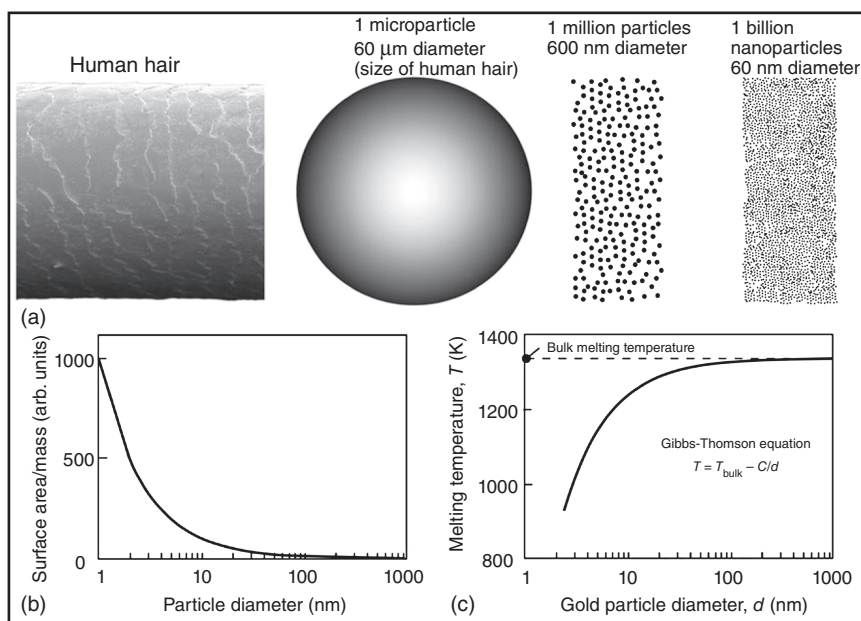


Figure 1.2 Visualization of nano versus microscopic objects. Effect of size on surface area and melting is shown. (Buzea *et al.*, 2007. Reproduced with permission of American institute of Physics.)

applications, nanoparticles normally constitute the core of the nanobiomaterial. This can be used as a suitable surface for the design of molecular assembly comprising inorganic or polymer materials. It may be in the form of a nanosize vesicle enveloped by a membrane layer. The mean size and its distribution are important in many cases, for example, if transportation through porous cellular membrane is required. In semiconductor nanoparticles, again the size and its distribution are very relevant when quantum size effects are applied to tune the material properties. A fine control of the mean particle size and a narrow size distribution allow for the creation of efficient fluorescent probes that may emit narrow linewidth radiation over a wide range of wavelengths. For instance, by combining the magnetic and the luminescent layers, it is possible to detect and structurally manipulate the nano-object simultaneously.

A pertinent question arises here. What is the main difference between nanomaterials and bulk materials? Two primary factors differentiate the nanomaterials from the bulk: (i) surface effects, which cause the smooth properties to scale due to the large fraction of atoms located at the surface, and (ii) quantum effects, which show discontinuous behavior due to the effects of quantum confinement in materials with delocalized electrons. These factors influence their chemical reactivity and their thermomechanical, optoelectronic, and magnetic properties. The fraction of the atoms located at the surface of nanoparticles is much higher compared with bulk particles. Thus, compared with microparticles, nanoparticles have a much larger surface area and high particle density. For example, one carbon microparticle with a diameter of 60 μm possesses a mass of 0.3 μg and a

surface area of 0.01 mm^2 . The same mass of carbon in nanoparticle form (with diameter of 60 nm) will consist of 1 billion nanoparticles and will have a surface area of 11.3 mm^2 (gain by a factor of ≈ 1000 ; see Figure 1.2). Because the material in nano form possesses a larger surface area for reactions, chemical reactivity is enhanced typically 1000-fold. Though chemical reactivity normally increases with the decrease in particle size, surface functionalization and capping can have complex effects; even reduction in reactivity with decreasing particle size has been observed in few cases.

