# Chapter 2
# Basic Chemistry and Biomedical Significance of Nanomaterials

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## 2.1 Introduction

Nanotechnology that has emerged in the recent past has progressed dramatically during the last two decades and is expected to have an indelible impact on different agricultural and industrial products of the present-day world and has to play a special role in the fields of medicine and biology. With their unique chemical, physical, and mechanical properties, nanomaterials (NMs) have a wide range of their industrial and biologicalapplications. They work as highly organized, self-repairing, self-replicating, and information-rich molecular tools and can enable easy and efficient transfer of biochemical materials at the cellular and subcellular levels. Given this, NMs can be used for developing a better understanding about the molecular motors, enzyme activities, protein dynamics, DNA transcription, cell signaling, and molecular, genomic, proteomic, and metabolic reactions.

Nanomaterials are the entities of extremely small size, often measuring 1–100 nm, occasionally up to 1000 nm (Table 2.1). Research in this area is progressing leaps and bounds; development of quantum-confined nanocrystalline and doped nanocrystalline materials and evolution of smart drug delivery system through nanostructures are the major cynosures of experts today (Albrecht et al. 2006; Bennet and Kim 2014; Rajput 2015).

Nanostructures have unique physicochemical properties and an array of potential applications due to their minute size and large surface area (Fig. 2.1). Based on the

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**Table 2.1** The nanostructures and their sizes

| Type of nanostructure | Size (diameter) | Materials |
|---|---|---|
| Nanocrystals and clusters | 1–10 nm | Metals, semiconductors, magnetic materials |
| Other nanoparticles | 1–100 nm | Ceramic oxides |
| Nanowires | 1–100 nm | Metals, semiconductors, oxides, sulfides, nitrides |
| Nanotubes | 1–100 nm | Carbon, layered metal chalcogenides |
| Nanoporous solids | 0.5–10 nm | Zeolites, phosphates, etc. |
| 2-D arrays (of nanoparticles) | Several $nm^2$–$\mu m^2$ | Metals, semiconductors, magnetic materials |
| Surfaces and thin films | 1–1000 nm | A variety of materials |
| 3-D structures (superlattices) | Several nm in 3-D | Metals, semiconductors, magnetic materials |

specific nanomaterial characteristics, improved efficiencies or new functionalities can be achieved for a wide range of nanoproducts (Husen and Siddiqi 2014; Siddiqi and Husen 2016a, b, 2017a, b; Siddiqi et al. 2016, 2018a, b, c; Husen 2017). However, these efforts can cause increased loads and the consequent harms to the environment and living beings (humans in particular) when nanomaterials are released from the NM-based products and applications.

In fact, nanosized materials are common natural constituents of proteins, enzymes, nucleic acids, viruses, magnetite, ferritin, atmospheric tiny particles and fires, and volcanic eruptions. The nanoparticle properties are distinct from those of the analogous bulk materials mainly in their chemical reactivity, molecular and electronic structure, and mechanical behavior (Ehrman et al. 1999; Fendler 2001). The nanosized structures, typically those less than 10 nm in size, are markedly different from the bulk materials, depending on their surface area, bond, shape, and energy in nanometer dimensions, which cause a profound effect on the structure, phase transformations, strain, and reactivity of materials. Certain phases may exist

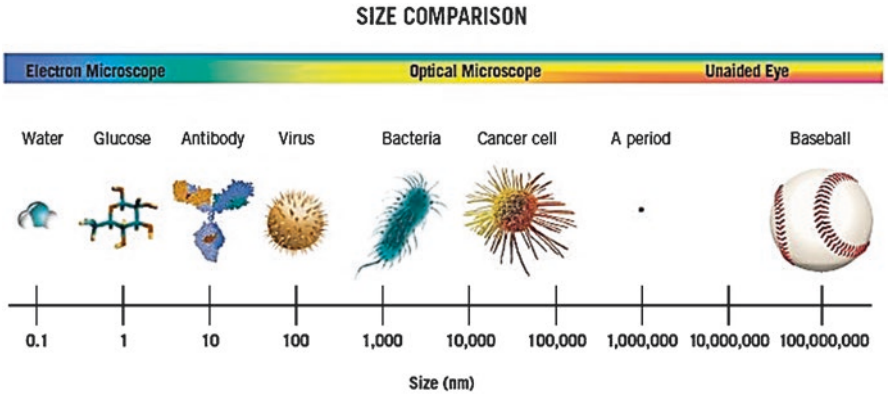


**Fig. 2.1** Schematic wide spectrum of small structures of nano-dimensions in comparison to objects visible with the naked eye. (Mitchnick et al. 1991)

only as nanoparticles and require transformations in chemistry, stoichiometry, and structure with their evolution to larger sizes. It is because in the nanometer dimension, materials exhibit novel properties, different from isolated atoms and bulk materials, and thus the properties of materials depend largely on the size of particles they are composed of (Adachi 2000). This chapter aims to elucidate some important chemical/biochemical characteristics of nanomaterials with emphasis on their use in bio-systems and, hence, their influence on the quality of life.

## 2.2 Importance of Nanoscale

The wave properties of electrons are affected by changes in the nanoscale. By patterning the material over the nanometer, it is possible to change the basic characteristics of materials such as melting point, magnetic effect, and electrical charge without changing their chemical composition. Furthermore, nano promises to let us introduce new artificial components and assemblies inside the cell to make new systems. The large surface areas of nanostructures make them ideal for use in composite materials, reacting systems, drug delivery, and energy storage. The finite size of material entities, as compared to the molecular scale, determines an increase of the relative importance of surface tension and local electromagnetic effects, making the nanostructured materials harder and less brittle (Jain et al. 2009; Jiang et al. 2007). In short, nanostructures now have potential application almost in every sphere of science and technology such as agriculture (nanofertilizers, nanopesticides), chemicals and cosmetics (paints, coatings), electronics (nanoparticles, carbon nanotubes, biopolymers), energy and environment (water- and air-purifying filters, fuel cells, solar cells, photovoltaics), food science (nanocapsules, nutraceuticals, food processing), materials (semiconductor chips, memory storage, optoelectronics, photonics), microscopy (atomic force microscope, scanning tunneling microscope), military equipment (biosensors, nanoweapons, sensory enhancement technology), nanomedicine (nano drugs, medical devices, tissue engineering), etc.

## 2.3 Nanochemistry

Nanochemistry is a branch of solid-state chemistry, which synthesizes nanoscale materials in one, two, or three dimensions. Synthesis and organization of a nanosized structure under controlled situations should provide a reproducible method of developing materials that are perfect in size and shape down to atoms. Structures and properties of nanosized systems are designed to obtain materials with new chemical, physical, and pharmaceutical behavior. Chemical properties of nanomaterials (NMs) considerably change at the nanoscale. As the percentage of surface atoms in nanoparticles (NPs) is large, compared to bulk objects, the reactivity of NPs is greater than that of the bulk materials. The nanoscale materials owe for their main chemical

properties to the increased population of surface atoms in nanoscale dimensions, the higher average energy of atoms than in the bulk material, the structure and nature of chemical bonding at the surface, and the mutual interaction among NPs. Although the composition, structure, and molecular weight may be important for some NMs, yet the properties like particle shape, size, and distribution, electronic surface characteristics, state of dispersion/agglomeration, and conductivity have a pivotal role in the majority of these materials. The quantum confinement, phase transition, and surface plasmon resonance are some other important characteristics of nanosized structures (Brune et al. 1998; Jolivet et al. 2004).

### *2.3.1 Quantum Confinement*

Quantum confinement refers to the change of electronic and optical properties when the material attains a small size of 10 nm or less. It is indicative of a restriction on the motion of randomly moving electrons present in a material to specific discrete energy levels rather than the quasi-continuum of energy bands. When dimensions of a material are small enough to be comparable to the de Broglie wavelength of the electrons involved, the electrons present in the material behave like those in atoms. Plainly speaking, electrons occupy discrete energy levels rather than a quasi-continuum of energy in a band.

Quantum confinement effect is one of the most popular terms in the nano world. As explained above, this effect sets in due to change in the atomic structure brought about by the impact of ultrasmall length scale on the energy band structure. As a result of "geometrical" constraints, electrons "feel" the presence of the particle boundaries and respond to changes in the particle size by adjusting their energy, and this is what we call the quantum confinement effect. When the particle dimension of a semiconductor nears the Bohr exciton radius, properties of the material become size-dependent. Quantum confinement results in a collapse of the continuous energy bands of a bulk material into discrete energy levels as in atoms. This creates a discrete absorption spectrum, in contrast to the continuous absorption spectrum of a bulk semiconductor. Thus, in a quantum-confined structure, the motion of the charge carriers (electrons and holes) is confined by potential barriers. Based on the nature of confinement, a quantum-confined structure is classified as a quantum dot (or nanocrystal), quantum wire, or quantum well. In quantum dots, the charge carriers are confined in all three dimensions, and the electrons exhibit a discrete energy spectrum as in atoms. Quantum wires are formed when two dimensions of the system are confined. In quantum well, only one dimension is confined, and the charge carriers are free to move in two dimensions (Arivazhagan 2013; Parker 2017).

The confinement effect usually varies with different classes of material, each of which normally has a characteristic length scale, e.g., (a) exciton Bohr radius (i.e., electron-hole pair radius) for semiconductors, (b) typical size of a domain for ferromagnetic materials, and (c) coherence length of Cooper pairs for superconductors. So, when the size of a given material is comparable to these characteristic length

scales, the electrons present in the material are said to be confined to discrete energy levels. The spacing between the energy levels increases with a decrease in the size of the material. Moreover, nanocrystals have a large surface area and a large population of surface atoms depending on the size of the particle (Chang and Waclawik 2014).

Thus, significant changes in the electrical and optical properties of materials are observed for the descending size. In small nanocrystals, the electronic energy levels are discrete – and not continuous as in the bulk material – due to confinement of electronic wave function to the physical dimensions of the particles (Fig. 2.2).

### *2.3.2 Surface Plasmon Resonance (SPR)*

Surface plasmon resonance (SPR) is an optical effect that can be utilized to measure the binding of molecules in real time without using labels. It is used to measure the binding kinetics and affinity of molecular interactions; for instance, it can measure the binding between two proteins, a protein and an antibody, a protein and DNA, and so on. Unlike the traditional techniques such as ELISA, SPR allows determination of binding kinetics and not just binding affinity, because it provides real-time binding data of both the association and dissociation phases of the interaction and hence offers deep insight into the binding strength and stability of the interaction (Schasfoort 2017). This physical process can occur when plane-polarized light hits

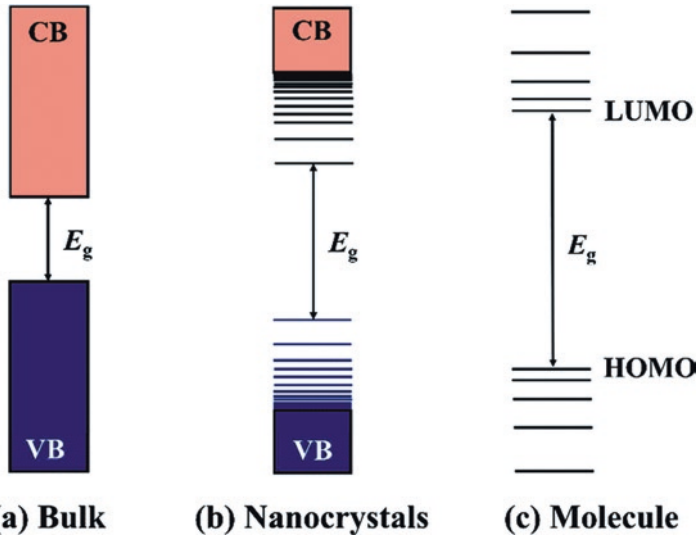


**Fig. 2.2** A comparison of the electronic energy states of different types of semiconductor materials: (**a**) bulk inorganic semiconductors, (**b**) inorganic semiconductor nanocrystals, and (**c**) molecular semiconductors (Chang and Waclawik 2014). CB conduction band, Eg band gap energy, HOMO highest occupied molecular orbital, LUMO lowest unoccupied molecular orbital, VB valence band

a thin metal film under total internal reflection (TIR) conditions. In fact, the photon and electron behavior can be described only when they have both wave and particle properties. As per the quantum theory, a plasmon is the particle name of the electron density wave. When the photons convert to plasmons, a "gap" occurs in the reflected light intensity.

