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A CRITICAL REVIEW ON NANOPARTICLE SYNTHESIS: PHYSICOCHEMICAL V/s BIOLOGICAL APPROACH

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ABSTRACT

The term nanotechnology encompasses the production of new materials at nano scale. Nano particles with interesting shapes can be prepared by different methods like physical and chemical method. Now day's biological methods of synthesis are used because it is environment friendly, cost effective, and easily scaled up process for large scale synthesis. Nano particles have vast applications in magnetic devices, microelectronics, bio medicals, electro catalysis, photo catalysis, anticorrosive coatings and powder metallurgy, out of which clinical applications are in high demand due to their biocompatibility, antibacterial activity, anti-inflammatory activity, effective drug delivery ,tumour targeting , bioactivity, bioavailability and bio absorption. The goal of the present study is to develop better understanding about the different aspects of Nano particle synthesis and biomedical applications.

KEYWORDS: Nanotechnology, Nano-particles, Nanoparticle synthesis, biocompatibility, antibacterial activity, anti-inflammatory activity.

INTRODUCTION

Nanotechnology represents the designing, production and application of nano sized materials. "The principles of physics do not speak against the possibility of manoeuvring things atom by atom." these are the words which buried the seed for nano-technology in the scientific mind of number of researchers who were attending the talk of famous physicist RICHARD FEYNMAN in 1959. The word actually signifies our complete control over the matter.

Nanotechnology is emerging as a rapidly growing field with its application in Science and Technology for the purpose of manufacturing new materials at the nano scale level.[1]

Methods employed for the synthesis of nano particles are broadly classified under two processes such as “Top-down” process and “Bottom-up” process (figure-2).

Top-down approach: Bulk material is broken down into particles at nano scale with various lithographic techniques e.g.: grinding, milling etc.

Bottom-up approach: Atoms self-assemble to new nuclei which grow into a particle of nano scale[2].

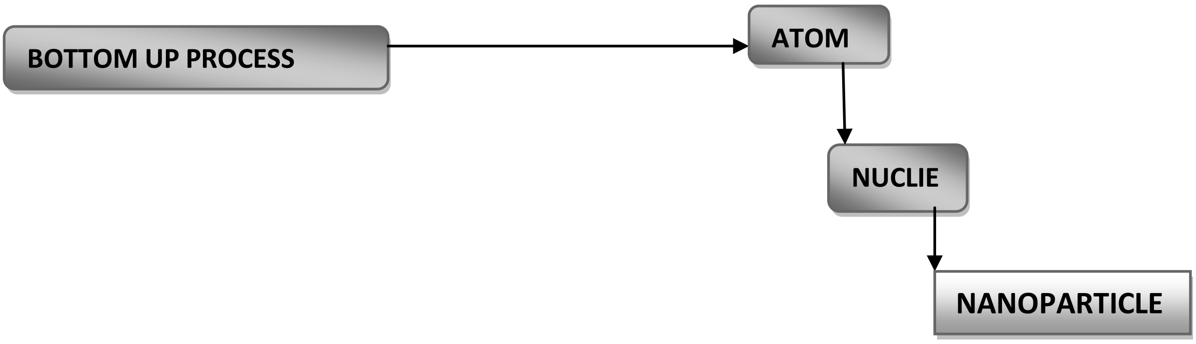


Figure 1: Protocols employed for the synthesis of nano particles.

An array of physical, chemical and biological methods has been used to synthesize nano materials. Specific methods have been used to synthesize noble metal nano particles of particular size and shape. Nano carriers ,'such as nano particles, solid lipid nano particles, polymeric micelles, and dendrimers , are colloidal particulate systems with a size range of 10-1,000 nm and have been successfully utilized in the diagnosis, treatment, and monitoring of various diseases.

The word “nano” is derived from a Greek word meaning dwarf or extremely small.[3] As the material becomes smaller the percentage of atoms at the surface increases relative to the total number of atoms of the material bulk i.e. The surface-to-volume ratios of materials become large and their electronic energy states become discrete. Moreover, the increased catalytic activity due to morphologies with highly active facets and the tailoring of its synthesis as per the requirement makes the nano particles an attractive tool to solve various technological problems.[4-5]

Nano particles with one half hydrophilic and the other half hydrophobic are termed Janus particles and are particularly effective for stabilizing emulsions. They can self-assemble at water/oil interfaces and act as solid surfactants.[6]

Types of Nanoparticles

A. On The Basis of Morphology

Nano materials have extremely small size which having at least one dimension 100 nm or less. Nano materials can be nano scale in[7]

1. **One dimension (e.g. surface films):** One dimensional system, such as thin film or manufactured surfaces, has been used for decades in electronics, chemistry and engineering.