With decreasing particle size, the atoms located at the surface have fewer neighbors compared with bulk atoms, resulting in smaller binding energy per atom. This reduced binding energy per atom is manifested in lowering the melting point with particle size, which is described by the Gibbs–Thomson equation. For instance, the melting point of 3 nm gold nanoparticles is at least 300 K less than the melting temperature of the bulk material, which is depicted in Figure 1.2 (Roduner, 2006). Quantum concepts are best captured by the quantum dots, which are nanocrystalline structures with a size of a few nanometers (Figure 1.3). Their electronic structure is very close to that of individual atoms, and hence, these quantum dots are conceived as artificial atoms. The consequence of quantum confinement is the existence of magnetic moments in nanoparticles of materials that show nonmagnetic property in their bulk phase, like in gold, palladium, and platinum. Magnetic moments normally result from the presence of unpaired electron spins in nanoparticles. Quantum confinement does give rise to quantified changes in the ability to exchange electrical charge, called the electron affinity. This is manifested as the catalytic ability of the nanomaterial concerned. An interesting example is the chemical reactivity of cationic platinum clusters in the catalytic decomposition of N_2O , which is governed by the number of atoms present in a given cluster. Atomic clusters containing 6–9, 11, 12, 15, and 20 atoms are known to be highly reactive, while those the same with 10, 13, 14, and 19 atoms show lower reactivity (Roduner, 2006).

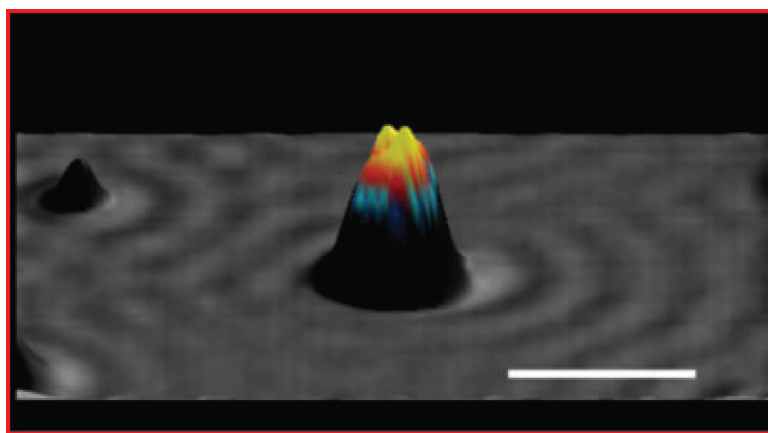


Figure 1.3 STM image of a single Lander molecule, which is seen to create a circular electronic wave modulation, 0.008 nm in amplitude, on the Cu (111) surface (scale bar: 3 nm). (Moresco *et al.*, 2003. Reproduced with permission of American Chemical Society.)

Another property that is modified quite dramatically with decrease in particle size is the catalytic property of several metals. For instance, in bulk form, gold is known to be chemically inert to chemisorption and consequently a weak catalyst, but gold nanoparticles exhibit surprisingly high catalytic activity for a large range of chemical reactions (Bond, 2001; Grisel *et al.*, 2002). Similar to gold, Pt nanoparticles also show extraordinary catalytic properties. Pt nanoparticles have, for instance, been used in the catalysis of oxygen electroreduction (Takasu *et al.*, 1996; Savadogo and Essalik, 1996) or in the oxidative dehydrogenation of ethanol (van den Tillaart *et al.*, 1996). In several cases a correlation between catalytic activity and particle size has been established; for example, in the case of electrooxidation of methanol, the specific activity of particles was found to decrease with decreasing particle size in the range from 4.5 to 1.2 nm (Frelink, Visscher, and van Veen, 1995). In the area of catalysis, nowadays, nanoscience has become quite important. In addition to the properties discussed earlier, other properties such as ferromagnetism and mechanical properties will also be affected. Recent years have seen enormous interests in the study of nanoparticles, both fundamental and applied. For more details the reader may consult reviews or books (Cao, 2004; Meiwes-Broer, 2000).

The primary reasons why nanostructured materials exhibit properties distinctively different from their bulk are because of their surface effects. Roduner (2006) has defined it as follows:

“Atoms at surfaces have fewer neighbours than atoms in the bulk. Because of this lower coordination and unsatisfied bonds, surface atoms are less stabilized than bulk atoms. The smaller a particle is, 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. Among them are the melting, and other phase transition temperatures. Edge and corner atoms have an even lower coordination, and bind foreign atoms and molecules more tightly.”

