1.1 Nanotechnology

Nanotechnology is a rapidly developing field in modern science, however the central concepts of nanotechnology are developed long years ago (Sadhasivum 2010). The main goal of nanotechnology is to develop the materials smaller than 100 nanometers (nm). The prefix of nanotechnology derives from ‘nanos’ – the Greek word for dwarf. A nanometer is a billionth of a meter, or to put it comparatively about 1/80,000 of diameter of a human hair (Karkare 2008). The idea of nanotechnology was first offered by physicist Richard Feynman, in a lecture entitled Room at the Bottom, he revealed the possibilities available in the molecular world; Feynman’s vision spawned the discipline of nanotechnology, and we are now gathering the tools to make his dream a reality (Goodsell 2004). Zsigmondy is attributed with coining the term nanometer for characterizing the particle size. He was who determined it as 1/1,000,000 of a millimeter. He was developed a system of classification based on particle size in the nanometer range (Sadhasivum 2010). Richard Smalley was the foremost leader in nanotechnology. He has often been noted as the “Father of Nanotechnology.” Richard Smalley is mostly known for his work with carbon nanotubes (Mongillo 2007). Nanotechnology provides tuneable material properties were stated in Norio Taniguchi’s paper where the term nanotechnology was first used in scientific publication (Zhang and Webster 2009).

In recent years, research in this field has grown exponentially continue to develop nanomaterials with unique and enhanced properties. Nearly every field of science has been affected by the tools and ideas of nanotechnology, and breakthroughs have been made in computing, medicine, sensing, energy production, and environmental protection (Poole and Owens 2009). Advances in this field largely depend on the ability to synthesize nanoparticles.
of various materials, sizes, and shapes, as well as to efficiently assemble them into complex architectures (Evanoff and Chumanov 2005).

1.2. Nanoparticles

Nanoparticles (NPs) are being viewed as fundamental building blocks of nanotechnology (Leela and Vivekanandan 2008). Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm (Mohanraj and Chen 2006). Nanoparticles or nanocrystals derived from metals, semiconductor or oxides and they are interest for their mechanical, electrical, magnetic, optical, chemical and other properties and they have used in various applications (Sadhasivum 2010).

Nanoparticles have large surface area and there is no inner mass, that is their surface-to-mass ratio is extremely high (Theodore and Kunz 2005). Nanoparticles have been used for a very long time, probably the earliest use being in glazes for early dynasty Chinese porcelain. A Roman cup, called the Lycurgus cup, used nanosized gold clusters to create different colours depending on whether it was illuminated from the front or the back (Holister et al., 2003b). Nanoparticles of gold and silver were used by the artisans of Mesopotamia to generate a glittering effect to pots. The first scientific description of the properties of nanoparticles was provided in 1857 by Michael Faraday in his famous paper “Experimental relations of gold (and other metals) to light” (Faraday 1857).

Mineral nanomaterials such as silica (SiO$_2$) and the various forms of asbestos are among the oldest natural, environmental nanomaterials. Silica, asbestos and black carbon represents prominent nanomaterials in antiquity as well as the present, and probably in the future. Other mineral oxides such as hematite (Fe$_2$O$_3$) and rutile or anatase (TiO$_2$) also represent nanomaterial materials having ancient product value which has persisted for thousands of years to the present (Murr 2009).
Nanoparticles can be broadly grouped into two namely organic and inorganic nanoparticles. Organic nanoparticles may include carbon nanoparticles and the inorganic nanoparticles may include magnetic nanoparticles, Nobel metal nanoparticles (like gold and silver) and semiconductor nanoparticles like (titanium dioxide and zinc oxide) (Prathna et al., 2010). Smallness of structure has various advantages as well as achievement of new properties of materials such as tremendous increment of surface capability due to enlarged surface-volume ratio, shortened transport time of molecules by short distance, high linear flow rate acquirement with tiny sample loading system, almost vast development of detection spot in the case of arrays, etc (Choi et al., 2007b).

Nanoparticles exhibit completely new or improved properties based on specific characteristics such as size, distribution and morphology, if compared with larger particles of bulk material. Nanoparticles present a higher surface to volume ratio with decreasing size. As specific surface area of nanoparticles is increased, their biological effectiveness also increases due to the increase of surface energy (Song and Kim 2009). Nanoparticles of free metals have been extensively researched because of their unique physical properties, chemical reactivity and potential applications in catalysis, biological labelling, biosensing, drug delivery, antibacterial activity, antiviral activity, and detection of genetic disorders, gene therapy and DNA sequencing.

1.3. Synthesis of NPs

Basically two approaches are used for the synthesis of nanoparticles namely Bottom-up approach and Top-down approach. Bottom-up approach where materials are formed by self-assembly with an atom by atom or molecule by molecule design creating complex structures. In Bottom-up approach, the limitations are incomplete understanding of the synthesis processes, including how to control the factors to obtain desirable materials and the types of structures created. Top-down approach starts with bulk materials ends in the
formation of nanomaterials through a series of degradation processes. The limitations of top-

down approach are the size, the shape and poor reproducibility of the materials formed. There

are basically two broad areas for the synthesis of nanostructured materials including physical

tochemical methods. Some of the commonly used physical and chemical methods

are inert gas evaporation, ion sputtering, solvothermal synthesis, Chemical vapor deposition,

reduction and sol gel technique (Smith et al., 2006; Prathna et al., 2010).

1.4. Properties of NPs

Nanoparticles have much larger ratio of surface area to mass than ordinary

materials, at the surface of materials the biological and chemical reactions take place and so

we would expect that the nanoparticles to be more reactive than bulk material (Davies 2009).

Nanoparticles have different properties such as optical, electrical, magnetic, chemical, and

mechanical than bulk material because of size range, quantum effects start to predominate

due to surface area to volume ratio is increased (Holister et al., 2003b).

The increase of relative surface area makes them very interesting for industrial

applications, and high surface area is a critical factor for instance efficient catalysis and in

structures like electrodes. Nanomaterials have been engineered to have both high strength and

ductility, two properties which have been mutually limited characteristics for conventional

materials. Nanoparticles coating is the technique of dressing materials with thin layers of

nanoparticles. The coating can improve toughness and resistance to wear, corrosion,

oxidation and cracks. By controlling the size of constituent grains and surface structures,

optical properties of nanostructured materials, such as reflectance and transmission of light

can be engineered. Nanoparticles can able to absorb or scatter light selectively by controlling

their grain sizes. One new feature of the atomic arrangement in nanostructured materials is

that, a high percentage of atoms are at grain surfaces because surface atoms are more
chemically reactive than bulk atoms, nanostructured materials have also used in chemical processes (Wang and Dortmans 2004).

1.5. Various Types of NPs

Different types of nanoparticles are present; they are including Quantum Dots, Photonic, Crystals, Liposome, Gliadin nanoparticles, Polymeric nanoparticles, Solid Lipid Quantum nanoparticles, others-gold, carbon, silver, etc. They have been synthesized and used for various applications.