SPR is size-dependent; the density of states and the spatial length scale of the electronic motion are reduced, when dimensions of the matter decrease. In fact, when a nanoparticle is smaller than the wavelength of light, coherent oscillation of the conduction band electrons is induced by interaction with an electromagnetic field which causes surface plasmon resonance to occur (Levchenko et al. 2006; Louchet et al. 2006; Zielińska-Jurek 2014). When noble metal nanoparticles (MNPs) are influenced by electromagnetic radiations, their conduction electrons show collective oscillations, i.e., SPR (Fig. 2.3). Beside the size of NPs, the other parameters affecting the SPR are shape and dielectric properties of NPs, which cause selective photon absorption, scattering, and local electromagnetic field enhancement in the SPR phenomenon (Johnson and Johal 2018).

SPR signals of nano-dimensions are desirable in several technological applications such as coupling in linear chains of metallic NPs, light transportation, and the direction of the chain. For example, when Au NPs absorb light, the oscillating electromagnetic field of the light triggers polarization of the conduction band electrons on the surface of NPs, and thus the polarized electrons pass through the collective coherent oscillations with respect to the positive ions in the metallic lattice; these oscillations are called surface plasmon oscillations (Fig. 2.4). Because of having the same frequency as the incident light does, these oscillations are also known as surface plasmon resonance. The frequency of this parameter depends largely on the size and shape of NPs. A single plasmonic frequency is responsible for the intense

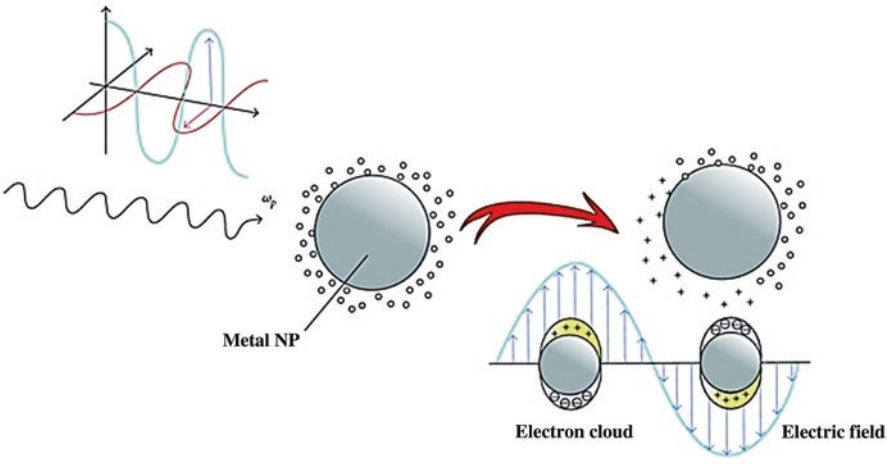


**Fig. 2.3** Localized surface plasmon resonance of noble metal (Ag, Au) nanoparticles, a collective electron density oscillation caused by the electric field component of incoming light. (Zielińska-Jurek 2014)

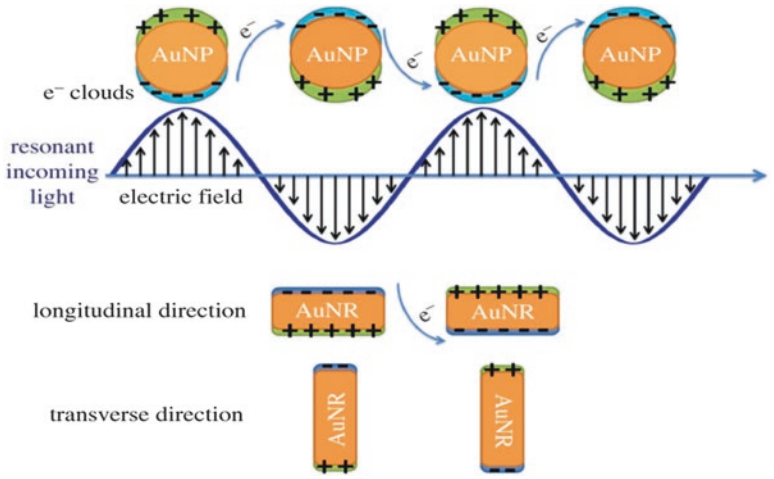


**Fig. 2.4** Surface plasmon oscillations in spherical gold nanoparticles (Au NPs) and gold nanorods (Au NRs). (Reproduced with permission from Yasun et al. (2013))

red color of the spherical gold NPs. For gold nanorods (Au NRs), however, there are two plasmonic frequencies, known as the longitudinal and transverse bands. The transverse band depends on the electron oscillations that occur along the transverse direction as a weak absorption band in the visible region similar to the SPR frequency of the spherical Au NPs. The longitudinal band, related to the electron oscillations along the longitudinal direction, is a strong absorption band in the vis-NIR region (Yasun et al. 2013).

The dataobtained from SPR have proved to be of great help in (a) screening and developing new pharmaceuticals and new bio-therapeutics, (b) controlling quality in bioprocess monitoring, (c) developing new diagnostic assays, and (d) discovering and characterizing protein function and disease mechanism, etc.

After the light absorption, the plasmonic electrons cause plasmonic scattering or convert the absorbed energy to thermal energy via its transfer to the metal lattice. In this case, the high temperature of metal network is decreased by photon interaction and transferred to the surrounding environment (Park et al. 2004). This forms the basis of all plasmonic NP-based photothermal therapy applications. Because the plasmon resonance band of NPs contains both scattering and absorption components, tuning of the shape and size of the NPs can dramatically change their scattering and absorptionproperties (Fig. 2.5).

### *2.3.3 Nanoparticle Size Effects*

Nanoparticles benefit from their small size and dimensions. In fact, if the surface energies of polymorphs differ significantly, at small sizes, the order of phase stability can be changed (Sanders 2018). Also, decreasing the size of particles changes

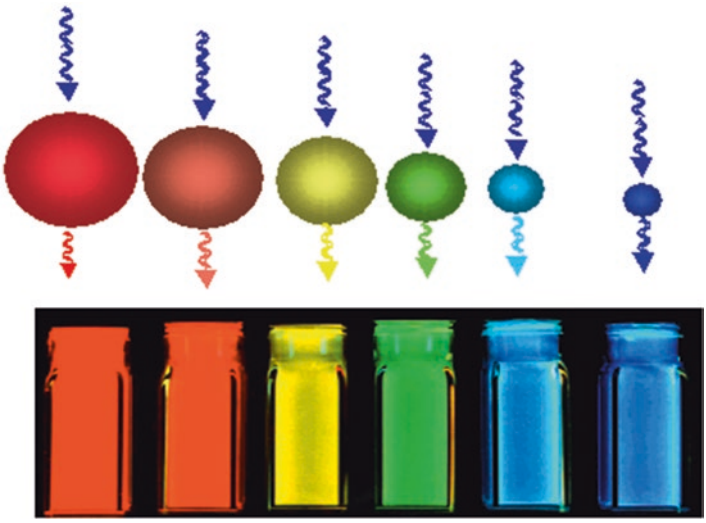

**Fig. 2.5** Effect of the size of nanocrystals on the emitted color of the absorbed light. (Lundquist et al. 2017)

**Table 2.2** Correlation among the size, abundance, and surface area of particles

| Particle diameter (nm) | Abundance (N/cm$^3$) | Surface Area (μm$^2$ cm$^{-3}$) |
|---|---|---|
| 5 | 153,000,000 | 12,000 |
| 20 | 2,400,000 | 3016 |
| 250 | 1200 | 240 |
| 5000 | 0.15 | 12 |

the crystalline habit such as morphology, crystallinity, and miller indices. Furthermore, evolution of structural, thermodynamic, electronic, spectroscopic, electromagnetic, and chemical features of these finite systems is related to change in particle size. Therefore, properties of a material depend on its electron movements (Lv et al. 2009; Kang et al. 2012; Sanders 2018). If the physical size of the material is reduced to the nanoscale, its properties change dramatically and become sensitive to size and shape. Size effects thus constitute a peculiar and fascinating aspect of nanomaterials (Table 2.2).

### *2.3.4 Size Distribution of Nanostructures*

The particles in nanoscale have a high proportion of atoms near their surfaces, a feature responsible for several important deviations from the bulk structure and chemistry at different size scales (Fig. 2.6). Other aspects influencing variations between the bulk material and nanomaterial properties include restriction on wave

function radius, separation of defects and interacting strain fields, relative dominance of bulk or surface energy, and changes in vibrational properties (Johnson and Johal 2018). Assessment of nanoscale characteristics requires information on solid-state properties and their dimensions as well as on nucleation and initial growth of precipitates. Thus, according to the classical nucleation theory (CNT), all substances pass through a nanosized regime, either on or just after nucleation. As the nucleation is generally a crucial rate-controlling step in precipitation, understanding of NP characteristics is a prelude to evaluating the kinetics of precipitation and other phase transformations (Li et al. 2010; Nasir 2010).

Among the various methods for calculating the NP size distribution, small-angle X-ray scattering (SAXS) technique, which takes into consideration the mean particle radius, the width of the size distribution, and the particle concentration, is held to be sufficiently accurate and reliable. This uncomplicated bulk nanostructural quantification technique is particularly sensitive to the smaller end of the nanoscale. Results from SAXS have repeatedly been demonstrated to agree well with findings from electron microscopy and have also shown inter-instrument reproducibility. It is a suitable laboratory-independent reference method for in situ nanoparticle analysis, at least for monomodally distributed particles in suspension (Pauw et al. 2017).

### *2.3.5 Shape of Nanoparticles*

Movement of electrons often determines the properties of materials. When the electrons move on a nanoscale dimension, unusual effects appear. For example, gold NPs in size less than 100 nm have red color in transparent media, but, in size less than 3 nm, they act as a catalyst for chemical reactions (Fig. 2.5). Furthermore, the optical properties of nanostructures change on changing their size, shape, aggregation state, and local environment. The nanostructures have various shapes such as particles, rods, and prisms (Fig. 2.7), which determine their functions and properties. There are many synthetic methods, such as top-down, bottom-up, bulk material applications; physical, chemical, and mechanical processes; application of high

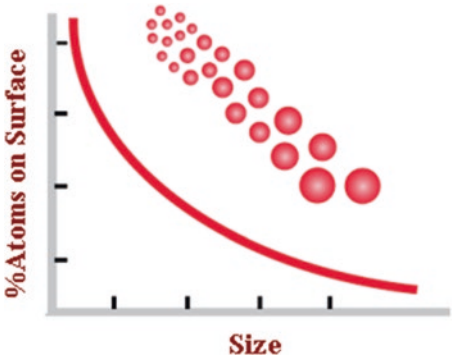


**Fig. 2.6** Percentage of surface atoms in a particle is strongly dependent on the particle size. (Nasir 2010)

temperature; and assembly from building blocks and solution-based methods, to produce the shape-controlled NPs. These processes of synthesizing nanostructures are classified into metallic (monometallic, bimetallic, and magnetite or metal oxides) and organic (mainly lipids or polymers) types (Sajanlal and Pradeep 2009; Ragaei and Sabry 2014).