Equilibrium thermodynamics is based on state variables (temperature, pressure, volume, etc.) and potentials (like Gibbs, Helmholtz free energy, etc.). For nanosystems, these are not adequately defined. There are many other concepts of equilibrium thermodynamics that may break down, particularly when the system of interest is a single isolated cluster with a few atoms. Phase transitions in statistical thermodynamics are cooperative phenomena. For nanostructures (comprising few atoms), phase transition is not well defined. For example, Gibbs' phase rule loses its meaning because components and phases are difficult to distinguish. Small clusters act more like molecules than as bulk matter. Hence, these systems must be treated as isolated objects. Several other consequences pertaining to nanostructures are discussed in the following.

Atoms are associated with well-defined atomic orbitals. But, depending on the degree of overlap, they do combine to form extended energy bands in metals or semiconductors. The core orbitals are mostly localized to a relatively smaller volume and remain confined. Typically, each of the N atoms contributes its

individual atomic states to a band in such a way that the width of a given band increases with the addition of more atoms. The density of states (DOS) within a band can be assumed to be proportional to the number of atoms present in an ensemble having a band-like state. Since the bandwidth approximately amounts to a few electronvolts, the DOS is on the order of N (per eV), which is significantly large for a bulk matter (N is Avogadro's number, N_A), but is very low for small nanoparticles. Thus, the DOS scales with the size, but with a scaling behavior that is different from that observed from the surface effects. In a highly symmetric system, there are many degenerate states, and when one of these is occupied, the next electron must occupy the next higher energy state. Such discontinuities get blurred because the symmetry is mostly reduced when additional atoms are added to a well-defined symmetric system. An important balance may be reached when the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) state (called the *Kubo gap*) equals the thermal energy. Thus, when the thermally excited electrons jump the Kubo gap, a low-temperature insulator may turn into a semiconductor and at higher temperatures into a metal. The dependence of DOS with particle (cluster) size is depicted in Figure 1.4.

Recently, nanomaterials have found applications in a wide variety of pharmaceutical products. Since the applications targeted are biological, several preconditions must be met at the synthesis level. When the nanoparticles

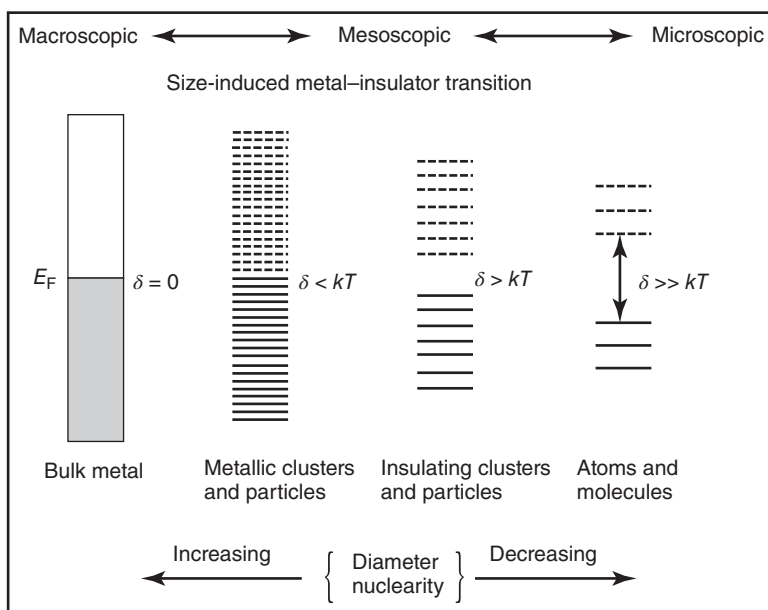


Figure 1.4 Dependence of band gap and the DOS on the number of atoms present in a cluster (nanoparticles). It increases from right to left for metal clusters and bulk metals and decreases from left to right for insulating clusters and individual atoms/molecules. The parameter d is called the Kubo gap. (Roduner, 2006. Reproduced with permission of Royal Society of Chemistry.)