1.5.1. Photonic crystals

Photonic crystals are periodic dielectric or metallo-dielectric nanostructures that are designed to affect the spread of electromagnetic waves (EM) in the same way; the periodic dielectric potential in a semiconductor crystal affects the electron motion by defining allowed and forbidden electronic energy bands. The absence of allowed propagating EM modes inside the structures, in a range of wavelengths called a photonic band gap, gives rise to distinct optical phenomena such as inhibition of spontaneous emission, high-reflecting omnidirectional mirrors and low-loss-wave guiding among others (Bandyopadhyay and Miller 2001).
Photonic crystals are attractive optical materials for controlling and manipulating the flow of light. They are of great interest for both fundamental and applied research, and are expected to find commercial applications soon (Lodahl et al., 2004) as shown in figure 1.

1.5.2. Liposomes

Liposomes are lipid-based small vesicles consisting of one or more concentric lipid bilayer surrounding aqueous compartments and used extensively in the pharmaceutical and cosmetic industries because of their capacity for breaking down inside cells, once their delivery function has been met. Liposomes are the first engineered nanoparticles used for
drug delivery but limitations such as their propensity to combine together in aqueous environments and release their payload have lead to replacement of liposomes (Tallury et al., 2010; Rao et al., 2011).

1.5.3. Solid Lipid Nanoparticles (SLN)

Solid lipid nanoparticles have been developed as alternative delivery system to conventional polymeric nanoparticles. SLNs are sub-micron colloidal carriers (50-1000 nm) which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. SLNs are the combine advantages of polymeric nanoparticles, fat emulsions and liposomes. They are biodegradable, biocompatible and non-toxic (Muller et al., 2000).

1.5.4. Metal Nanoparticles

Synthesis of noble metals has become compulsory issue in the present due to the increase of their market values in recent times (Binupriya et al., 2010). The metals such as gold, silver and copper have been widely used for the synthesis of stable dispersion of nanoparticles, which are being useful in the area of photography, biological labelling, photonics, optoelectronics and surface-enhanced Raman scattering (SERS) detection (Sharma et al., 2009; Simth et al., 2006; Kearns et al., 2006).

The synthesis of metal Nanoparticles synthesis using various physical and chemical methods, these methods intended at controlling the physical properties of particles. (Sadhasivum et al., 2010). Nowadays noble metal nanoparticles play a vital role in the fields of medicine, biology, physics, chemistry, material science (Welchons 2007).

1.5.5. Carbon Nanotube (CNT)

In 1991 Iijima published fundamentals about carbon nanotube, make it a key component in Nanotechnology. In the past decade research in the field of carbon nanotube has grown extremely (Paul and samdarshi 2011). Among carbon nanostructured materials carbon nanotubes are one of the representative paradigms, continue to attract tremendous
attention in the past two decades because of their unique physical and chemical properties (Yi-jun et al., 2011).

Due to their stable structure of elemental carbon, CNTs are insoluble in organic solvents and have very high long range van der Waals forces of attraction so they have a tendency to aggregate together and it is very difficult to disperse (Dutta et al., 2011). The CNTs are used in power electronics, molecular electronics, energy storage, biomedicine due to their novel structure and remarkable mechanical, thermal and electrical properties (Bianco et al., 2005).

1.5.6. Dendrimers

Dendrimers are large and complex molecules with very well defined chemical structures. Dendrimers are monodisperse (basically meaning of a consistent size and form) macromolecules with a regular and highly branched three dimensional design. They consist of three major architectural components; they are core, branches and end groups (Holister et al., 2003a). Dendrimers are a relatively new class of synthetic, nanospherical and low dispersity macromolecules. Dendrimers have wide range of applications including delivery carriers of drug, and DNA, imaging agents, and as tissue engineering scaffolding (Oliveira et al., 2008).

1.5.7. Early history

The concept of nanotechnology though considered to be a modern science has its history dating to as back as the 9th century. Nanoparticles of gold and silver were used by the artisans of Mesopotamia to generate a glittering effect to pots. The first scientific description of the properties of nanoparticles was provided in 1857 by Michael Faraday in his famous paper “Experimental relations of metals (gold) to light” Faraday (1857). In 1959, Richard Feyman gave a talk describing molecular machines built with atomic precision. This was
considered the first talk on nanotechnology. This was entitled “There’s plenty of space at the bottom”. The 1950’s and the 1960’s saw the world turning its focus towards the use of nanoparticles in the field of drug delivery. One of the pioneers in this field was professor Peter Paul Speiser. His research group at first investigated polyacrylic beads for oral administration, then focused on microcapsules and in the late 1960s developed the first nanoparticles for drug delivery purpose and for vaccines. This was followed by much advancement in developing systems for the transport of drugs across the blood brain barrier. In Japan, bound 5-fluorouracil to the albumin nanoparticles, and found denaturation temperature dependent differences in drug release as well as in the body distribution in mice after intravenous tail vein injection. An increase in life span was observed after intraperitoneal injection of the nanoparticles into Ehrlich Ascites Carcinoma-bearing mice.

1.5.7. Nanomaterials

Nanomaterials are engineered structures having all of their physical dimensions between 1-100 nm (Niemeyer 2001). Their physical structure is therefore larger than the atomic but smaller than the bulk scale of materials gain interesting optical, electronic and catalytic properties. Some metal nanoparticles display intense surface Plasmons that result in very strong optical, electronic and catalytic properties. Some metal nanoparticles display intense surface plasmons that result in very strong optical absorbance (Lee et al., 2004: West and Halas 2003). Semiconductor nanoparticles with dimensions below a material-specific threshold undergo quantum confinement of their electrons, and convert ultraviolet absorbance into fluorescence. Catalytic properties are observed in nanoparticles made of reactive elements (e.g. silver) because their high surface to volume ratio exposes a large proportion of atoms to the surface (Narayanan and Sakthivel 2010.). These properties can be exploited and have obvious biomedical applications. A common feature of nanotechnology applications is their dependence on the size, shape and composition of the material. This dependence of
function on structure provides engineers with a mechanism to tune optimize the behaviour of materials towards specific applications.

A second advantage of nanomaterials is that their scale overlaps with that of biologically relevant molecules (i.e. deoxyribonucleic acid and proteins) and structures (i.e. ribosomes, viruses). The integration of synthesized nanomaterials with biomolecules can therefore have profound effects on either or broth, providing an additional basis for novel applications. For example, small (i.e. 2 nm diameter) metallic particles can be conjugated to antibodies (approximate hydrodynamic diameter (HD) of 15 nm) and provide a tag for sensing their presence in an assay. Alternatively, large (100 nm) particles could have their surface covered with antibodies; increasing the antibody’s binding kinetics through higher avidity and providing a mechanism for the particle interact with a target, or to be captured on a substrate (Lee et al., 2004). The interaction of nanotechnology with biomaterials also provides a means for predictable assembly of synthetic materials into multi-component devices.