Despite a particular seed shape of nanomaterials, their shape and size essentially relate to such factors during synthesis as the type and concentration of reducing agents, stabilizing agents and temperature of the reaction solution. Among the NP-shape-controlling methods, reduction of metal cation using the reducing agents (such as sodium borohydride), which also act as the stabilizing agents and affect the growth of the particles, is very important (Maham et al. 2017; Maryami et al. 2017; Momeni et al. 2017; Nasrollahzadeh et al. 2016a, b, 2017, 2018a, b, c, d, 2019; Sajjadi et al. 2017). Any change in the stabilizing agent and the molar ratio of stabilizer to metal source and also the variation of temperature alter the shape (of seeds) and size of NPs by influencing their growth in a particular direction (Murphy et al. 2005). For instance, to achieve the spherical NPs, the whole surface of NPs should be covered by the stabilizing agent during anisotropic growth process (Fig. 2.8). Likewise, increasing the reaction temperature tends to increase the average adsorp-

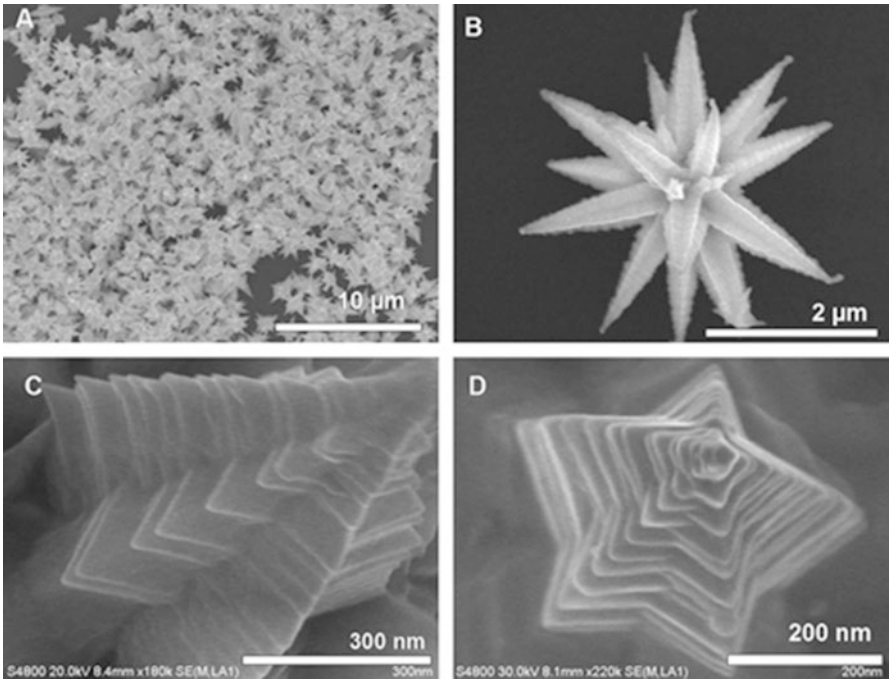


**Fig. 2.7** Large area (**a**) and corresponding single particles. (**b**) Field-emission scanning electron microscopy (FESEM) images of gold mesoflowers (Au MFs). (**c**) An enlarged FESEM image of a single stem of the MF showing ridges along the edges. (**d**) Top view of a single stem of the MF showing the pentagonal structure. (Sajanlal and Pradeep 2009)

tion of capping molecules on NPs. In fact, the particle morphology depends largely on supersaturation of the solution, which is regulated by its temperature. Reduction in the surface is responsible for the grain boundary enlargement, and therefore the particle size increases as a function of the temperature. With increase in the NP size, its sensing response decreases. It is also found that operable temperature of sensors fabricated with small particles is lower than those with large particles (Cao and Wang 2011).

Lee et al. (2014) obtained shape transformation of Ag NPs (from spherical to others) under irradiation of green light-emitting diodes (LEDs) at different temperatures. The spherical NPs got converted to nanoplates at 60 °C and decahedral NPs at 0 °C. Moreover, the tips and edges of decahedral NPs gradually became blunt at ambient temperature, while the nanoplates could retain their morphology for long. Both the nanoplate colloids and the decahedral NP colloid synthesized at 60 °C and 0 °C, respectively, exhibited good surface-enhanced Raman spectroscopy (SERS) activities for the probe molecule R6G in the absence of polyvinylpyrrolidone (PVP).

In most of the cases, NP size grows through the mechanism of "Ostwald ripening" (for more soluble materials) or "oriented attachment" (for less soluble crystals). The former facilitates the growth of large particles due to dissolution of smaller ones, whereas the latter involves merging of smaller particles. Both processes are influenced by the temperature (at least through the diffusion via kT). Ostwald ripening occurs because the larger particles are energetically more stable than the smaller ones. Temperature affects the process by influencing the interfacial energy, growth rate coefficients, and solubility. On the other hand, oriented attachment takes place because aggregation reduces the interphase boundary and the total (surface) energy of the system. On the whole, heating or cooling of the reaction system heavily affects the reaction capability of components in reduction, surfactant adsorption/desorption, formation and growth rate, and hence the shape, size, and size distributions.

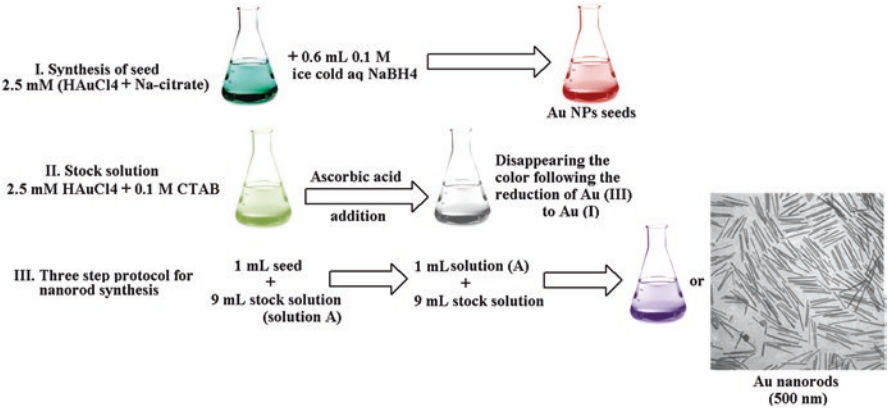


**Fig. 2.8** Seed-mediated growth approach to making gold nanorods of controlled aspect ratio. Bottom right is the transmission electron micrograph of gold nanorods of 500 nm long in average. (Murphy et al. 2005)

### 2.3.6 Agglomeration of Nanoparticles

Agglomeration refers to a loose particle assemblage in a suspension that can be broken simply by mechanical force. It is different from aggregation which is a definite pattern of molecule clubbing. Agglomeration represents a mechanism that leads to destabilization of colloidal systems. During this process, particles dispersed in the liquid phase stick to each other and spontaneously form irregular clusters. The high surface area of nanoparticles and the strong attraction among them result in aggregation/agglomeration.

The agglomeration of NPs reduces the potential enhancement of mechanical properties in nanocomposites due to the restriction of interfacial area. Therefore, the main challenge in production of nanocomposites includes not only the achievement of small NPs but also their good dispersion (Ashraf et al. 2018). In some applications, agglomeration is a beneficial process causing enlargement of particles to improve powder properties and is widely used in chemical processes to overcome problems such as segregation, difficult flow, low bulk density, and particle-size distribution monitoring. The way in which NPs may agglomerate stems from the type of forces between NPs in the solution. Under certain conditions NPs can assemble in a crystallographically oriented mode, leading to a type of crystal growth with different kinetics than one characterizing the classical layer-by-layer growth, and consequently differ in growth forms and habits (Joshi et al. 2012; Kuntworbe et al. 2012).

Upon exposure to biological systems, NPs may interact with the outer surface of the cellular membrane and subsequently enter the cells by different endocytic routes. Targeting of specific cellular structures, the release of NPs by the cells, and, on the contrary, their degradation in lysosomes are vital features that can markedly influence the NP toxicity/safety and also the efficacy of novel nanomedicines. Various endocytic pathways may be involved in the NP uptake depending on the features of the cell lines and the NPs used (Halamoda-Kenzaoui et al. 2017).

It is well explored that the mechanism of the cellular uptake and endocytosis is affected by the size, shape, surface chemistry, and charge of NPs, but the effect of agglomeration state of NPs on this process is still poorly understood, despite the fact that agglomeration is one of the predominant features of NP suspensions. Changes to the pH and ionic strength or the presence of biomolecules, particularly proteins, can easily modify the NP surface properties, leading to the loss of colloidal stability and the formation of agglomerates. It was noted by Halamoda-Kenzaoui et al. (2017) that the level of cell uptake and the mechanism of endocytosis of silica NPs were strongly dependent on their agglomeration state. Well-dispersed 80 nm Rubipy-$SiO_2$ NPs were internalized mainly by the caveola-mediated endocytosis, whereas 30 nm Rubipy-$SiO_2$ NPs entered the cells via a combination of different endocytic pathways. Interestingly, with the increase of NP agglomeration, the cellular uptake was highly enhanced, and the mechanism of endocytosis was slightly modified with a predominant role of macropinocytosis. This indicates that a modified environment can easily induce NP agglomeration and consequently influence a biological response.

Agglomeration, a process involving mass conservation and a reduction in surface area and number of particles, shifts the particle distribution toward larger sizes, covering the aerosols and colloids that tend to settle more rapidly under gravity but diffuse more slowly. In other words, agglomeration principally occurs because of the high surface energy of NMs, due to which they tend to agglomerate to diminish this energy. Agglomeration of NPs is influenced by environmental factors. For instance, adding bad solvent into the NP solution leads to agglomeration of NPs due to minimization of interface. Likewise, when the temperature is lowered, the enthalpy change is negative; to compensate this change, the system tries to maximize the entropy by separating the media (gas/liquid molecules) from huge NPs (Peddieson and Chamkha 2016). Several factors such as pH, temperature, ionic strength, and mixing rate may affect agglomeration, or the breakup of agglomerates (Fig. 2.9).

### 2.3.7 *Effect of pH, Ionic Strength, and Temperature on Agglomeration*

In the absence of agglomeration, a colloidal dispersion is stable as the potential barrier in this state is sufficiently high to prevent particles from joining one another. The stability of dispersions relates to the surface electrostatic potential (which depends on the pH of the solution) and the ion concentration of the solution. The net interaction potential between particles can be used to predict the pH and salt concentration regimes expected to promote agglomeration. For instance, if the repulsive barrier to agglomeration is less than or equal to the thermal energy in the system ($K_BT$), the stability map demonstrates that agglomeration appears near the

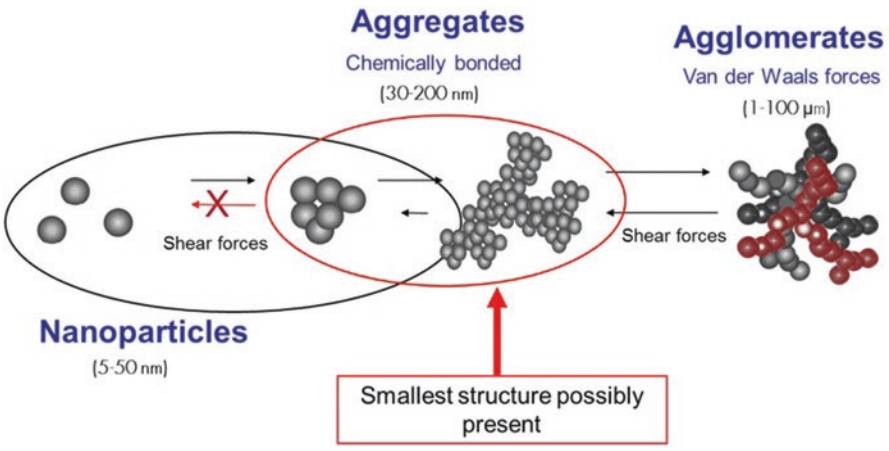


**Fig. 2.9** Agglomeration and aggregation of nanoparticles. (Peddieson and Chamkha 2016)

isoelectric point around the neutral pH (Tan et al. 2001). As the salt concentration increases, instability regime widens. The schematic form of a stable and non-stable colloidal system is shown in Fig. 2.10.