2. **Two dimensions (e.g. strands or fibres)**

a. **Carbon Nano Tubes (CNTs)**

Carbon nano tubes are hexagonal network of carbon atoms, 1 nm in diameter and 100 nm in length, as a layer of graphite rolled up into cylinder.

3. **Three Dimensions (e.g. particles)**

a. **Fullerenes (Carbon 60)**

Fullerenes are spherical cages containing from 28 to more than 100 carbon atoms, contain C60.

b. **Dendrimers**

Dendrimers are repetitively branched molecules. The name comes from the Greek word δένδρον (Dendron), which translates to "tree". The pharmaceutical applications of dendrimers include nonsteroidal anti-inflammatory formulations, antimicrobial and antiviral drugs, anticancer agents, pro-drugs, and screening agents for high-throughput drug discovery.[8]

c. **Quantum Dots (QDs)**

Quantum dots are small devices that contain a tiny droplet of free electrons. It can be used for optical and optoelectronic devices, quantum computing, and information storage.

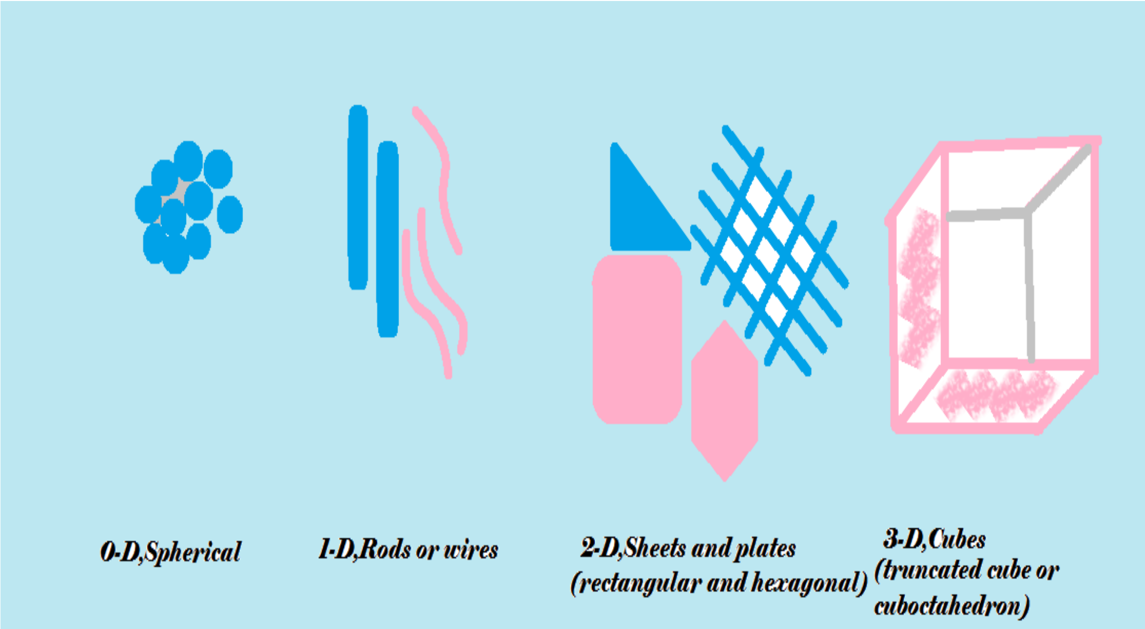


Fig. showing types of nanoparticle on the basis of morphology.

B. On the Basis of Nature

1. Organic Nano-Particles

a. Liposome (50-100 nm)

Phospholipids vesicles with a belayed membrane similar to the biological membrane and an aqueous core.

b. Polymersomes (50-100 nm)

Similar to liposome's but made with synthetic polymers or biopolymers.

c. Dendrimers (<15 nm)

This is a synthetic polymer made of a core, an internal area and a surface crown of functional groups.

d. Carbon Nano Particles (<100nm)

Fullerene (C60, C70), Carbon nanotubes, Nanodiamonds.

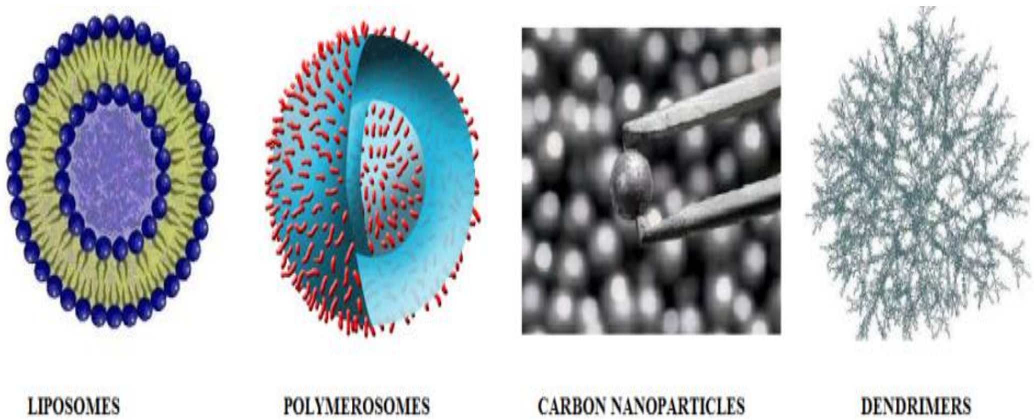


Fig.ORGANIC NANOPARTICLES

2. Inorganic Nano Particles

a. Magnetic Nano Particles (5-20 nm)