Nanotechnology-based devices can be considered as complexes of either a single or various types of nanomaterials, assembled or co-operating in a manner that provides some emergent function (Niemeyer et al., 2001). For example, an engineered implant for drug delivery could include multiple nanomaterials integrated together, with the whole providing an improved drug release profile versus a single nanoparticle design (Tasciotti et al., 2008). This relatively new concept has emerged from the rationale that biomedical knowledge of DNA hybridization and protein binding can be applied to allow predictable assembly of inorganic structures (Niemeyer et al., 2000; Aldaye et al., 2008, Aldaye et al., 2009).
1.5.8. Nanoparticles

Nanoparticle are particles, having one or more dimensions of the order of 100nm or less have attracted great attention due to their unusual and fascinating properties, and applications advantageous over their bulk counterparts (Daniel et al., 2004). Nanoparticle may provide solutions to technological and environmental challenges in the areas of solar energy conversion, catalysis, medicine, and water treatment (Dahl et al., 2007; Hutchison 2008). Nanomaterials often show unique and considerably changed physical, chemical and biological properties compared to their macro scaled counterparts (Li et al., 2001).

1.5.9. Properties of nanoparticles

A quantity of physical phenomena become more pronounced as the size of the system decreases. Certain phenomena may not come into play as the system moves from macro to micro level but may be significant at the nanoscale. One example is the increase in surface area to volume ratio which alerts the mechanical, thermal and catalytic properties of the material. The increase in surface area to volume ratio leads to increasing dominance of the behaviour of atoms on the surface of the particle over that of those in the interior of the particle, thus modifying the properties. The electronic and optical properties and the chemical reactivity of small clusters are completely different from the better known property of each component in the bulk or at extended surfaces. Some of the size dependant properties of nanoparticles are quantum confinement in semiconductors, surface Plasmon resonance in some metallic nanoparticles and Para magnetism in magnetic nanoparticles.
Surface Plasmon resonance refers to the collective oscillations of the conduction electrons in resonance with the light field. The surface Plasmon mode arises from the electron confinement in the nanoparticle. The surface Plasmon resonance frequency depends only on the metal, but also on the shape and size of the nanoparticle and dielectric properties of the surrounding medium (Jain et al., 2008). For example, noble metals, especially gold and silver
nanoparticles exhibit unique and tunable optical properties on account of their surface Plasmon resonance as shown in Fig.2.

1.5.10. Microorganism

Sulfate-reducing bacteria form a physiological group with the common property of using sulfate as the main electron acceptor during anaerobic and aerobic metabolism (Widdel and Bak 1992: Widdel and Hansen 1992). They can be differentiated on the basis of numerous criteria including complete or incomplete oxidation of electron donors species that exhibit incomplete oxidation produce low-molecular weight fatty acids, mainly acetate, as the end products their metabolism. Bacteria sulfate reduction is an important process of mineralization of organic matter in anoxic environments, especially in marine and hyper saline systems (Jorgensen 1982: Oren 1988: Caumette 1993),

**Kingdom:** *Serratia nematodiphila*

**Phylum:** Proteobacteria

**Class:** Gammaproteobacteria

**Order:** Enterobacteriales

**Family:** Enterobacteriaceae

**Genus:** *Serratia*

The genus *Serratia* belongs to the family *Enterobacteriaceae*. Some members of the genus *Serratia* have clinical importance (Grimont and Grimont 1992: Brenner 1984) and other members produce pigments identified as prodigiosin. The novel strain was associated symbiotically with the entamopathogenic nematode. *Serratia nematodiphila* (*ne*-ma.to.di’phi.la N.L. n. Nematodum nematode: Gr.adj. pjilos loving; N.L. fem. Adj. nematodiphila nematode *Heterorhabditidoides chongmingenis*. *S. nematodiphila* cells are
gram-negative, short rods, red-pigmented, non-spore forming; fluorescent strain was isolated from the intestine of the nematode *Heterorhabditidoides chongmingenis* (Zhang et al., 2007). *Serratia sp.*, are opportunistic pathogens and are one of the ten most common causes of bacteria in North America.

**Kingdom:** Klebsiella pneumoniae

**Phylum:** Proteobacteria

**Class:** Gammaproteobacteria

**Order:** Enterobacteriales

**Family:** Enterobacteriaceae

**Genus:** Klebsiella

**Species:** pneumoniae

*Klebsiella* was named after the German bacteriologist Edwin Klebs (1834 -1913). Multiple -resistant *Klebsiella pneumoniae* have been killed *in vivo* interperitoneal intravenous or intranasal administration of phages in laboratory tests. *Klebsiella pneumoniae* is a gram-negative, non-motile, encapsulated, lactose fermenting, facultative aerobic, rod shaped bacterium found in the normal flora of the mouth, skin and intestine. The choice of specific antimicrobial agents depends on local susceptibility patterns and on the other part of the body that is infected.