Study of size distribution of NPs using spectrophotometric techniques is a valid way to investigate the surface charge in agglomeration process. At a low pH with all particles positively charged, the particles are dispersed, and the agglomerate size is almost identical to the primary particle size. At the isoelectric point, the particles have little surface charge, and the primary particles stick to each other to form large agglomerates. At an alkaline pH, with all the particles negatively charged, one might expect to see primary particles. However, the particles are somewhat agglomerated due to high salt content of the solution.

Higher temperature of the system during the process of agglomeration affects the process gradually and favors the formation of more regular agglomerates with mechanically stronger and denser clusters. Maghsoodi and Yari (2014) obtained spherical, dense, and strong agglomerates with optimized temperature. Esmailpour et al. (2015) observed that the size of agglomerates decreased by increasing the gas velocity at a constant temperature. Moreover, the minimum fluidization velocity and the agglomerate size increased with rise in temperature due to increasing van der Waals cohesive force. Fluidization, a process similar to liquefaction, converts the granular material consisting of micron-sized particles from a static solid-like state to a dynamic fluid-like state, when a fluid (liquid or gas) is passed over the granular material. NPs are not fluidized individually but as agglomerates (very dilute clusters of around 200 μm consisting of ~$10^{10}$ primary particles). The NP fluidization is identified as agglomerate particulate fluidization (APF) and agglomerate bubbling fluidization (ABF). The APF is characterized by smooth fluidization, high bed expansion, and uniform distribution of agglomerates throughout the bed, while the ABF exhibits large bubbles and the low bed expansion ratio by increasing

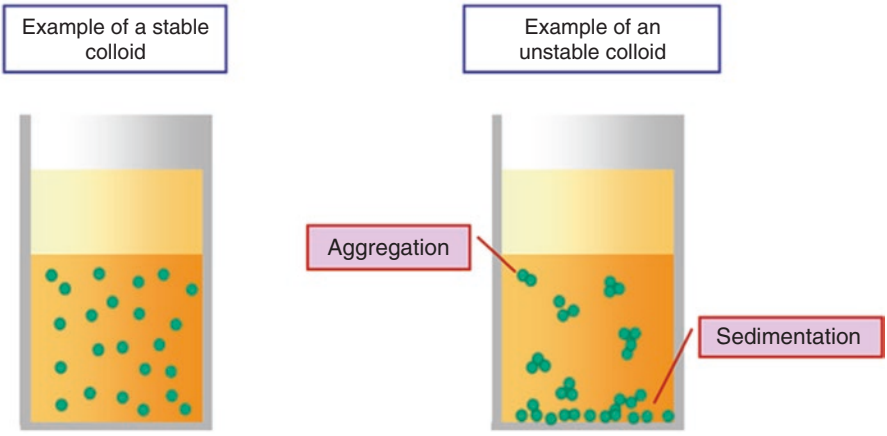


**Fig. 2.10** Schematic presentation of the stable and non-stable colloidal systems. (Elimelech et al. 1998)

the gas velocity. Smooth fluidization gives rise to highly porous agglomerates in the range of several hundred microns. They keep breaking and reforming during fluidization because of the contrasting cohesive forces among NPs and the separation forces originating from the fluid (Esmailpour et al. 2015).

In a recent study on hydrophobic silica (R972) and hydrophilic titania (P25) nanoparticles, Esmailpour et al. (2018) observed that increasing the bed temperature can convert the fluidization regime from APF to ABF for hydrophobic silica nanopowder. Large agglomerates and bubbles were formed in the bed at higher temperatures. In contrast, hydrophilic titania NPs fluidized in the ABF way at lower temperatures but in the APF way at elevated temperatures.

### *2.3.8 Solubility and Phase Transition of Nanoparticles*

In the bulk crystalline materials, properties of the material are independent on its particle size and chemical composition. In the nano regime, the minute size of the particle increases the surface area as well as the contribution of the surface energy to the overall energy of the crystalline system. The significant shift toward surface atoms of nanoparticulate matter is illustrated in Fig. 2.6 where the percentage of surface atoms in a particle is plotted against the particle size. This figure shows that in nanometer regime the large population of particle surface atoms markedly determines the properties of the material because the atoms located on the surface of a solid have less adjacent coordination state and therefore they are chemically more active, compared to the bulk atoms, and a large amount of energy is associated with this surface. The surface of NPs often plays a crucial role in determining the NP properties, including the stability, reactivity, solubility, and phase transition (Rector and Bunker 1995; LaFemina 1995a, b).

As mentioned earlier, almost all characteristic features of nanostructures stem from their size and the number of surface atoms; the solubility and reactivity of materials can, therefore, be optimized by altering the particle size. According to the Gibbs-Thomson theory, the NP solubility increases with the decreasing particle size. A solution is a homogeneous mixture of two or more substances, of which the solute dispersed among the molecules or ions of the solvent has the particles of less than 10 nm, which pass through a filter paper easily. A suspension is a heterogeneous mixture in which particle size of one or more components is greater than a few microns and particles are big enough to scatter light. After some time, the particles in aqueous suspension settle under water due to the influence of gravity. A colloidal solution is a mixture in which particles of a substance are of the size intermediate between those of a solution and suspension (10 nm–1 μm). These are too small to be filtered and/or seen with the naked eye. The particles in a colloid system are larger than in a solution but small enough to be dispersed evenly and maintain a homogeneous appearance; however they are large enough to scatter light. At a certain temperature, when a solid (solute) is mixed with a liquid (solvent) to form a solution, the molecules or ions on the solid disperse uniformly into the liquid and

move in the solvent. When they touch the solid surface, they are adsorbed back on it. Suspensions of NPs exhibit phase behavior similar to that of the molecular solution systems in the equilibrium state. The phases in the system can be manipulated through interactions between the solute particles and between the solute and the solvent particles (Batra et al. 2016). The effect of different variables such as density, temperature, concentration, and strength of colloidal interactions and pressure is taken into account while describing the phase transitions. In fact, the strength of interaction distinguishes colloidal suspensions most strongly from molecular systems. As the range and strength of attractions and repulsions can vary over an enormous range with colloidal particles, suspensions of NPs offer a unique test bed for treatments of the molecular phase behavior (Table 2.3).

## 2.4 Nanomaterials in Bio-systems

Among the nanostructures, nanocrystals find significant place in the modern medical technology, like biomolecular detection and diagnostics, and antimicrobial therapeutics (Fig. 2.11). In fact, the large surface area-to-mass ratio of nanomaterials heavily affects their reactivity. The most common nanostructures used in medicinalapplications, mainly as delivery systems, are ceramic-based NPs, polymeric NPs, metal NPs, micelles, liposomes, and dendrimers (Selmer-Olsen et al. 1996).

**Table 2.3** Differences between true solution, colloidal solution, and suspension

| Property | True solution | Colloidal solution | Suspension |
|---|---|---|---|
| Size of particles | <1 nm | 1 nm–1000 nm (1 μm) | >1 μm |
| Nature of solution Appearance | Homogeneous Transparent | Heterogeneous Translucent | Heterogeneous Opaque |
| Visibility | Solute particles not visible with the naked eye or through microscope | Solute particles not visible with the naked eye; can be seen with ultramicroscope | Suspension particles can be seen with the naked eye |
| Filterability | Solute particles pass through a filter paper or a parchment membrane | Solute particles pass through a filter paper but not through a parchment membrane | Solute particles cannot pass through a filter paper or a parchment membrane |
| Settling ability | Solute particles do not settle | Solute particles do not settle but can be made to settle by centrifugation | Solute particles settle down due to the force of gravitation |
| Light scattering | Solution does not scatter light (no Tyndall effect) | Solution shows Tyndall effect | Suspension may or may not show Tyndall effect |
| Particle movement | Solution does not show Brownian movement | Brownian movement of particles is visible | Brownian movement may or may not be visible |

Several other NP systems such as solid lipid NPs, inorganic NPs, and microemulsions have also been used in the formulation, encapsulation, and release of active compounds extracted or derived from natural resources. The main objective of nanomedicine is to ensure drug transport to action sites, to maximize the desired pharmacological influence of drugs, and to overcome the factors that may hinder effectiveness of the treatment (El-Say and El-Sawy 2017). The controlled drug delivery system comprises of four major modes of delivery, viz., (a) rate-programmed drug delivery, where drug diffusion from the system has to follow a specific release rate profile (in this type of delivery, the therapeutic formulation is totally or partially loaded in the reservoir space, which is covered by the pre-programmed polymeric membrane, the function of which can be optimized with block copolymers through multifunctionalization); (b) activation-modulated drug delivery, where the drug release is induced by various physical, chemical/biochemical, or environmental stimuli (e.g., various pressures, magnetics, electricity, salt concentration, pH, light, temperature, hypoxia) and facilitated by external supply of energy; (c) feedback-regulated drug delivery, where the rate of release is determined by the concentration of biochemical substance (triggering agent) via some feedback mechanism; and (d) site-targeting drug delivery, where diffusion rate and partitioning of drug release are regulated by the specific targeting moiety, solubilizer, and drug moiety (Bennet and Kim 2014).

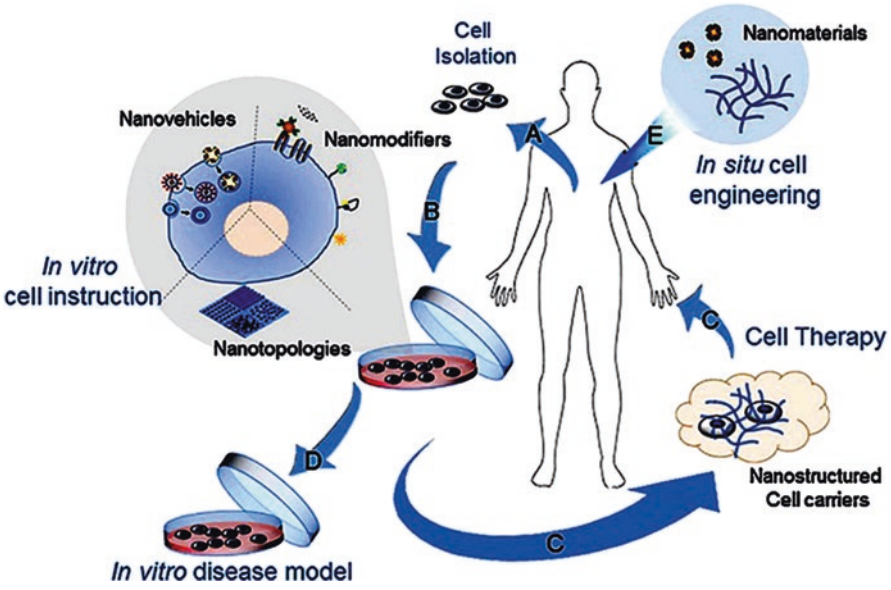


**Fig. 2.11** Multifacetedapplications of nanomaterials in the cell engineering and therapy. (Wang et al. 2016b)

### 2.4.1 Micelles and Liposomes

Certain nanostructures with walls composed of phospholipid moieties form a "core-shell structure," which provides a suitable platform for drug delivery to the central nervous system (CNS). They carry diverse amounts and types of therapeutic materials and, in some cases, accomplish target delivery to specific cell types within the CNS. The ability of some of these structures to traverse the blood-brain barrier (BBB), avoiding the checks of the immune surveillance system, enables them to enter the CNS without any neurosurgical procedure. Micelles and liposomes are most prominent among these structures. Nanomicelles and nanoliposomes typically range in size from ten to several hundred nanometers. Micelles are typically spherical and have an outer surface of charged or hydrophilic moieties and an inner lipophilic region. Phospholipid micelles can be utilized to carry other amphiphilic molecules or hydrophobic substances within their inner lipophilic region. The use of amphiphilic block copolymers to produce clinical nanomicelles for drug delivery is quite common these days (Fiandaca and Bankiewicz 2013).