are synthesized for use as drug delivery systems, they need to comply with several essential requirements like biocompatibility and temporal stability. Depending on the synthesis route, various impurities may enter into the structure of the nanoparticles (monomers, solvent, surfactants, electrolytes, etc.). The elimination of the small molecules can be very difficult in many cases. The most commonly used methods of purification are the gel filtration, lyophilization, and ultracentrifugation techniques. These methods do have drawbacks, for example, dialysis eliminates only the small molecules, and it is a very slow process. The sample ultracentrifugation often leads to particle aggregation. The cross-flow filtration technique is a well-known industrial method to purify nanoparticles (Allemann and Doelker, 1993). In this method, the nanoparticles are channelized and filtered through a membrane into a cross flow oriented parallel to the membrane surface. In this way the clogging of the filter is avoided. This technique is relatively simple, avoids clogging of the filter, and can be used on an industrial scale.

An appropriate blending of a polymer matrix with a nanomaterial in the presence of an exfoliating agent yields a nanocomposite. Such materials are abundant in nature. For example, a natural bone is a bionanocomposite, consisting of hydroxyapatite crystallites dispersed in an organic matrix, mostly collagen. This makes the bone mechanically strong and, at the same time, elastomeric, which allows it to recover from mechanical deformation. The actual mechanism at the nanoscale leading to this remarkable manifestation of properties arises from the excellent interfacial enhancement. A hybrid nanocomposite material was produced using 15–18 nm ceramic nanoparticles by homogeneously dispersing it in poly(methyl methacrylate) matrix. This material has shown viscoelastic behavior (healing) mimicking the human teeth (de la Isla *et al.*, 2003) in tribology experiments.

It is a known fact that between the circulatory (blood streamline) and the central nervous system, there is the blood–brain barrier (BBB). BBB selectively allows only the exchange of ions to maintain a constant osmotic pressure and the passage of nutrients to keep the cells healthy. Thus, the brain and the spinal axis are protected from any possible chemical or bacteriological exposure. This protection comes at a certain price. It is nearly impossible to get drugs cross the barrier, making the therapy for the central nervous system extremely difficult. The BBB identifies the therapeutic agents as foreign chemicals and inhibits their passage. Because of this, finding a suitable pathway to deliver bioactive substances to the brain poses a real challenge. One of the ways to bypass the BBB and to transport the drug to the central nervous system is to send the drugs to their target using stealth nanoparticles. Due to their small size, these nanoparticles can successfully pass through the vascular endothelium of the BBB. Several studies have shown promising results in the treatment of brain tumors by using drug-loaded stealth nanoparticles (Schroeder *et al.*, 1998; Rousseau, Denizot, and Poulighen, 1997; Kharkevich, Alyautdin, and Petrov, 1998; Kreuter *et al.*, 1995). Regardless, the concern about the toxicity of certain nanoparticle platforms remains valid. Therefore, design and synthesis of biocompatible and environment-friendly nanomaterials is the need of the hour.

DNA is a molecule containing the genetic information, and the proteins and amino acids serve as the enzymatic and structural molecules. On the other hand, RNA is a very complex molecule that exhibits multiple functions in nature. Some

of the roles played include informational transfer function (mRNA), recognition and adaptor function (tRNA), catalytic function (ribozymes and large rRNA), and guide functions (snRNA), and there are poorly understood noncoding RNAs. Thus, no other biomolecules in the living system exhibits the multiple functional attributes of RNA. This raises the question, "How does one class of biomolecule show so many different functional behaviors?" This question is addressed and discussed in a recent review on "the emerging field of RNA nanotechnology" by Guo (2010). The bioavailability and stability of RNA can be suitably tailored to the desired function unlike other nanoparticle platforms. It has been known that certain motifs in RNA do trigger type I interferon response inside the cells. The simple addition of 2'-OMe can sufficiently terminate the activation of this response (Robbins *et al.*, 2007; Judge *et al.*, 2006). The 2'-OMe is biologically tolerated and nontoxic, and it is a naturally occurring modification found in tRNA and rRNAs. Guo has presented a comprehensive overview of the various physicochemical features of RNA, which makes it a promising nanoparticle platform for use as a nanocarrier for therapeutic and diagnostic applications. As far as the synthesis of RNA nanoparticles is concerned, the chemistry is relatively straightforward, and RNA structures with 80 base pairs can be easily synthesized with high yield (Zhou *et al.*, 2009). Further, the commercial availability of modified building blocks of 2'-fluoro and 2'-OMe RNA phosphoramidites has made it possible to integrate these into an automated RNA synthesis protocol. Both of these modifications are considered necessary for the biological applications of RNA nanoparticles as these provide stability against RNases and prolong their half-life.