**1.5.11. Biosynthesis of Nanoparticles**

Biosynthesis of stable nanoparticles has received considerable attention due to the unique physicochemical characteristics of nanoparticles, including catalytic activity, optical properties, electronic properties, antibacterial properties and magnetic properties (Bar et al., 2018).
2009; Tuutijarvi et al., 2009; Rassaei et al., 2008). Specific surface area is relevant to catalytic activity and other related properties such as antimicrobial activity of AgNPs (Bae et al., 2010; Gurunathan et al., 2009; Pal et al., 2007). Silver nanoparticle has wide range of applications in spectrally selective coatings for solar energy absorption, optical receptors, bio-labelling intercalation materials for electrical batteries, filters, antimicrobial agents and sensors (Smitha et al., 2008). Nanoparticles can be synthesized by physical, chemical and biological methods. Non-biological methods of nanoparticle synthesis used to cause accumulation of toxic and non-eco-friendly by products. The development of biological approaches for the synthesis of nanoparticles by intracellular or extracellular reduction is essential for the production of ecofriendly and non-toxic nanoparticles. Several biological systems including plants, bacteria, fungi and algae have been used for the synthesis of nanoparticles (Kalimuthu et al., 2008; Kowshik et al., 2003). Among the biological methods, plant extract based green synthesis of nanoparticles is the best ecofriendly alternative tool to available conventional chemical and physical methods (Willner et al., 2006). Plants provide a better platform for nanoparticle synthesis. Silver has a greater affinity towards sulfur or phosphorus-containing biomolecules present in the cells of plant leaves. Hence, sulfur orphosphorous containing proteins in the membrane or inside the cells are considered to be the preferential sites for silver nanoparticle binding (McDonnell and Russell, 1999). The plant material based production of silver nanoparticles has wide range of application in medical industries in food processing industries (Tankhiwale and Bajpai, 2010) and in textile industries. In medicines, silver and silver nanoparticles deliver extensive application including skin ointments and creams containing silver to infection of burns and open wounds (Duran et al., 2005). Plants have been used for low-cost, energy efficient and non-toxic production of metallic nanoparticles. Silver nanoparticle synthesis have been reported by Rastogi and Arunachalam (2011) in Allium sativum, in Anacardium occidentale, and
(Chandran et al., 2006) in *Aleovera* plant extract. Also the formation of gold and silver nanoparticles was reported for the first time by using living plants (Gardea-Torresdey et al., 2002). Wound healing process occurs in several steps that involve blood coagulation, inflammation, cell proliferation, remodelling of connective tissue and acquisition of wound strength (Suresh Reddy et al., 2002). The aim of wound care is to promote wound healing in the shortest time possible, with minimal pain, discomfort, and scarring to the patient and must occur in a physiological environment conductive to tissue repair and regeneration. Physiologically, wound healing is mainly depends on interaction between a variety of cells, biochemical mediators and extra cellular matrix molecules (Singer and Clark, 1999). Development of drugs/medicines to treat wounds has been conducted for several years. At present different medicinal plants included into the healthcare systems. Among them Naringi *crenulata* plant crude extract possess skin lighting and cosmetic activities or exhibit antimicrobial properties which are beneficial uses in skin wound repair mechanisms. *N. crenulata* (Roxb.) belonging to the family Rutaceae occurs naturally in Southeastern Asia. Its synonym is *Hesperethusa crenulata* (Roxb.) M. Roem or *Limonia crenulata* Roxb. Traditionally, *N.crenulata* have long been valued for their medicinal and cosmetic property. The important ingredients present in the *N. crenulata* leaf extracts are octadecanoic acid, T-tetradecenal (Z) and n-hexadecanoic acid protein, lipid, carbohydrate, reducing sugar, phenol, tannin, flavonoid, saponin, and alkaloids (Sampathkumar and Ramakrishnan, 2011). In survey of historical accounts on old folk medicines all parts of *N. crenulata* viz. root, stem, bark, leaf and fruit are used in several ailments. The leaves of *N. crenulata* used in the treatment of epilepsy (Ramani et al., 2010). Root is used as remedy for cobra bite (Sekhar et al., 2011) stem powder serve as antiaging (Kanlayavattanakul et al., 2009) and bark is used to treat puerperal fever (Murty et al., 2010). Although various parts of *N. crenulata* plant are being used for treatment, skin lightening agent, Arbutin was found to be high in leaf extracts.
Different medicinal plants extracts have been widely used for the treatment of wound healing process in the recent past. Hence an effective and powerful wound healing agents from medicinal plants are not available at present. Therefore, the investigation for the development of efficient wound healing agents from medicinal plants has become a thrust area of current research.

1.5.12. SYNTHESIS OF SEMICONDUCTOR NANOPARTICLES

The reliance of future technologies on developing scalable and cost-effective methods for the fabrication of one-dimensional (1D) systems has spurred intense and rapid progress in the area of materials synthesis. Semiconductor nanocrystals constitute an important class of nanomaterials due to their unique size dependant physical and chemical properties that render them applicable in the emerging field of nanoelectronics (Brown et al., 2002). Therefore developing reliable protocols for the synthesis of nanometer scale semiconductor nanoparticles is a problem of great importance. Among semiconductor nanocrystals or colloidal quantum dots (QD’s) have concerned to a great extent interest in both essential research and technical applications since their interesting and novel electronic and optical properties (Sanghi et al., 2009). Sulfide nanoparticles like CdS and ZnS are tremendously explored and find applications as mesoscopic electronic, optoelectrics such as non linear optics, flat panel displays, light emitting diodes, transistor components, fluorescent biolabeling and photocatalysis (Hoffmann et al., 1995), sensor, photoelectric and thermoelectric materials (Cao et al., 2004), photo imaging and photodetection (Mitchell 1998). The lot of interesting properties of semiconductor sulfide nanocrystals are because of electronic quantum confinement and the large number of exposed atoms in the large surface (Roucoux et al., 2002). Quantum confinement in luminescent semiconductors enables modification of the absorption and emission via particle size and shape (Murray et al., 1995: Qiao et al., 2000). Transition metal sulfides are useful as dry lubricants, catalysts and solar
cells (Bonneau et al., 1991). There are few reports on the synthesis of nanocrystals of transition metal sulfides like iron and nickel which show magnetic properties. These magnetic sulfides act as a soft magnetic field paleoclimatic magnetism point of view (Roberts et al., 1995).

Numerous protocols have been designed for the synthesis of sulfides nanocrystallites over a range of composition size and shape (El-Sayed et al., 2004). However most of the methods employ non-polar organic solvents or caustic chemicals. Recently, the biological methods for the synthesis of sulfide nanoparticles are gaining importance since they occur in aqueous medium under ambient experimental conditions of temperature and pressure. Biological methods comprise use of microorganism, small molecules of biological origin, biological templates and small peptides for the synthesis of metal sulfide nanoparticles. Also biological molecules have been used for the capping of sulfide nanoparticles. Living organism can exert tight control on the synthesis of materials (Mann 1996). Therefore, most of the work till date is centered on the use of microorganism for the synthesis of sulfide nanoparticles.
# Table 1: Biosynthesis of Sulfide nanoparticles

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Nanoparticles</th>
<th>Size (nm) /Shape</th>
<th>Location</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfate-reducing Bacteria</td>
<td>FeS</td>
<td>2 / Spherical</td>
<td>Extracellular</td>
<td>Watson et al., 1999</td>
</tr>
<tr>
<td><em>Fusarium oxysporum</em></td>
<td>CdS</td>
<td>5–20 Spherical</td>
<td>Extracellular</td>
<td>Ahmad et al., 2002</td>
</tr>
<tr>
<td><em>Rhodobacter Sphaeroides</em></td>
<td>ZnS</td>
<td>10.5 ± 0.15 Spherical</td>
<td>Extracellular</td>
<td>Bai and Zhang 2009</td>
</tr>
<tr>
<td><em>Desulfobacteraceae</em></td>
<td>CdS</td>
<td>2–5 / Hexagonal lattice</td>
<td>Intracellular</td>
<td>Bai et al., 2006</td>
</tr>
<tr>
<td><em>Rhodobacter Sphaeroides</em></td>
<td>CdS</td>
<td>8 Hexagonal lattice</td>
<td>Intracellular</td>
<td>Dameron et al., 1989</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>CdS</td>
<td>2–5 Wurtzite crystal</td>
<td>Intracellular</td>
<td>Sweeney et al., 2004</td>
</tr>
<tr>
<td><em>Schizosaccharomyces pombe</em></td>
<td>CdS</td>
<td>1–1.5 Hexagonal lattice</td>
<td>Intracellular</td>
<td>Kowshik et al., 2002</td>
</tr>
<tr>
<td><em>Lactobacillus</em></td>
<td>CdS</td>
<td>4.9 ± 0.2 Spherical</td>
<td>Intracellular</td>
<td>Prasad and Jha 2010</td>
</tr>
<tr>
<td><em>Schizosaccharomyces pombe</em></td>
<td>CdS</td>
<td>2 Hexagonal lattice</td>
<td>Intracellular</td>
<td>Dameron et al., 1989</td>
</tr>
<tr>
<td><em>Schizosaccharomyces pombe</em></td>
<td>CdSe quantum dots</td>
<td>-</td>
<td>Extracellular</td>
<td>Sanghi and Verma 2009</td>
</tr>
<tr>
<td><em>Rhodopseudomonas palustris</em></td>
<td>CdS</td>
<td>8 Cubic</td>
<td>Intracellular</td>
<td>Bai et al., 2009</td>
</tr>
<tr>
<td>Magnetotactic Bacterium</td>
<td>Probably polyphosphate</td>
<td>-</td>
<td>Extracellular</td>
<td>Arakaki et al., 2010</td>
</tr>
<tr>
<td>Multicellular Prokaryotes</td>
<td>Fe3S4</td>
<td>-</td>
<td>Intracellular</td>
<td>Lef`ever et al., 2010</td>
</tr>
<tr>
<td><em>Fusarium oxysporum</em></td>
<td>CdSe quantum dots</td>
<td>-</td>
<td>Extracellular</td>
<td>Kumar et al., 2007</td>
</tr>
<tr>
<td>Klebsiella aerogenes</td>
<td>CdS</td>
<td>20–200 nm Spherical</td>
<td>Extracellular</td>
<td>Holmes et al., 1995</td>
</tr>
<tr>
<td>Gluconoacetobacter xylinus</td>
<td>CdS</td>
<td>Cellulose fibre 30 nm</td>
<td>Extracellular</td>
<td>Li et al., 2009</td>
</tr>
<tr>
<td>R. sphaeroides</td>
<td>PbS</td>
<td>1-10 / Spherical</td>
<td>Extracellular</td>
<td>Bai et al., 2009</td>
</tr>
<tr>
<td>M13 bacteriophage</td>
<td>ZnS, CdS</td>
<td>20-nanowires</td>
<td>Extracellular</td>
<td>Mao et al., 2002</td>
</tr>
<tr>
<td>Tobacco mosaic virus (TMV)</td>
<td>CdS, PbS</td>
<td>Nanotubes on surface</td>
<td>Extracellular</td>
<td>Shenton et al., 1999</td>
</tr>
</tbody>
</table>
1.5.13. METAL NANOPARTICLES