Thus, micelles, which are lipid molecules with amphipathic nature of fatty acids due to the presence of both hydrophilic and hydrophobic regions, arrange themselves in spherical form in the aqueous solutions (Fig. 2.12). Their hydrophilic head faces to water, but hydrophobic tails are inside and away from water. Fatty acids from micelles usually have a single hydrocarbon chain as opposed to two hydrocarbon tails. This allows them to conform to spherical shape for lesser steric hindrance within a fatty acid. Fatty acids from glycolipids and phospholipids have two hydrophobic chains that are too bulky to fit into the spherical shape as micelles do and, therefore, prefer to form glycolipids and phospholipids. Micelles are formed spontaneously in water due to the amphipathic nature of the molecule. In fact, when lipids form micelles, the hydrophobic tails interact with each other, releasing water from them and increasing the system disorder or entropy (Du et al. 2003, Li et al. 2009).

On the other hand, liposomes are spherical objects comprising mainly of lipids (Fig. 2.12). Sometimes other constituents are also added to modify their chemical and physical properties. Liposomes typically consist of double-chain phospholipid amphiphiles combined with cholesterol, forming spheroidal bilayer membrane structures that encompass an aqueous internal domain (Torchilin 2005). The length of the fatty acid chains and the presence or absence of double bonds within the liposome bilayer lipids influence the membrane fluidity, as does the combination of different phospholipids within the membrane structure. Cholesterol moieties strengthen and stabilize the bilayer membrane and reduce the cation leakage in physiological systems. Increasing the molar cholesterol content of the liposomal drug carriers typically decreases the release kinetics of the therapeutic from the nanocarrier (Panwar et al. 2010). Therefore, specific liposomal properties can be tailored by regulating the membrane components (Panwar et al. 2010). Liposomes are typically formed by adding energy to amphiphilic phospholipids in aqueous solution. Depending on lipid monomer concentration and environmental factors,

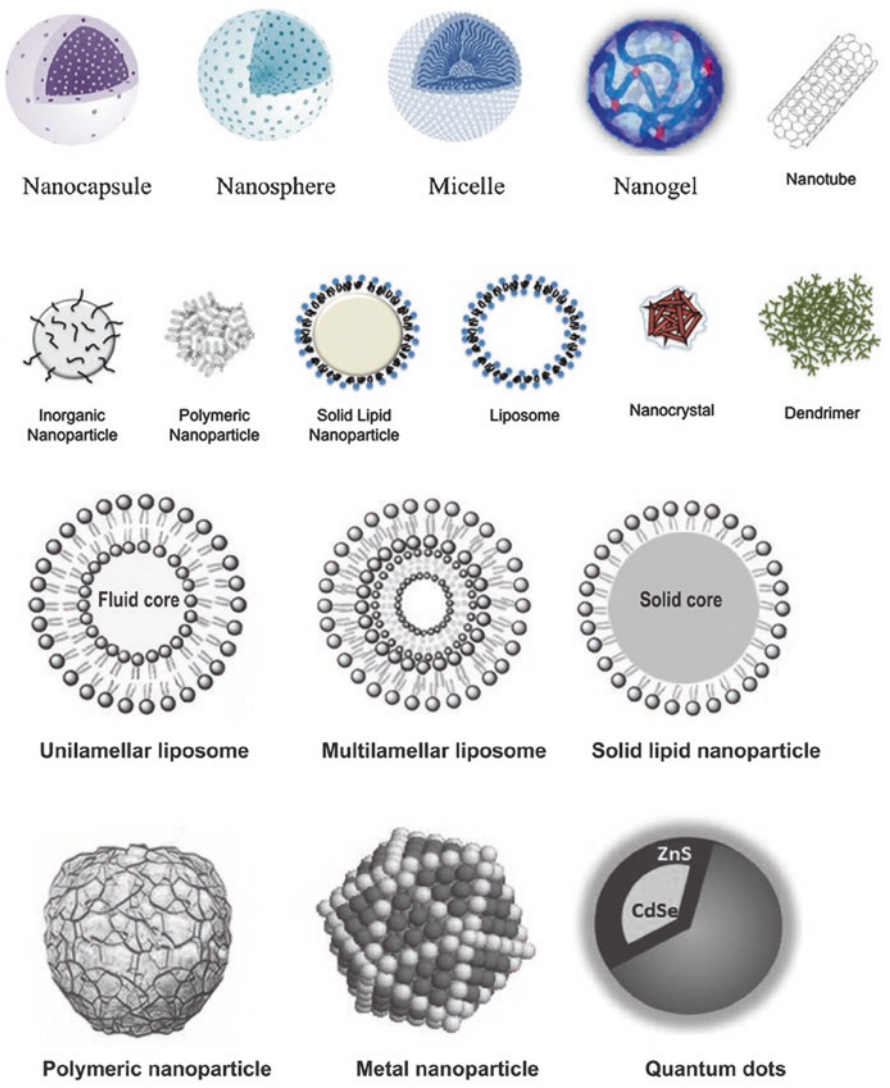


**Fig. 2.12** Schematic morphological representation of different types of nanostructures. (Veszelka et al. 2015)

liposomal structures can range from long tubules to spheres, with dimensions ranging from several hundred angstroms to several hundred micron meters. A prototypical liposomal vesicle has a single, closed lipid unilamellar bilayer confining a single internal aqueous volume (Fiandaca and Bankiewicz 2013).

Liposomes are different from micelles as they are composed of a lipid bilayer, separating an aqueous internal compartment from the bulk aqueous phase. Micelles, by contrast, are closed lipid monolayers with a fatty acid core and polar surface or

a polar core with fatty acids on the surface (inverted micelle). Thus, liposomes are an important drug-carrier system due to their ability to encapsulate drugs, their stability and long shelf life, controllable size and charge, ability to function and modify the surface due to presence of many functional groups, and finally for their biocompatibility and degradability. However, they have a short half-life in the circulation system, although it can be enhanced by a better control of the size and composition of liposome vesicles. Although liposomes are suitable to encapsulate nonpolar drugs in the hydrophobic bilayer of the vesicle, sometimes such drugs affect the integrity of these vesicles rendering them unsuitable for nonpolar drugs (Endo et al. 2010). Wang et al. (2017) synthesized a series of novel derivatives of EEDQ (*N*-ethoxycarbonyl-2-ethoxy-1, 2-dihydroquinoline), which showed significant anticancer activity. Using the Tf-modified liposomes as carriers, they could achieve successful delivery of therapeutic, which could improve tumor cell uptake and antitumor effect.

### *2.4.2 Microemulsions*

The term "microemulsion" (ME) refers to a thermodynamically stable and isotropically clear dispersion of two immiscible liquids, such as oil and water, which is stabilized by an interfacial film of surfactant molecules. As these molecules have both polar and apolar groups, they get adsorbed at the interface, where they can fulfill their dual affinity with the hydrophilic groups located in aqueous phase and with the hydrophobic groups in oil or air (Saini et al. 2014). The dispersed phase typically comprises of small particles or droplets, with a size range of 5 nm–200 nm, and has very low oil/water interfacial tension (Fig. 2.12). Because the droplet size is less than 25% of the wavelength of visible light, MEs are transparent. They are formed readily and sometimes spontaneously, generally without high-energy input. In many cases a co-surfactant or cosolvent is used in addition to the surfactant, the oil phase and the water phase (Saini et al. 2014). Their formation is facilitated by the ultralow interfacial tension of the component systems. Thus, they consist of aqueous and oily phases, and the disperse system is stabilized by the surfactant and cosurfactant components. MEs are thermodynamically stable (in contrast to emulsions) and exhibit characteristics of macroemulsion (particles can be measured with diffraction of laser light) but sometimes behave as a real solution (active substances have a saturation solubility and do not show active substance distribution as in macroemulsions). When MEs are added into water, their lipid phase precipitates to form small particles.

As one of their several important applications, MEs offer an efficient drug delivery system and enable the selective release of active pharmaceutical ingredients along specified lengths in the gastrointestinal tract by inverting a water-in-oil emulsion to an oil-in-water emulsion. MEs provide promising drug delivery systems due to their easy formulation, thermodynamic stability, and ability to facilitate delivery of lipophilic and hydrophilic drugs into the skin. The composition and quantities of

the ME components, as also the included active substances, affect the droplet size, distribution, and viscosity of the ME. Their particle size (5–200 nm) enhances their penetration through cellular membranes, making them suitable as drug carriers. Due to the presence of amphipathic components in MEs, they are very good dissolving agents (Mocan 2013). The surfactant and co-surfactant may enhance drug penetration, disrupting the lipids of the stratum corneum (Juškait et al. 2015). The concept of ME was first introduced by Hoar and Schulman (1943) who developed the formulation by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co-surfactant.

### *2.4.3 Other Relevant Materials*

Solid lipid nanoparticles (SLNs), introduced in 1991, represent an alternative carrier system to traditional colloidal carriers such as emulsions, liposomes, and polymeric micro- as well as nanostructures. This system is composed of nanosized spherical solid lipid particles, which are dispersed in water or some aqueous surfactant solution. It resembles an oil-in-water emulsion for parenteral nutrition with the difference that the liquid lipid (oil) of the emulsion has been replaced here by a solid lipid (Bagul et al. 2018). SLNs are primarily made of a solid lipid core with a monolayer phospholipid shell. The solid state of the nanoparticulate matrix provides protection to chemically labile drugs and facilitates a prolonged drug release (Lin et al. 2017). The solid core contains the drug dissolved or dispersed in the solid high-melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have the potential to carry lipophilic or hydrophilic drugs or diagnostics (Ramteke et al. 2012).

The SLNs (50–1000 nm) thus consist of physiologically tolerated lipid components that remain in solid state at room temperature and are dispersed in water or in aqueous surfactant solution. They possess the characteristic positive traits including small size, large surface area, high drug loading, and the interaction of phases at the interface. Their hydrophobic core provides a suitable environment for entrapment of hydrophobic drugs to improve their bioavailability (Bagul et al. 2018; Lingayat et al. 2017). They resemble the other types of nanocarriers in being suitable to encapsulate nonpolar insoluble drugs in their polymeric core and shielding them from the outside environment, to increase drug stability and reduce its toxicity to the body (Fig. 2.12). Besides, they are easier to prepare and cheaper for the scale-up productions in comparison to other drug delivery systems. They ensure a sustained and slow release of the drug in the targeted site.

SLNs have certain advantage over other nano-delivery systems, e.g., they have lower chronic or acute toxicity, enhanced bioavailability and productivity, higher reproducibility, limited use of organic solvents in preparation, ability to protect liable drugs, possibility of incorporating both hydrophilic and hydrophobic compounds, and ability to bypass the spleen or liver filtration for 120–200 nm particle size. Given this, the SLNs are most appropriate for oral delivery of phyto-bioactive

compounds, such as curcumin, resveratrol, quercetin, and other polyphenols. However, the bulk release of such compounds in the stomach at a lower pH of about 1–3 renders the SLN delivery system inadequate. To meet this challenge, SLNs are subjected to surface modification, and the surface-modified SLN (SMSLN) could improve the delivery output, preventing the high release of phyto-bioactive compounds in the stomach (Ganesan et al. 2018).