Application of nanoscience in biology necessitates the requirement to surface functionalize the nanoparticles with suitable protein, nucleic acid, or carbohydrate molecules. Thus, the biological functions one targets to meet may span over a wide range of specific interests. An illustrative list is provided in Table 1.1.

The desire to develop green chemistry methods for the synthesis of nontoxic nanoparticles is driven by the increasing awareness toward environmental concerns. The liberal use of toxic chemicals in the synthesis severely limits the application potential of nanoparticles in the pharmaceuticals. Unlike the physical and chemical methods, devastated crops can be used as agents for the biosynthesis of nanoparticles in an approach that is both cost effective, and eco-friendly. The rich diversity of plant extracts, and their innate potential to act as bio-reducing agents, has allowed for the synthesis of a variety of metal and metal oxide nanoparticles following the green chemistry route. More involved research on the agricultural waste-based synthesis of nanoparticles will help in preparing stable nanoparticles of uniform shape, size, and morphology. Thus, the development of biocompatible and eco-friendly methods for the synthesis of nanostructures deserves merit.

The biosynthesis of customized nanoparticles has emerged as an alternative method where the fields of nano- and biotechnology intersect. Several synthesis protocols have been adopted for the plant extract-based synthesis of metal nanoparticles from salt precursors of the concerned metals. The plant extracts do act as reducing and stabilizing agents in the synthesis protocol. Such synthesis has drawn attention because of its reduced environmental impact compared to the wet chemical methods. Further, these methods can be used to produce large quantity of nanomaterials that are free of chemical contamination. Madhumitha

Table 1.1 List of biopolymers used for surface functionalization of nanoparticles for specific *in vivo* targeting applications.

Serial no.	Biopolymer/type	Biological function	References
1	Albumin/protein	Major serum protein; can bind to many types of lipophilic and charged molecules including steroids	Baker (1998)
2	Ceruloplasmin/protein	An antioxidant for a wide variety of free radicals and principal carrier of copper in plasma, important for iron homeostasis	Lauffenburger (1993), Gupta and Curtis (2004)
3	Elastin/protein	Constitutes extracellular matrix and provides elasticity to tissues and blood vessels	Debelle and Tamburro (1999)
4	Folic acid/protein	Poorly immunogenic; facilitates internalization of target drugs and is useful in preferential cancer cell targeting	Zhang, Kohler, and Zhang (2002)
5	Insulin/protein	Regulates blood glucose levels	Gupta <i>et al.</i> (2003)
6	Lactoferrin/protein	Anti-infective agent, immunoregulator, and modulator of inflammatory response and iron absorption	Lauffenburger (1993), Gupta and Curtis (2004)
7	Nerve growth factor/protein	Promotes neurite growth and neural cell survival	Boyle <i>et al.</i> (1985)
8	Pullulan/polysaccharide	Nontoxic, plasma expander; nonimmunogenic, nonantigenic	Yuen (1974), Kameo <i>et al.</i> (2001)
9	RGD peptide	Increases cell spreading and differentiation and enhances DNA synthesis	Bhadriraju and Hansen (2000)
10	Tat peptide	Membrane-permeating molecule; enhances intracellular delivery	Lewin <i>et al.</i> (2000); Josephson <i>et al.</i> (1999)
11	Transforming growth factor- α /protein	Assists in the proliferation and differentiation of cells and in wound healing	Tanji, Aoki, and Yokoyama (2001)
12	Transferrin/protein	Targeting of anticancer agents like proteins and genes to proliferating cells through transferrin receptors	Berry <i>et al.</i> (2004); Moore <i>et al.</i> (2001); Qian <i>et al.</i> (2002)



Figure 1.5 Various plant resources used for the synthesis of nanoparticles: (a) olibanum, (b) Euphorbiaceae plant extract, (c) lemon, (d) neem kernel, (e) *Annona squamosa*/cannon, (f) *Crossandra infundibuliformis* leaf, (g) banana peel, (h) *Hibiscus rosa-sinensis*, and (i) rice hull. (Madhumitha and Roopan (2013). <https://www.hindawi.com/journals/jnm/2013/951858/>. Used under creative commons license: <https://creativecommons.org/licenses/by/3.0/>.)

and Roopan (2013) have written a fine review that provides a comprehensive discussion on the biosynthesis of metal nanoparticles (see Figure 1.5 and Table 1.2).