Nature world has made noble metals fraction of our daily life. Recently there has been great interest in the advance techniques for the biosynthesis of metal nanoparticle of well clear size, shape, as they discover the applications in areas such as biomedical sciences (Sperling and Parak 2011), drug delivery (Sanpui et al., 2008), catalysis (Hutchison 2008) and electronics. Conservative synthesis methods of metal nanoparticle have involved a number of chemical methods. There is rising pressure to increase clean, non toxic and environmentally benign synthetic technologies (He et al., 2007), various microbes can grow even at elevated metal ion concentration due to their struggle to the metal (Husseiny et al., 2007). As an end result of researchers in the field of nanoparticle synthesis and meeting have turned to biological structure of inspiration. Several microorganisms, both unicellular and multicellular, are well-known produce inorganic materials either intra or Extracellular frequently the nanoscale measurement and of exquisite morphology. Silver nanoparticle shows strong absorption of electromagnetic waves in the visible range due to surface Plasmon resonance (SPR). The conduction electrons of nanoparticles leading irradiation with visible light combined with oscillations due to surface Plasmon resonance (Basavaraja et al., 2008) as shown in Table.1..

Gold nanoparticles have been known as “colloidal gold” long before the development of modern technique. It dates back to the time when colloidal gold was used as a colorant to make ruby glass and ceramic in the 5th century B.C (Pollard et al., 1996). However, Faraday was the first to recognize that the brilliant color is due to the presence of the metallic gold in colloidal form in 1857. He reported the formation of deep red solutions of colloidal gold by reduction of an aqueous solution of chloroaurate using phosphorus a two phase system. With advent of nanotechnology, gold nanoparticles have turned out to play an important role in the field because they have the potential to serve as building blocks for putting nanotechnology
for practical use (Pellegrino et al., 2005; Elghanian et al., 1997). With the development of several synthetic techniques, the concern for environmental contaminations is also heightened as the chemical synthesis protocols needs some toxic chemicals for synthesis. Most of the physical methods deal with enormous consumption of energy to maintain high pressure and temperature employed in the synthesis procedure. Then the increasing interest in biological methods the development of ecofriendly and simple approach for the preparation.

1.5.14. Antibacterial activity

The emerging infectious diseases and the development of drug resistance in the pathogenic bacteria and fungi at an alarming rate is a matter of serious concern. Despite the increased knowledge of microbial pathogenesis and application of modern therapeutics, the morbidity and mortality associated with the microbial infectious still remains high (Kolar et al., 2001). Therefore, there is a pressing demand to discover novel strategies and identify new antimicrobial agents from natural and inorganic substances to develop the next generation of drugs or agents to control microbial infectious. Prior to the extensive use of chemotherapeutics in modern health care system, inorganic antimicrobials such as silver and copper were used since ancient times to treat microbial infections (Moghimi 2005). In the recent times, the advances in the field of nanosciences and nanotechnology has brought to fore the nanosized inorganic and organic particles which are finding increasing applications as amendments in industrial, medicine and therapeutics, synthetic textiles and food packaging materials (Gajjar et al., 2009).

1.5.15. Antibacterial mode of action

Bacteria have different membrane structures, which are the bases of their general classification as gram-positive or gram-negative. Structural differences reside in the organization of the key component of the cell, peptidoglycan, which is located immediately outside the cytoplasmic membrane. The cell wall of gram-positive bacteria contains a
peptidoglycan layer that is ~30 nm thick. Unlike the Gram-positive cell wall, the Gram negative cell walls has only a thin peptidoglycan layer that is ~2-3 nm thick. In addition to the peptidoglycan layer, the Gram –negative cell wall also contains an additional outer membrane composed of phospholipids and lipopolysaccharides, which face into the external environment.