Polymer nanoparticles, derived from biodegradable polymers, constitute a special type of nontoxic drug delivery system. The special features of this system, besides nontoxicity, are biocompatibility, biodegradability, prolonged circulation, controlled release, and a broad payload spectrum of a therapeutic agent (El-Say and El-Sawy 2017). Polymer nanoparticles may carry sugars, proteins, and many other naturally occurring macromolecules. Of late, encapsulation of anticancer agents within the polyhydroxyalkanoates, poly-(lactic-co-glycolic acid), and cyclodextrin-based nanoparticles has been tried to target exactly the specific cancer sites (Masood 2016).

Dendritic polymers and dendrimers belong to a special class of macromolecules composed of many monomer units that are chemically linked together (Fig. 2.12). They are good encapsulating agents for hydrophobic drugs due to their nonpolar core and are known for their structural perfection, water solubility, and monodispersity (Núñeza et al. 2014). Dendrimers are nanosized, radially symmetric molecules having a well-defined homogeneous and monodisperse structure comprising of a typically symmetrical core, an inner shell, and an outer shell. All varieties of dendrimers have the properties of polyvalency, solubility, self-assembling, electrostatic interactions, chemical stability, and low cytotoxicity (Abbasi et al. 2014). Dendrimers and dendritic polymers with unique inherent supramolecular features and multivalent properties are most suitable carriers in the fields of gene and drug delivery and biomimicry. Whereas dendritic polymers do not have the perfect dendrimer branched structure, they exhibit high surface functionality and are easy to produce. Dendrimer-based technologies provide a platform for mimicking the naturally occurring biological assemblies to design synthetic alternatives in the field of nanomedicine (Kretzmann et al. 2017).

Inorganic nanoparticles are classified into three main classes, viz., transition metal NPs, ceramic NPs, and carbon NPs. Transition metal nanoparticles have many applications as drug carriers (e.g., application of gold NPs as shuttles for site-specific delivery of toxic drugs) and as drugs themselves when excited by light radiation to damage the DNA and/or modify proteins, promote lipid peroxidation, and destroy the cell microenvironment, causing cell death in cancer therapy (Fig. 2.12). Also, they are used for imaging in diagnosis as well as therapy monitoring. Ceramic NPs are developed mostly from oxides, nitrides, and carbides with silica ($SiO_2$) and used as hollow shells or cores coated with biodegradable and biocompatible polymers (Fig. 2.12). These surface modifications enable them to be used as targeted delivery systems (Veszelka et al. 2015).

## 2.5 Preparation of Nanostructures for Use in Medicine

The mode of preparation has a role in determining the physicochemical characteristics of the polymer and the drug to be loaded. The primary manufacturing methods of nanoparticles include:

### *2.5.1 Emulsion-Solvent Evaporation Method*

This maximally used method of NP preparation comprises of (a) emulsification of the polymer solution into an aqueous phase and (b) evaporation of polymer solvent containing the polymer precipitation as nanospheres (Wang et al. 2016c). Finally, the NPs obtained are centrifuged and washed with distilled water to remove the possible contaminants and then lyophilized for storage (Fig. 2.13).

### *2.5.2 Double Emulsion and Evaporation Method*

This method is suitable for encapsulating the hydrophilic drugs. It involves addition of aqueous drug solutions to organic polymer solution under vigorous stirring to form water/oil (w/o) emulsion, which is then added into a second aqueous phase with continuous stirring to form the w/o/w emulsion. Finally, the solvent is removed from this emulsion by evaporation, and NPs are isolated by centrifugation at high speed (Noviendri 2014) and washed thoroughly before lyophilization. The amount of hydrophilic drug to be incorporated, the concentration of stabilizer used, the polymer concentration, and the volume of aqueous phase are some variables that affect the characterization of NPs in this process (Fig. 2.14).

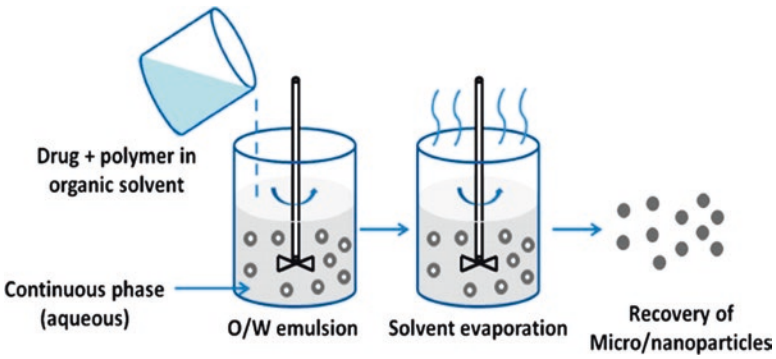


**Fig. 2.13** Emulsion-solvent evaporation method (Wang et al. 2016c)

### 2.5.3 Salting-Out Method

This method is based on separating the water-miscible solvent from aqueous solution. The polymer and the drug are initially dissolved in an emulsified media of an aqueous gel, containing an electrolyte or nonelectrolyte agent as the salting-out agent and a colloidal stabilizer (Wang et al. 2016c). This water/oil emulsion is diluted with a sufficient volume of aqueous solution to enhance the diffusion of solvent into the aqueous phase to form the nanospheres (Fig. 2.15).

### 2.5.4 Emulsion-Diffusion Method

In this method, the encapsulating polymer is dissolved in a partially water-miscible solvent and saturated with water to achieve a thermodynamic equilibrium of both liquids (Fig. 2.16). Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer based on the oil-to-polymer ratio, which leads to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules (Esmaeili et al. 2013).

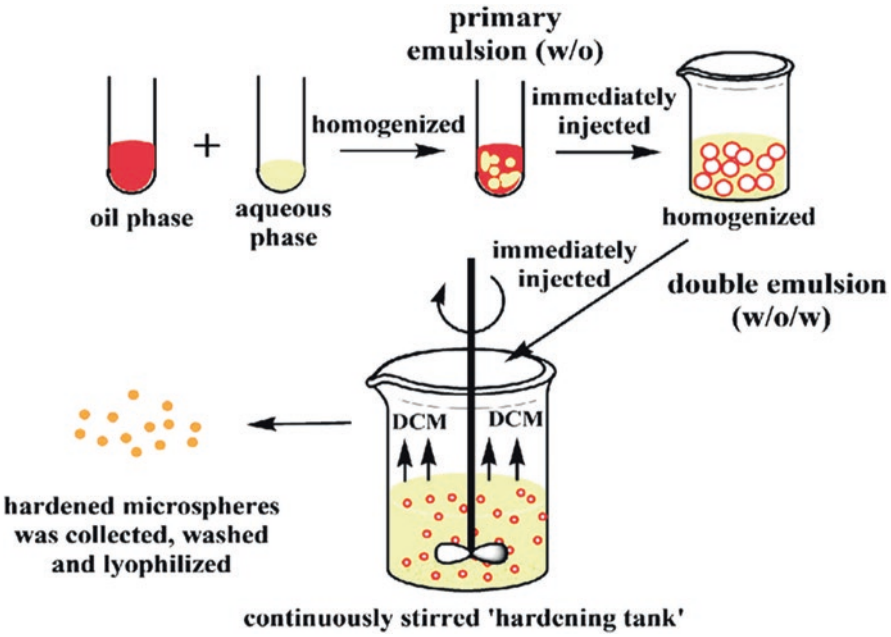


**Fig. 2.14** Double emulsion and evaporation method. (Noviendri 2014)

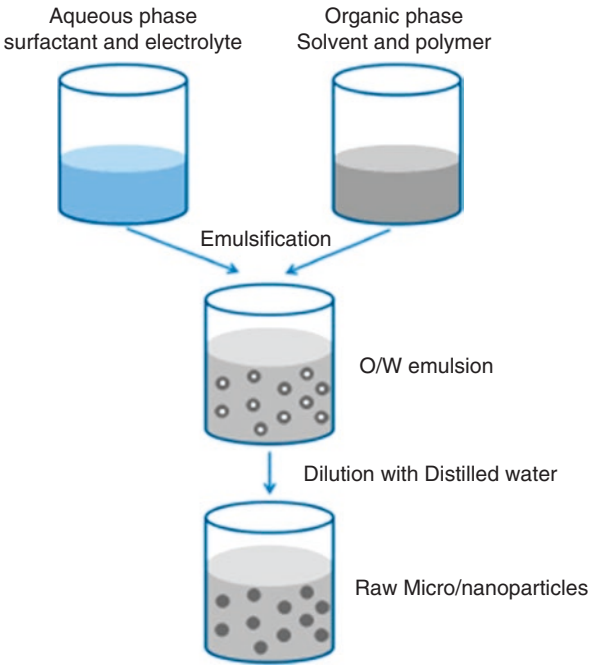


**Fig. 2.15** The salting-out method. (Reproduced with permission from Wang et al. 2016c)

### *2.5.5 Solvent Displacement/Precipitation Method*

Solvent displacement involves the precipitation of a polymeric organic solution and diffusion of an organic solvent in the aqueous medium, with or without a surfactant (Fig. 2.17). The polymers, drug, and lipophilic surfactant are dissolved in a polar water-miscible solvent such as acetone or ethanol. The solution is then transferred to an aqueous solution containing stabilizer under magnetic stirring to enable immediate formation of NPs (Ezhilarasi et al. 2012).

## 2.6 Nanoencapsulation and Nanoencapsulated Materials

Nanoencapsulation is a technology used to encapsulate substances in miniature form and pack bioactive materials at the nanoscale range. Delivery of bioactive material to different sites within a body is affected by the particle size, and, therefore, nanoencapsulation has the potential to improve bioavailability and controlled release of bioactive compounds and ensure their precise targeting. The nanocarriers (NCs) thus produced (10–1000 nm) are expressed as nanocapsules and nanospheres. Nanocapsules are vesicular systems in which the bioactive compound is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems where the bioactive compound is uniformly dispersed (Suganya and

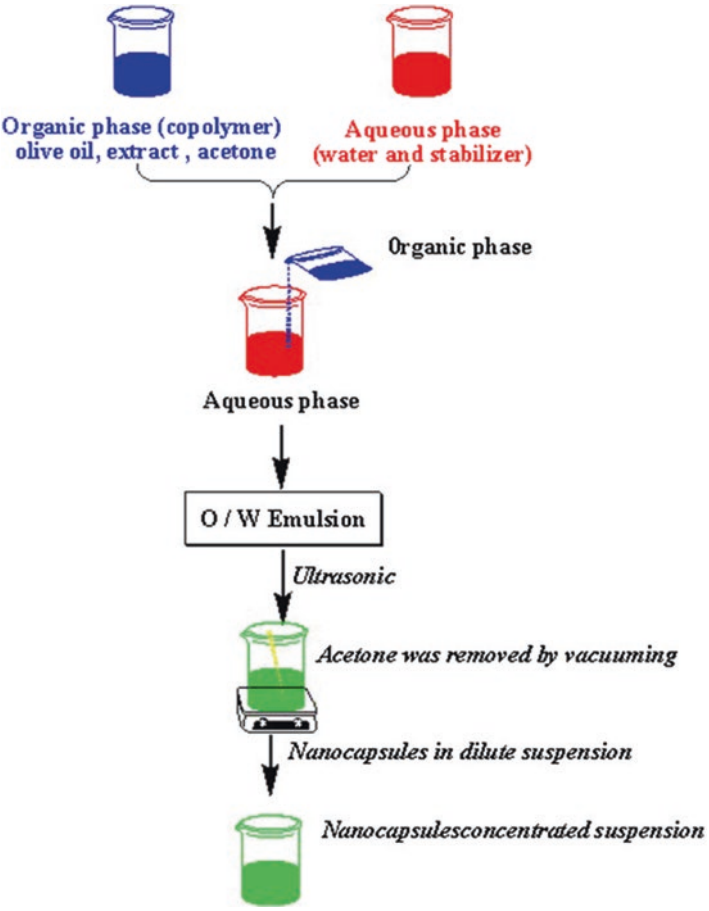


**Fig. 2.16** Emulsion-diffusion method. (Esmaeili et al. 2013)

Anuradha 2017). NCs protect their payload from premature degradation in the biological environment, enhance bioavailability, and prolong presence in blood and cellular uptake.