Magnetic nanoparticles are a class of nanoparticle which can be manipulated using magnetic field. Such particles commonly consist of magnetic elements such as Iron oxides (Fe2O3, Fe3O4), doped iron oxides (CoFe2O4, MnFe2O4) or metal alloys (FePt).[9]

b. Quantum Dots (2-10 nm)

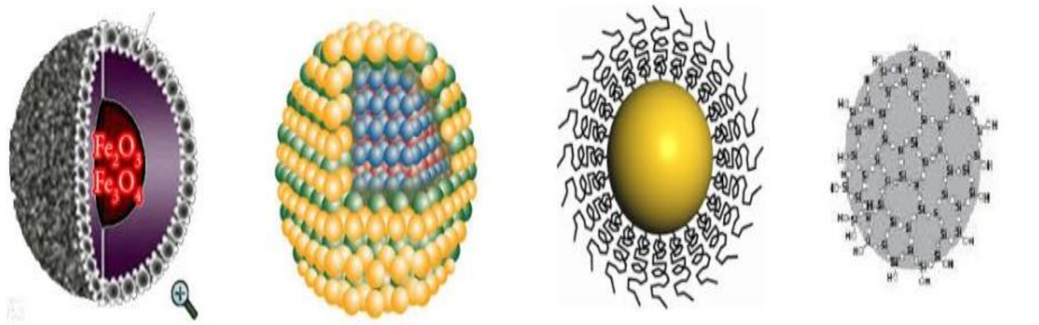
Semiconductor nano crystals composed of a core (CdSe, CdTe ..)Embedded in a layer of ZnS.[10]

c. Gold Nano Particles (<50 nm)

A kind of metal nanoparticles with a wide variety of geometries (spheres, rods, hollow spheres, cages).[11]

d. Silica Nano Particles (<100 nm)

A way to access mesoporous materials (drug encapsulation), increasingly used for encapsulating other types of nanoparticles (core-shell).[12]



MAGNETIC NANOPARTICLES QUANTUM DOTS GOLD NANOPARTICLES SILICA NANOPARTICLES

Fig.INORGANIC NANOPARTILES

Methods for Nano Particle Synthesis

Nano particle synthesis is done by Processing of bulk materials into nanostructure particles. Various methods for the synthesis of nano particles are described here as under:

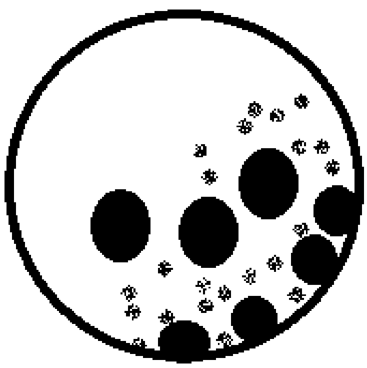
Physical Synthesis

Various physical methods have been employed to prepare silver nanoparticles with different sizes and shapes, such as UV irradiation,[13-14] microware irradiation,[15-16] photochemical method,[17] electron irradiation,[18] and sono-electrochemical method.[19].

Generally two physical methods are used for the synthesis of nano particles:

1. **Mechanical**

a) **High Energy Ball Milling:** It is the simplest method of nanoparticle synthesis in the form of powder. It consists of a container filled with hardened steel or tungsten carbide balls. The mass ratio of balls to materials is 2:1. Container may be filled with air or inert gas and then rotated at high speed around a central axis.[20]



Material is forced to the walls and pressed against the walls. Some materials like Co, Cr, W, Al-Fe, Ag-Fe etc are made nanocrystalline using ball mill.

b) **Melt Mixing**: It is used to form or arrest nanoparticles in glass. Nanopaticles can be formed by mixing molten streams of metals at high velocity with turbulence, for.ex: a molten stream of Cu-B and molten stream of Ti form nano particles of TiB_2.[21]

2. **Vapour**

a) **Physical vapour deposition:** Material of interest used as source of evaporation are

i. An inert or reactive gas
ii. A cold finger(water or liquid N_2 cooled)
iii. Scraper

All processes are carried out in a vacuum chamber so that the desired purity of end product can be obtained. Materials to be evaporated are held in filaments or boats of refractory metals like W, Mo etc .Density of the evaporated material is quite high and particle size is small (< 5 nm).

b) **Laser ablation:** Vaporization of the material is effected by using pulses of laser beam of high power.