1.5.16. Pesticide

A bacterium is the one of the major causative agents for the human beings and plant diseases around the world. Apart from antibacterial activity of nanoparticles are growing vigorously in many of the medicinal fields. To use the nanotechnology for detection the pesticides very advance one in the agricultural and plant nanotechnology. The detected pesticides were mainly those applied for post harvest treatments and some of them contain chlorine atoms in their structure. DDT chemically known as 1,1,1-trichloro-2,2-bis (4chlorophenyl) ethane was one of the most widely used organochlorine pesticides world over from when its insecticidal properties were first recognized by Muller in 1939 (Anfossi et al., 2004). DDT has proved highly effective in both agricultural and public health applications and more than one million tons of this organochlorine pesticide had been used worldwide (Bochkareva et al., 2002). DDT is banned in many countries due to its deleterious effects on wildlife, human, animal and persistence in the environment. Along with widespread use of different pesticides and their mixtures in the agricultural field, people and governments all over the world have compensated increasing attention to the problem of pesticide multiresidues in the environment and food products. Thus, it is often necessary to identify several pesticides in a complex sample, and the availability of rapid and reliable methods for the on-site detection of multiple pesticides is an urgent need for environmental monitoring purposes. Recent years have witnessed considerable progress in analytical methods for the determination of pesticides residues. Immunoassay has been confirmed as an
alternative for pesticide measurement by virtue of its high selectivity and reliability as well as its rapidity (Aga et al., 1997). Gold nanoparticles have been well utilized for the detection of many pollutants present in the environment. Mercury has been detected in water samples by different research group using different types of gold nanoparticles (Rex et al., 2006; Chen et al., 2007). Various research groups show the possibility to detect endosulfan at parts per million (ppm) levels using gold nanoparticles (Nair et al. 2003). Gold nanoparticles are covalently coupled with acetyl cholinesterase (AChE) to create a biosensor and have been used for the detection of paraxon (Lin et al., 2006). AChE electrode was stabilized by an electrodeposited gold nanoparticle layer and has been used for the detection of carbofuran (Shulga and Kirchho 2007). AChE was immobilized on gold nanoparticle-chitosan interface and was tested for the detection of Malathion (Du et al. 2007). Gold nanoparticle-based surface enhanced fluorescence has been studied for the detection of organophosphorus agents by Dasary et al., 2008. The kind of determination requires expensive equipments and enzyme immunoassays are time consuming. The nano colloidal gold particles could replace the enzymes to be labeled to antibodies in pesticide immunoassay and were used for the detection of pesticide. Furthermore colloidal gold is much more stable than other type of labeling agents such as fluorescent dyes and enzymes (Tanaka et al., 2006).

1.5.17. Applications of silver nanoparticles

In the ever expanding field of nanomaterial research, metal nanoparticle received particular attention due to their wide application in catalysis, electronics, sensing (Huang et al., 2007), photonics, environmental cleanup, imaging, and drug delivery (Guo et al., 2005). Among the metal nanoparticles silver nanoparticles have more applications in many areas, including biomedical, materials science, and catalysis (Fig. 1). This is because of their unique properties when compared with their bulk solid.
1.5.18. Silver Nanoparticles in human health

Nanoparticles have many different effects on human health relative to bulk material from which they are produced (Albrecht et al., 2006). Increase the biological activity of nanoparticles can be beneficial or detrimental. Colloidal silver has also been marketed as a putative health tonic (White et al., 2003). However, when ingesting this material (and silver nitrate) has led to conditions such as argyria (greying of skin pigment), and adversely impact the intestinal flora, although this is largely untested. Exposure of metal containing nanoparticles to human lung epithelial cells generated reactive oxygen species, which lead to oxidative stress and damage of the cells (Limbach et al., 2007). A study on toxic effects of silver nanoparticles was done on zebra fish as a model due to its fast development and transparent body structure. The results show a deposition of particles on organs and severe developmental effects. The biocompatibility and toxicity of silver nanoparticles were exhibited by observing single silver nanoparticle inside embryos at each development stage. The types of abnormalities in zebra fish were strongly dependent on the dose of silver nanoparticles (Asharani 2008) as shown Fig.3.
1.5.19. Catalyst

The application of nanoparticles as catalysts is a rapidly growing field in nanoscience and technology. The properties of noble metal nanoparticles make them ideal materials for nanocatalysis, where reaction yield and selectivity are dependent on the nature of the catalyst surface. Compared to bulk materials, silver nanoparticles have high surface-area-to-volume ratio and thus found to exhibit higher turnover frequencies. Liu and Zhao (2009) used silver nanoparticles supported halloysite nanotubes, with Ag content of about 11% to catalyze the reduction of 4-nitrophenol with sodium borohydride in alkaline aqueous solutions. AgNPs was found to catalyze the chemiluminescence from luminol–hydrogen peroxide system with catalytic activity better than Au and Pt colloid (Guo et al., 2008). Catalytic activity of silver
nanoparticles can be controlled by its size, as redox potential depends on the nanoparticle size (Jana et al., 1999).

1.5.20. Nanoparticles as bactericidal agent

Nanoparticles are incorporated into the wound dressing, and the silver enhanced wound dressings were found invitro consistently kill *Pseudomonas aeruginosa* cultures entirely and kill *Staphylococcus aureus* cultures with >99.99% efficiency (Ong et al., 2008). Silver nanoparticle-impregnated bacterial cellulose exhibited strong antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*. That impregnation, instead of coating the wound dressing with silver nanoparticle or nanocrystal improved the antimicrobial activity of the wound dressing and lowered possibility of the normal human tissue damage (Maneerung et al., 2008). Silver nanoparticles have been used to impart antimicrobial activity to cotton fibers. Cotton samples were immersed in silver nanoparticle solutions and then subjected to a curing process to allow the nanoparticles to adhere to the cotton (El-Rafie et al., 2010). The silver nanoparticles were synthesized using *Klebsiella pneumoniae* and evaluated its antimicrobial activity against *S. aureus* and *E. coli* (Shahverdi et al. 2007a).

1.5.21. Environmental applications

Silver nanoparticles are of great concern to wastewater treatment utilities and to biological systems. The nitrifying bacteria were susceptible to inhibition by silver nanoparticles, which could have detrimental effects on the microorganisms in wastewater treatment. Uses of Ag NPs in domestic products are becoming more common in washing machines, fridges (Maneerung et al., 2008) and food containers to reduce surface mould growths. Ag NPs embedded into socks, to reduce odours, has been shown to leach silver into the environment from washing (Benn and Westerhoff 2008).

Silver may leach from anti-fouling membranes, when used as an application in water purification. Polysulfonate ultrafiltration membranes impregnated with silver nanoparticles were found effective against *E. coli* K12 and *P. mendocina* bacteria strains showed a
significant improvement in virus removal (Zodrow et al., 2009).) reported that separation of cobalt from water samples and silver nanoparticles as a new solid phase extractor provide a simple, selective, fast and precise procedure for the separation and pre-concentration of cobalt. Biofouling formation on the membrane was one of the major contaminations of water. Nanosilver impregnated membranes were resistant to biofouling because the attachment of bacteria to the membrane surface was prohibited by silver ions. Phytoremediation uses plants to purify the water and soil contaminated with heavy metal ions, such as silver. During phytoremediation, metallic ions are absorbed by plants. Accumulation of these ions eventually leads to the synthesis/formation of metal nanoparticles inside the plant’s tissues (Gleba et al., 1999). In phytoremediation, the synthesis of metal nanoparticles in plant tissue results in very high concentrations of the nanoparticles in the plant (Gardea-Torresdey et al., 2005).

1.5.22. Nanoparticles as Sensors

Sensor is a device giving a signal for the detection or measurement of a physical or chemical property to which it responds. Sensors at a nanoscale are very wide spread in biology. Optical sensors based on the absorption method for sensing mercuric ions have great attention due to their easy readout and high throughputs format potential (Nolan and Lippard 2008; Balaji et al., 2006). A nanosensor is a sensor built on the atomic scale based in measurements of nanometers. There have been a number of advances in the research and development of nanosensors for a number of different applications. Some of the major applications are the medical field, national security, aerospace, integrated circuits, and many more. Nanosensors are also used in DNA test to recognize the similar properties of two blood cells. Smitha et al., 2009 Nanosensors are also reduced and discovered strong air pollutants. Wang et al., (2009) synthesized EDTA coated silver nanoparticles as sensor for nitrate determination. Mercuric ions detecting sensors have high sensitivity, short response
time, and selectivity. Nanoscale metal particles are of current interest because they mark a material transition range between quantum and bulk properties (Wang and Asher 2001) as shown in Table 2.