Recent nanoencapsulation methodology encompasses nanoemulsification, electrospinning, electrospraying, formation of nanostructures via cyclodextrins, and synthesis of nanoliposomes, solid lipid nanoparticles, nanostructured lipid carriers, etc. (Jafari 2017). The selection of technique for NC synthesis is made according to the chemical structure of therapeutic agent, type of application, and time of retention inside the body. NCs of different dimensions can be synthesized by using different matrices. Size and size distribution of NCs affect their cellular uptake and penetration across the biological barriers. Size and surface chemistry of NCs determine their in vivo performance. Drug release mechanisms can also be modulated depending upon the nature of therapeutic agent and type of NCs (Kumari et al.

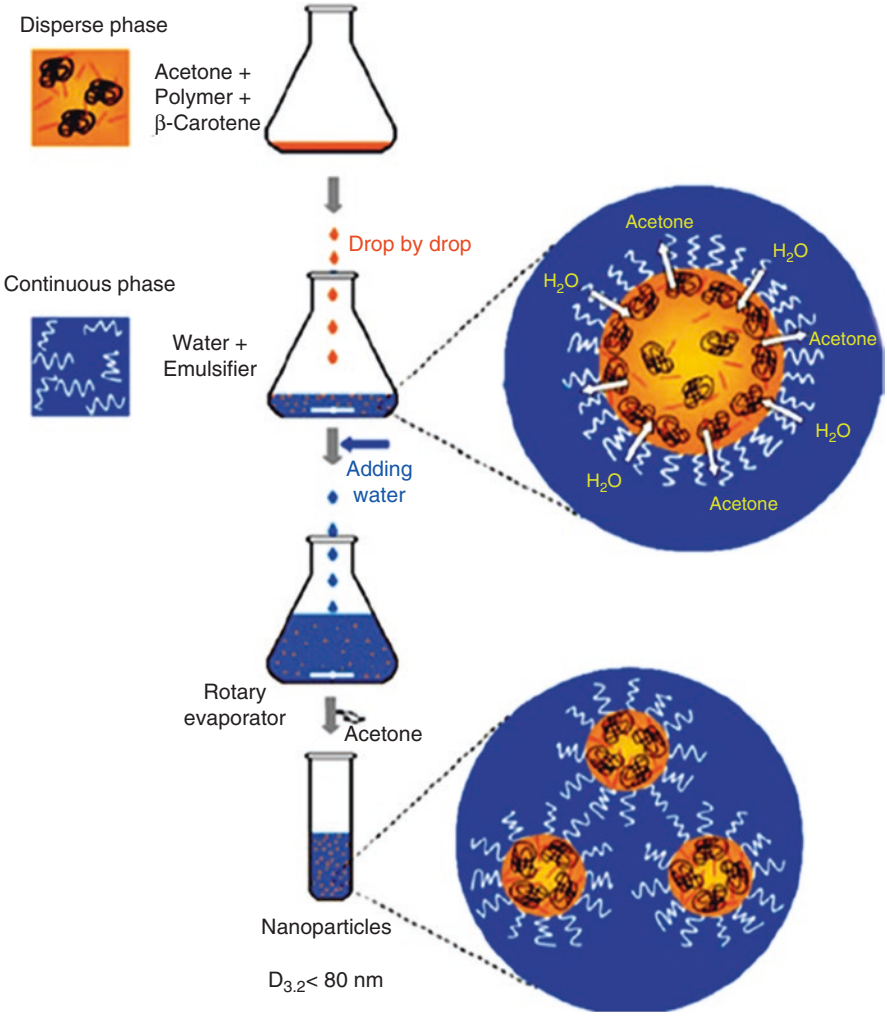


**Fig. 2.17** The solvent displacement/precipitation method (Ezhilarasi et al. 2012)

2014). The mononuclear phagocytic system (MPS) in the body recognizes NCs as foreign particles and rapidly removes them from the systemic circulation. Given this, if a prolonged presence of NCs in blood is desired, surface of NCs has to be modified to avoid phagocytosis. Surface modification of NCs is conducted either by tagging ligand or hydrophilic polymers on their surface. Further, surface charge is another important factor that affects the cellular response of NCs. In general, NCs with cationic charge are taken up readily by negatively charged cell membranes, compared to neutral or positively charged ones (Kumari et al. 2014).

The encapsulated material is concerned with the internal phase, core material, and filler. Particle size is also an important factor for the formulations of encapsu-

lated materials. Core materials used for nanoencapsulation are lipophilic (soluble in lipids and organic solvents but insoluble in water) as well as hydrophilic (soluble in water but insoluble in lipids and organic solvents) compounds. Lycopene, beta-carotene, lutein, phytosterols, and docosahexaenoic acid are examples of lipophilic compounds, whereas ascorbic acid and polyphenols, etc. represent hydrophilic compounds (Suganya and Anuradha 2017). The commonly used materials are polymer-based, solid lipid-based, inorganic porous-based, and clay-based nanomaterials (Nuruzzaman et al. 2016), as depicted in Fig. 2.18.

Biodegradable polymers are frequently used to produce nanosized controlled release drug formulations. Active ingredients are encapsulated as polymer nanocomposites in which nanofillers are dispersed within the polymer matrix (Mora-Huertas et al. 2010). Produced by green sources, these structures are environment-friendly and do not form any degradation by-products. The majority of these formulations are designed for oral administration, though recently such devices have also been introduced for parenteral administration, ocular insertion, and transdermal application. Natural polymers include protein-based polymers (collagen, albumin, gelatin) and polysaccharides (alginate, cyclodextrin, chitosan, dextran, agarose, hyaluronic acid, starch, cellulose), whereas biodegradable synthetic polymers include several polyesters, polyanhydrides, polyamides, phosphorus-based polymers, and many others such as polycyanoacrylates, polyurethanes, and polyacetals (Gavasane and Pawar 2014). Synthetic polymers are preferred over the natural ones because the latter suffer from some disadvantages, such as microbial contamination, climate-based batch-to-batch variation, and uncontrolled rate of hydration, while the former are free from these defects (Shah et al. 2011).

Lipid-based nanovectors (liposomes) are among the best delivery systems with better encapsulating efficiency and low toxicity. They have great potential to encapsulate the ingredients having various polarities and simplify the in vivo dispersion and absorption of the bioactive compounds (Aina et al. 2007). Of the various types of lipid-based NMs, nanoliposomes and solid lipid NPs have already established their suitability to encapsulate active ingredients. Lipids, especially charged lipids,

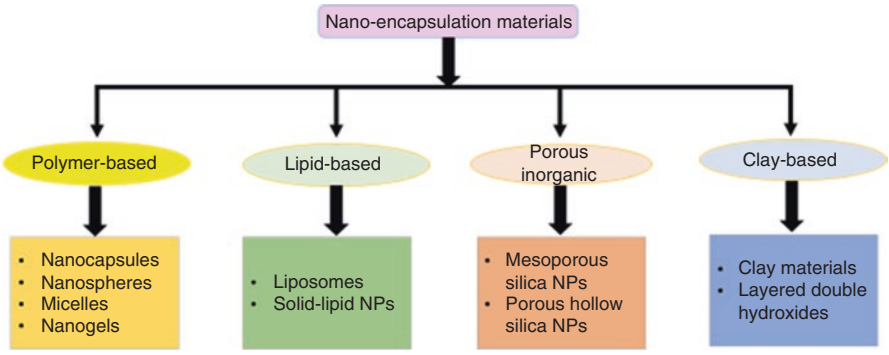


**Fig. 2.18** Various types of nanoencapsulation materials and the structures they produce

are used to design NPs characterized by a core-shell structure, wherein a lipid shell interacts with a core having different biomaterials. Drugs carrying a net charge can be condensed in the core, which is then covered by the lipid shell. This approach works well with the delivery of macromolecular drug (e.g., nucleic acids) and small molecules (e.g., bisphosphonates) (Campani et al. 2018).

Inorganic porous nanomaterials have also attracted the interest of researchers as being highly capable of encapsulating the bioactive compounds. In fact, the polymeric nanoencapsulated materials suffer from various limitations such as poor thermal and chemical stability, rapid elimination of the plant enzyme system, degradation of some polymers obtained during the formation of acidic monomers, and decreased pH value within the polymer matrix. In comparison to polymeric nanoencapsulated materials, these inorganic materials offer a nontoxic, biocompatible, and stable alternative and have been used for controlled release applications (Hillyer and Albrecht 2001, Lao et al. 2010).

Both natural and synthetic nanoporous materials consist of pores with diameter roughly in the range 0.4–100 nm and are classified on the basis of their pore size as microporous ($\leq$2 nm), mesoporous (2–50 nm), and macroporous (>50 nm) materials. Utilization of the pores in impregnation of nanoparticles/proteins/ions or in transporting the latter across the pores of membranes is of practical and scientific interest. Their surface area design and pore size determine their applications in diverse areas such as fuel cells, solar cells, Li-ion batteries, super capacitors, hydrogen storage, catalysis, gas purification, separation technologies, drug delivery, and cell imaging. Typical examples of nanoporous solids are zeolites, activated carbon, metal-organic frameworks, ceramics, silicates, aerogels, pillared materials, various polymers, and inorganic porous hybrid materials. Zeolites and mesoporous silica have come up as important materials for applications in drug delivery and imaging. Properties of biocompatibility, low toxicity, large surface areas, and their ability to control the physicochemical properties make them especially apt for biomedical applications (Datt et al. 2012; Bhaumik 2017).

These porous nanomaterials can be synthesized by using inorganic, organic, or organic-inorganic hybrid framework building units/metal ions with or without using template molecules as the structure-directing agents. Historically, the field has evolved from synthetic Al-rich zeolites, followed by high-silica zeolites and then metallosilicates, followed by aluminophosphates, mesoporous silica, and a range of allied mesoporous materials. The development of periodic mesoporous organosilicas (PMOs), mesoporous carbons, metal-organic frameworks (MOFs), zeolitic imidazolate frameworks (ZIFs), porous organic polymers (POPs), covalent organic frameworks (COFs), and porous metal phosphates/phosphonates has added further dimensions to the family of porous nanomaterials. Their pore topologies, sizes, and surfaces can be tuned as per the requirement (Bhaumik 2017).

The use of various inorganic nanoparticles as drug carriers is becoming increasingly common. The functionality of nanocarriers in real-life environments explains the enthusiasm for their use. However, the foremost consideration regarding the use of NMs in medicine pertains to their safety. Several functionalities are typically added onto nanocarriers, but the most crucial feature to be administered is that they

should possess a long residence time in blood circulation. This sufficiently relates to their coatings because it is the outmost layer which dictates their first interactions with the surroundings and often determines their biofate (Tamarov et al. 2018). The use of porous inorganic nanoparticles as drug carriers for cancer therapy has the potential to improve the life expectancy of the patients affected by this disease. However, much work is needed to overcome their drawbacks, which are aggravated by their hard nature (Baeza et al. 2017).