The principal reasons why nanomaterials exhibit properties remarkably different from those of the bulk are the following (Roduner, 2006):

(i) Surface effects: Atoms residing at the surface of nanoparticles have fewer neighbors compared with the atoms located in the bulk. Atoms located at the edges and corners have even lower coordination. Due to this lower coordination number, there are many unsatisfied bonds, which makes the surface atoms more reactive than bulk atoms. For nanoparticles, a large fraction of atoms resides at the surface. The aspect ratio (surface area/volume) scales with the inverse of particle size, and there are many properties that obey the same scaling behavior. For example, the melting and other phase transition temperatures exhibit similar scaling law.

(ii) Quantum size effects: Semiconductors and metals have wave functions of conduction electrons that are delocalized over the entire system. Therefore these electrons are described in the “particles in a box” concept, where the DOS and the energy of the particles exhibit dependence on the box size. When the system becomes bigger in size, the shells get filled up, and discontinuities do appear when new high energy shells start getting populated. These discontinuities, however, do not allow simple scaling. Further, the electron affinities and ionization potentials

Table 1.2 List of some representative biosynthetic methods for preparation of metal nanoparticles (NPs).

Serial no.	Plant source	Product/size (nm)	References
1	Olibanum gum	Ag NPs/7.5	Kora, Sashidhar, and Arunachalam (2012)
2	Euphorbiaceae	Ag NPs/62	Patil <i>et al.</i> (2012)
3	Lemon extract	Ag NPs/50	Prathna <i>et al.</i> (2011)
4	Neem kernel	Ag NPs/8.25	Shukla <i>et al.</i> (2012)
5	Cannon/ <i>Annona squamosa</i>	Ag NPs/60	Kumar <i>et al.</i> (2012)
6	Cannon/ <i>Annona squamosa</i>	Pd NPs/80	Roopan <i>et al.</i> (2012)
7	<i>Crossandra infundibuliformis</i>	Ag NPs/38	Kaviya, Santhanalakshmi, and Viswanathan (2012)
8	<i>Hibiscus rosa-sinensis</i>	Ag NPs/13 and Au NPs/14	Philip (2010)
9	Banana peel	Pd NPs/50	Bankar <i>et al.</i> (2010)
10	Rice husk	Silica NPs/51	Farook, Thiam-Seng, and Jeyashelly (2011)

Table 1.3 Some representative differential properties of bulk and nanoscale antimony oxide (AO) materials.

Serial no.	Property	Bulk AO	AO nanoparticles
1.	Absorbability	Weak	Strong
2.	Abrasive resistance	Low	High
3.	Colorant loading	High	Low
4.	Hydrophobicity	Low	High
5.	Impact strength	Low	High
6.	Particle size	More than 100 nm	Less than 100 nm
7.	Proton conductivity	$<2.89 \times 10^{-3}$ S/cm	$\approx 2.89 \times 10^{-3}$ S/cm
8.	Refractive index	<2	>2
9.	Tensile strength	<4.05 MPa	≈ 4.05 – 9.35 MPa
10.	UV-vis absorption	Low	High

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are tunable between their atomic values and the work function of their bulk state by change of the particle size. These properties are related to the availability of electrons for participating in redox reactions. Thus, the catalytic activity becomes dependent on the particle size.

The size-dependent physicochemical properties are discussed in excellent details by Roduner (2006) in a textbook. An illustrative example of the differential properties shown by bulk versus nanoscale antimony oxide materials is given in Table 1.3. It must be realized that antimony oxide exists in three different forms: trioxide (Sb_2O_3), tetroxide (Sb_2O_4), and pentoxide (Sb_2O_5). These three have

distinctive physicochemical properties (Chin, Cheong, and Razak, 2010). Recent advances in liquid phase synthesis of inorganic nanoparticles has been reviewed by Cushing *et al.* (2004).

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