Table 2. Clinically approved nanoparticle-based therapeutics

<table>
<thead>
<tr>
<th>Composition</th>
<th>Trade name</th>
<th>Company</th>
<th>Indication</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal platforms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>Abecot</td>
<td>Enzon</td>
<td>Fungal infections</td>
<td>iv.</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>Ambisome</td>
<td>Glaxo Sciences</td>
<td>Fungal and protozoal infections</td>
<td>iv.</td>
</tr>
<tr>
<td>Liposomal imatinib</td>
<td>DepoCy</td>
<td>SykePharma</td>
<td>Malignant lymphomatous meningitis</td>
<td>i.t.</td>
</tr>
<tr>
<td>Liposomal daunorubicin</td>
<td>Daunorube</td>
<td>Glaxo Sciences</td>
<td>HIV-related Kaposi's sarcoma</td>
<td>iv.</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>Myocet</td>
<td>Zeneus</td>
<td>Combination therapy with cyclophosphamide in metastatic breast cancer</td>
<td>iv.</td>
</tr>
<tr>
<td>Liposomal IRN vaccine</td>
<td>Epival</td>
<td>Berna Biotec</td>
<td>Hepatitis A</td>
<td>i.m.</td>
</tr>
<tr>
<td>Liposomal IRN vaccine</td>
<td>Inflexal V</td>
<td>Berna Biotec</td>
<td>Influenza</td>
<td>i.m.</td>
</tr>
<tr>
<td>Liposomal morphine</td>
<td>DepoDur</td>
<td>SykePharma, Endo</td>
<td>Postsurgical analgesia</td>
<td>Epidural</td>
</tr>
<tr>
<td>Liposomal verteporfin</td>
<td>Visudyne</td>
<td>CLT, Novartis</td>
<td>Age-related macular degeneration, pathologic myopia, ocular histoplasmosis</td>
<td>iv.</td>
</tr>
<tr>
<td>Liposome-PEG doxorubicin</td>
<td>Doxil/Caelyx</td>
<td>Ortho Biotec, Schering Plough</td>
<td>HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer</td>
<td>i.m.</td>
</tr>
<tr>
<td>Micellar estradiol</td>
<td>Estrasorb</td>
<td>Novavax</td>
<td>Menopausal therapy</td>
<td>Topical</td>
</tr>
</tbody>
</table>

Polymeric platforms

- L-Glutamic acid, N-tosyl-L-lysine, and L-tosyl-L-lysine copolymer toxol: Copaxone, TEVA Pharmaceuticals | Multiple sclerosis | s.c. |
- Methoxy-PEG-poly(L-lactide) toxol: Genexol-PM, Sanofy | Metastatic breast cancer | iv. |
- PEG-adenosine deaminase: Adagen, Enzon | Severe combined immunodeficiency disease associated with ADA deficiency | i.m. |
- PEG-anti-VEGF aptamer: Macugen, OSI Pharmaceuticals | Age-related macular degeneration | i.z. |
- PEG-α-interferon 2α: Pegasis, Nektar, Hoffmann-La Roche | Hepatitis B, hepatitis C | s.c. |
- PEG-GCSF: Neulasta, Amgen | Neutropenia associated with cancer chemotherapy | s.c. |
- PEG-HGF: Scavnert, Nektar, Pfizer | Acromegaly | s.c. |
- PEG-asparaginase: Oncaspar, Enzon | Acute lymphoblastic leukemia | i.x., i.m. |
- Poly(allylamine hydrochloride): Renagel, Genzyme | End-stage renal disease | Oral |

Other platforms

- Nanocrystalline aperitinant: Emend, Eli-Lilly, Merck | Antiemetic | Oral |
- Nanocrystalline fenofostat: Tricor, Eli-Lilly, Abbott | Anti-hyperlipidemic | Oral |
- Nanocrystalline sirolimus: Rapamune, Eli-Lilly, Wyeth Pharmaceuticals | Immunosuppressant | Oral |

ADA, adenosine deaminase; GCSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; HIV, human immunodeficiency virus; i.m., intramuscular; i.z., intravenous; IRN, immunopotentiating reconstituted influenza virus; i.x., intrathecal; iv., intravenous; PEG, polyethyleneglycol; s.c., subcutaneous; VEGA, vascular endothelial growth factor.
1.5.23. Nanoparticle-based therapeutics approved for clinical use