Nanoclays provide opportunities for developing economical and multifunctional nanocarriers. Functionalization of clay nanoparticles with different polymers and surfactants is essential to manipulate the electrostatic interactions between chemical loading and clay particles (Zhang et al. 2013). Nanoclays are naturally occurring clay minerals with at least one dimension in the range of 1–100 nm. These are found in the form of anionic as well as cationic clays, depending on the surface-layer charge and the types of interlayer ions. Montmorillonite, kaolinite, laponite, halloysite, bentonite, hectorite, laponite, sepiolite, saponite, and vermiculite are among the major nanoclays (Peña-Parás et al. 2018). Nanoclays are used widely as reinforcements for polymer matrix composites to improve the mechanical, thermal, and anticorrosion properties. Because of being nontoxic, nanoclays and their composites have been studied for biomedical applications such as bone cement, tissue engineering, drug delivery, wound healing, and enzyme immobilization, among others (Dasan 2015; Peña-Parás et al. 2018).

## 2.7 Medical Significance of Nanostructures

Nanotechnology-enabled drug delivery has created a great impact on every mode of drug administration, from oral to injectable. The nanotechnology-based drugs are able to permeate through cell walls. In various bone disorders, such as bone fractures, osteoarthritis, osteoporosis, or bone cancers, the traditional implant materials have a short lifetime and resistance inside the body and are affected by the loosening, inflammation, infection, osteolysis, and wear debris side effects. In fact, the bone is a nanocomposite consisting of a nano-dimension protein-based soft hydrogel template, water, and hard inorganic components such as hydroxyapatite, HA (20–80 nm long and 2–5 nm thick). This self-assembled nanostructure closely surrounds and affects the mesenchymal stem cell; osteoblast (bone-forming cell), osteoclast, and fibroblast adhesion; proliferation; and differentiation (Wang et al. 2016b). Another bone structure composed of nanosystems is the cartilage, which is a low regenerative tissue, containing a small percentage of chondrocytes but dense nanostructure rich in collagen fibers, proteoglycans, and elastin fibers. The limited regenerative capacity of cartilage relates to the lack of chondrocyte mobility in this dense nanostructure and to the absence of progenitor cells and vascular networks necessary for an efficient tissue repair (Wang et al. 2016b). The excellent mechanical and biomimetic properties of nanostructures have rendered them suitable for improving the bone cell and chondrocyte functions.

Due to their biocidal, anti-adhesive, and delivery characteristics, nanomaterials prevent the formation of biofilms within the oral cavity. Metal NPs in the size range of 1–10 nm have particularly shown significant biocidal activity against bacteria. The most common NPs used for orthodonticsapplications are those of Ag, Cu, Au, Zn, $TiO_2$, magnetite chitosan, quaternary ammonia NPs, fluorapatite, fluorohydroxyapatite, or hydroxyapatite (Khurshid et al. 2015). The success of various forms of NPs (including liposomes, polymer particles, micelles, dendrimers, quantum dots, gold NPs, and carbon nanotubes) that have been synthesized and tested for therapeutic applications depends primarily on their ability to avoid/minimize accumulation at undesired sites and reach the therapeutic site at necessary doses. In fact, their ultimate biodistribution is dependent on a variety of biological barriers they come across in the human body. For intravascular delivery of NPs, for instance, the barriers arise in the form of (a) immune clearance in the reticuloendothelial system comprising of the liver and spleen, (b) permeation across the endothelium in the target tissues, (c) penetration through the dense interstitial space and extracellular matrix of the target tissue, (d) endocytosis and intracellular localization in the target cells, and (e) diffusion in the cell vesicles and cytoplasm/nucleus (Barua and Mitragotri 2014). The alternative modes of NP penetration into the human body are mainly through the skin, lungs, and gastrointestinal (GI) tract (Yah et al. 2011; Wang and Wang 2014; Riasat et al. 2016).

The skin, the outermost and the largest organ surface, functions as the first-line barrier between the external environment and the internal organs of the human body. With increasing exposure of the human skin to NPs, the issue of the capacity of NPs to penetrate through the skin has become a crucial subject of research (Liang et al. 2013). NP penetration through the skin barrier depends on their size; particles of 500–1000 nm can penetrate to lower levels of the human skin in which the smaller particles penetrate deeper (Ryman-Rasmussen et al. 2007; Nasir 2010). Given the potential of solid NPs to penetrate the stratum corneum and diffuse into the underlying structures, their topical use raises a genuine health and safety issue (Wang and Wang 2014). These ultrafine particles can enter the body through skin pores, debilitated tissues, injection, and the olfactory, respiratory, and intestinal tracts and may lead to various adverse biological effects. Some efforts have been made to determine the portal routes of nanoscale materials on experimental animals (Yah et al. 2011; Lin et al. 2016).

The skin is known to protect the body by resisting the penetration of molecules and microorganisms present in the external environment and preventing excessive loss of water to maintain homeostasis. The main resistance comes from the stratum corneum, which is made of layers of flattened corneocytes surrounded by lipid bilayers composed of ceramides in particular. However, this also resists penetration of most of the topically applied compounds, although the transcellular route through corneocytes may help to some extent. Hair follicles and associated sebaceous glands as well as sweat glands, despite forming a minute portion (nearly 0.1%) of the total area of skin surface, provide potential routes of access into the skin and hence have importance for nanosystems (Nastiti et al. 2017).

Microemulsion (ME) and nanoemulsion (NE) have also been used as the potential delivery vehicles for transferring drug molecules through the stratum corneum. Terminology suggests that NE should have a smaller particle size than ME, as nano and micro refer to $10^{-9}$ and $10^{-6}$, respectively, but in fact the size range of the two systems is hardly different. Further, both have a low polydispersity (up to nearly 10%) and are similar in physical appearance and texture. However, while ME shows thermodynamic stability, NE is thermodynamically unstable but kinetically stable (McClements 2012; Gupta et al. 2016). Moreover, ME is broken by changes in temperature and/or dilution, whereas NE remains stable. So, the basic difference between NE and ME pertains only to their thermodynamic stability, the same being responsible for the higher energy input required for NE preparation (Nastiti et al. 2017).

Currently, lung ailments such as cystic fibrosis, COPD, and asthma are treated with inhaled drugs such as corticosteroids that adhere to the walls of air passages. Various polymeric nanoparticles, such as liposomes and dendrimers, among others, are now used as carriers, sometimes in combination with small molecules, cytokines, growth factors, and/or pluripotent stem cells. Thick mucus often built up on the route passages lessens the effectiveness of the delivery system of these muco-adhesive particles (MAPs). The hydrophobic and electrostatic forces within this mucus layer facilitate trapping of particles and preventing their access to the airway epithelium. Proper size and charge of NPs help overcome this challenge. Coating the NPs with a high density of low molecular weight polyethylene glycol (PEG) renders their surface neutrally charged, thus improving their transport across the mucus layer (Bonner 2016). Recently, researchers turned to NPs that are small enough to make their way through mucus membranes direct to the lining of the lungs, providing medication to affected areas. These mucus-penetrating particles (MPP) remain in the lungs for long, releasing medication for an extended period of time (Iyer et al. 2015; Schneider et al. 2017). Aerosolization or inhalation of colloidal systems has shown huge potential for targeted drug delivery. Moreover, the surfactant-associated proteins present at the interface strengthen the impact of these formulations by reducing surface tension (Paranjpe and Müller-Goymann 2014; Yeagle 2017).

On the other hand, certain NPs such as ceria (cerium dioxide NPs) could cause mitochondrial damage leading to a decrease in cell viability and a progress of apoptosis and induce autophagy in human peripheral blood monocytes (Hussain et al. 2012). Likewise, $TiO_2$nanoparticles could induce oxidative stress-mediated acute lung inflammation. Similarly, pulmonary exposure to ZnO NPs might cause transient increases in acute lung inflammation (Xia et al. 2016). Surface area of NPs and their dissolution property are important in deciding their toxic potential. Thus, toxicity caused by the ultrafine NP penetration to the lungs, if any, merits special attention. Exposure to NPs in occupational or environmental settings often causes pulmonary diseases or exacerbates the preexisting ones on one hand, while the same NPs prove highly useful for therapeutic applications in nanomedicine, on the other.

The gastrointestinal (GI) tract offers extensive surface area (300–400 $m^2$) for drug absorption by absorptive epithelial cells (enterocytes). It contains many other types of cells including mucin-secreting goblet cells, specialized M cells associated with Peyer's patches responsible for antigen transportation through dendritic cells,

endocrine cells, and Paneth cells, which may facilitate the process of drug absorption. However, many hydrophobic and hydrophilic drugs have poor bioavailability, when administered orally, due to their inadequate physicochemical (solubility, stability) and/or biopharmaceutical (permeability, metabolic stability) properties. Oral delivery is even more challenging for biologics (e.g., peptides, proteins, and nucleic acids) due to their hydrophilicity (leading to low permeability), high molecular weight, and poor chemical/enzymatic stability in the GI tract (Date et al. 2016). Penetration of NPs into the human body through intestinal barrier depends strongly on their size; the smaller the particle diameter, the faster they could penetrate the mucus to reach the colonic eutrocytes; 14 nm diameter permeated within 2 min, 415 nm particles took 30 min, while 1000 nm particles were unable to cross this barrier (Hillyer and Albrecht 2001).

Due to the presence of marked physiological and biochemical barriers to peptide absorption in the GI tract, oral delivery of peptide drugs remains a challenge. Nano formulations can improve drug stability in the harsh GI tract environment, increasing drug solubility and bioavailability, enabling the targeting of specific sites, and providing sustained release in the GI tract. However, the unique and diverse physiology along the GI tract, including the widely varying pH, mucus that varies in thickness and structure, and numerous cell types, forms a significant barrier to effective delivery (Date et al. 2016; Riasat et al. 2016). Especially designed NPs, which may be able to (i) protect their cargo against enzymatic breakdown in the gut lumen and by intestinal cells, (ii) take the peptide safe across the mucus barrier, and also (iii) pass the intestinal epithelium that lines the intestinal lumen, are expected to deliver goods. To overcome the problem, absorption enhancers have been incorporated in many oral peptide delivery systems. Efforts have been made in pharmacological trials to adopt the paracellular route via tight junctions and the transcellular transcytosis route to pass the epithelial layer. Tight junctions can be modulated by MLC phosphorylation via MLCP inhibition, resulting in significant absorption of peptides. The transcellular pathways via relatively well-explored transcytotic pathways (as those for vitamin B12 and IgG) have proved promising for the oral delivery of peptides encapsulated in NPs (Lundquist and Artursson 2016). However, it is to be seen how far the promising results observed with tight junction regulation and transcytosis in small animals can be applicable to humans. It is believed that mucoadhesive surface properties on particles delivered to the GI tract improve oral absorption or local targeting of various difficult-to-deliver drug classes. Delivering drugs in non-muco-adhesive MPP might provide enhanced particle (drug) distribution in the GI tract (Maisel et al. 2015).

## 2.8 Conclusion

Besides the important role of size in nanosystems, the chemical properties of NMs, such as composition, structure, and molecular weight, determine their effectively significant roles vis-à-vis human health. Further, their applications as drug delivery

systems and their potential for diagnosis and therapy are the major tools in nanomedicine. The nanosized systems are vital factors in developing the intracellular systems, architecting the biomimetic polymers, and controlling the delivery and action of advanced polymers in bio-systems for therapeutic purposes. In conclusion, it can be genuinely expected that a variety of nanostructures, with their unique physical and chemical properties, are likely to bring a great revolution in the field of medicine and healthcare, provided serious investigations are undertaken to understand the various apparent and hidden aspects of their toxicity and its adverse effects on the human biological systems.

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