In the past two decades, there has been a progressive increase in the number of commercially available nanoparticle-based therapeutic products. (Parson et al., 2007). A global survey conducted by the European Science and Technology Observatory in 2006 showed that more than 150 companies are developing nanoscale therapeutics. So far, nanotechnology-based therapeutic products have been approved for clinical use, with total sales exceeding $5.4 billion (Raffi et al., 2007). Among these products, liposomal drugs and polymer drug conjugates are two dominant classes, accounting for more than 80% of the total amount (Table 1). Liposomes are spherical lipid vesicles with a bilayered membrane structure composed of natural or synthetic amphiphilic lipid molecules. Liposomes have been widely used as pharmaceutical carriers in the past decade because of their unique abilities to (a) encapsulate both hydrophilic and hydrophobic therapeutic agents with high efficiency, (b) protect the encapsulated drugs from undesired effects of external conditions, (c) be functionalized with specific ligands that can target specific cells, tissues, and organs of interest, (d) be coated with inert and biocompatible polymers such as polyethylene glycol (PEG), in turn prolonging the liposome circulation half-life in vivo, and (e) form desired formulations with needed composition, size, surface charge, and other properties. (Dubey et al., 2010). Table 1 lists some liposomal products that have been approved in the past 15 years. (Huang et al. 2006; Kim et al., 2001). Doxil was the first liposomal drug formulation approved by the Food and Drug Administration, USA (FDA) for the treatment of AIDS associated with Kaposi’s sarcoma in 1995. By encapsulating doxorubicin (a widely used anticancer chemotherapeutic drug) into stealth liposome carriers comprised of hydrogenated soy phosphatidylcholine, cholesterol, and PEGylated phosphoethanolamine, Doxil has dramatically prolonged doxorubicin circulation half-life and enhanced drug deposition in the tumor tissue. Other liposomal drugs used in clinical practice today include AmBisome
(amphotericin B liposomes), DaunoXome (daunorubicin liposomes), DepoCyt (cytarabine liposomes), and Visudyne (verteporfin liposomes). (Khajeh and Sanchooli 2011). Another extensively studied nanoparticle drug delivery platform currently in clinical practice is polymer–drug conjugates. Small-molecule therapeutic agents, especially anticancer chemotherapeutic agents, usually have two unfavorable properties: short circulation half-life, which leads to frequent administrations, and non-site-specific targeting, resulting in undesired systemic side effects. (Herrera et al., 2013) The conjugation of small-molecule drugs to polymeric nanocarriers can improve the undesirable adverse effects. Polymer-drug conjugates not only prolong the in vivo circulation time from several minutes to several hours, but also reduce cellular uptake to the endocytic route. This enhances the passive delivery of drugs to tissues with leaky blood vessels, such as tumors and atherosclerotic plaques. Many polymers have been proposed as drug delivery carriers, but only a few of them with linear architecture have been accepted into clinical practice. Challenges abound, but major challenges come from polymer toxicity, immunogenicity, nonspecific biodistribution, in vivo circulation instability, low drug-carrying capacity, rapid drug release, and manufacturing. PEG was first introduced into clinical use in the early 1990s. It can enhance the plasma stability and solubility of the drug while reducing its immunogenicity. Today, there are six examples of PEGylated drugs in clinical practice. For example, Adagen (PEG–adenosine deaminase) is used to treat immunodeficiency disease; Macugen (PEG–anti-vascular endothelial growth factor aptamer) is used to treat agerelated macular degeneration; Pegasys (PEG–a-interferon 2a) is used to treat hepatitis B and hepatitis C; and Oncaspar (PEG–L-asparaginase) is used to treat acute lymphoblastic leukemia. (Geranio et al., 2009) Besides PEG, other linear polymers such as polyglutamic acid, polysaccharide, and poly (allylamine hydrochloride) have also been harnessed as polymeric drug delivery carriers. Other macromolecule–drug conjugates or adducts that have a hydrodynamic size of 5–200 nm have also been developed as drug carriers.
(Daniel and Astruc 2004). One example is Abraxane, a 130-nm albumin-bound paclitaxel drug that was approved by the FDA in 2005 as a second-line treatment for patients with breast cancer. Abraxane concentrates in the tumor partly through the passive enhanced permeability and retention effect and partly through the transendothelial transport mechanisms via the albumin-binding protein gp60 (Vaidyanathan et al., 2009). Clinical studies have shown that Abraxane almost doubles the therapeutic response rate and also increases time to disease progression and overall survival in patients with breast cancer.

1.5.24. Nanoparticle-based therapeutics in clinical trials

The medical application of nanoparticles is gaining popularity with an increasing number of nanoparticle-based therapeutics occurring in clinical development. (Gericke and Pinches 2006). Drug-encapsulated liposomes and polymer–drug conjugates such as PEGylated drugs dominate clinical trials. One drawback of the use of liposomes is the fast clearance of liposomes from the blood by phagocytic cells of the reticuloendothelial system, resulting in unfavorable therapeutic index. Several strategies have been developed to reduce this problem. The most widely used strategy is to formulate long-circulating liposomes by coating the liposome surface with inert and biocompatible polymers such as PEG. (Lourith et al., 2010). The polymer layer provides a protective shell over the liposome surface and suppresses liposome recognition by opsonins, and therefore subsequent clearance by the reticuloendothelial system. Another strategy is to increase the accumulation of liposomes in the desired cells, tissues, and organs (Alivisatos 1996). By attaching targeting ligands such as antibodies, peptides, and small molecules (e.g., folate and transferrin) to the liposome surface, targeted liposomes have been developed for differential drug delivery. An example is Onco TCS, a liposomal formulation of vincristine developed by INEX Pharmaceuticals (Burnaby, British Columbia, Canada) for the treatment of aggressive non-Hodgkin’s lymphoma. Using INEX’s liposome-based transmembrane carrier systems (TCSs), Onco
TCS has the ability to target intracellular delivery of vincristine (Jose-yacamann et al., 2003). Its clinical trial data (phase I and II) have demonstrated that Onco TCS has longer blood circulation half-life, higher accumulation in tumors, and more sustained drug release profiles than free vincristine. Therefore, liposomal vincristine can potentially increase the efficacy of vincristine and decrease adverse side effects of the drug (Philip et al., 2011). In addition, releasing the drug in a controlled manner can also increase the therapeutic efficacy of liposomal drugs. (Jeong et al., 2000). By incorporating a fraction of pH-sensitive phosphatidylethanolamine, dimethyldioctadecylammonium bromide, or oleyl alcohol into the liposome membrane, smart liposomes have been developed for preferential intracellular drug delivery. These liposomes are generally stable in blood while undergoing phase transition under endosomal pH. PEG has been widely used to enhance the pharmacokinetics of various nanoparticle formulations. (kumar et al., 2006). PEG is a highly hydrated flexible polymer chain that reduces plasma protein adsorption and biofouling of nanoparticles while reducing renal clearance of relatively smaller drug molecules, and thus prolongs drug circulation half-life. PEG is also non-toxic and non-immunogenic, making it suitable for clinical applications. (Sheny et al., 2011). These favorable characteristics have led to many new PEGylated products under various phases of clinical evaluation; for example, NKTR-118 (PEG–naloxol) in phase I for treating opioid-induced constipation, Hepacid (PEG–marginine deaminase) in phase II for hepatocellular carcinoma, and Puricase (PEG–uricase) in phase III for hyperuricemia (Riddin et al., 2006). Another attractive polymer that has been employed to formulate polymer–drug conjugates is N-(2-hydroxypropyl) methacrylamide (HPMA). HPMA is a linear hydrophilic polymer with functionalizable side chains that can be activated to enable drug attachment or conjugation with targeting ligands. (Mandal et al., 2006). By conjugating small hydrophobic drugs such as paclitaxel to an HPMA polymer, drug water-solubility is highly improved. (Shahverdi et al., 2007). This makes drug formulation and
patient administration easier. In addition, HPMA is biodegradable and non-immunogenic. Owing to these desirable attributes, a number of HPMA products have been developed and are currently in clinical trials. Examples include ProLindac (HPMA copolymer–diaminocyclohexane palatinate) in clinical phase II for treating recurrent ovarian cancer, FCE28069 (HMPA copolymer–doxorubicin-galactosamine) in phase II for hepatocellular carcinoma, and PNU166945 (HPMA copolymer–paclitaxel) in phase I to document its toxicity and pharmacokinetics for treating refractory solid tumors (Sanghi and Verma 2009). Besides drug-encapsulated liposomes and polymer–drug conjugates, other nanoparticle platforms such as nanoemulsions, dendrimers, and inorganic nanoparticles have also shown therapeutic potential (Kreibig and Vollmer 1995). These platforms have greatly enriched the pool of therapeutic nanoparticles and have demonstrated novel strategies for medical applications. One interesting example is NB-001, a nanoemulsion-based therapeutic product that just entered its phase II trial in 2007 as topical treatment for genital herpes infection. Another example is VivaGel, a poly-L-lysine dendrimer-based pharmaceutical that is currently in its phase I trial as a safe, convenient, and affordable drug for women to protect themselves from genital herpes and HIV infection (Mohanpuria et al., 2008).