The set up is

i. An Ultra High Vacuum (UHV) or high vacuum system.
ii. Inert or reactive gas introduction facility, laser beam, target and cooled substrate
iii. Laser giving UV wavelength such as Excimer laser is necessary.[23] Single Wall Carbon Nanotubes (SWNT) is mostly synthesized by this method.

c) **Laser pyrolysis:** This is a processor which employ thin film synthesis using lasers

Mixture of reactant gases is deposited on a powerful laser beam in the presence of some inert gas like helium or argon. Many nanoparticles of materials like Al_2O_3 and WC synthesized by this method. Gas pressure decides particle size and distribution.The CO2 laser pyrolysis technique is classified as a vapour-phase synthesis process for the production of NPs. In this class of synthesis routes, nanoparticle formation starts abruptly when a sufficient degree of supersaturation of condensable products is reached in the vapour phase. [24]

d) **Sputter deposition:** It is a widely used thin film technique, specially to obtain stoichiometric thin films from target material (alloy, ceramic or compound).

Very Good Techniques to Deposit Multilayer Films are

1) **DC sputtering:** In this method target is held at high negative voltage and substrate used may be at positive, ground or floating potential. Argon gas is introduced at a pressure <10 Pa. After this High voltage (100 to 3000 V) is applied between anode and cathode, which result in visible glow is observation when current flows between anode and cathode.[25]

2) **RF sputtering:** If the target to be spluttered is insulating then high frequency voltage is applied between the anode and cathode. Also keep on changing the polarity and the resulting oscillating electrons cause ionization, 5 to 30 MHz frequency can be used but 13.56 MHz frequency is most commonly used.[26]

3) **Magnetron sputtering:** RF/DC sputtering rates can be increased by using magnetic field. Magnetron sputtering use powerful magnets to confine the plasma to the region closest to the ‘target’.[27]

4) **Electric arc deposition:** It is simplest and most useful method for nanoparticle synthesis which include mass scale production of Fullerenes, carbon nanotubes etc Inert or reactive gas introduction is necessary in this method; also gas pressure is maintained in the vacuum system. When an arc is set up, anode material evaporates. This is possible as long as the discharge can be maintained.[28]

e) **Ion implantation:** This process is used to change the physical, chemical, or electrical properties of the solid. Ion implantation is used in semiconductor device fabrication and in metal finishing, as well as various applications in materials science research.[29]

These processes usually require complicated instruments, electrical and radiative heating as well as high power consumption, which results in high operating cost. The main advantage of the physical approach is that nano particles with high purity and desired size can be selectively synthesized.[30] However, most of the reported methods involve more than one step, high energy requirement, low material conversions.[31]

Chemical Synthesis

Chemical reduction of nano particles is the most frequently applied method for the preparation of stable, colloidal dispersions in water or organic solvents.[32] This is relatively simple technique uses a minimum number of chemicals, these including water, a soluble metallic salt, a radical scavenger (often a secondary alcohol), and a surfactant (organic capping agent).[33] This synthetic method usually employs chemicals such as hydrazine, sodium borohydride and hydrogen as reducing agents.[34] Synthetic or natural polymers such as natural rubber,[35] chitosan,[36] cellulose[37] and copolymer micelles[38] have been used as stabilizers against oxidation and coalescence in nano composites.

There is various advantage of chemical synthesis over physical method of nanoparticle synthesis, some of them are

a. It is a simple technique.
b. It requires inexpensive instrumentation.
c. Low temperature (<350ºC) requirement for synthesis.
d. Doping of foreign atoms (ions) is possible during synthesis.
e. Large quantities of material can be obtained by chemical synthesis.
f. Synthesis of variety of sizes and shapes are possible.
g. Also self assembly or patterning is possible.

Nano particles have been synthesized, most recurrently by three chemical techniques

a. Dispersion of preformed polymers.
b. Polymerization of monomers.
c. Ionic gelation or coacervation of hydrophilic polymers.[39-43]

Synthesis of metal nano particles by colloidal route include reduction of some metal salt or acid [44].

For ex. highly stable gold particles can be obtained by reducing chloroauric acid ($HAuCl_4$) with tri sodium citrate ($Na_3C_6H_5O_7$).

$$HAuCl_4 + Na_3C_6H_5O_7 \longrightarrow Au^{+} + C_6H_5O_7^{-} + HCl + 3\ NaCl.$$

Metal gold nanoparticles exhibit intense red, magenta etc., and colours depending upon the particle size. Gold nanoparticles can be stabilised by repulsive columbic interactions it can also be stabilised by thiol or some other capping molecules. In a similar manner, silver, palladium, copper and few other metal nanoparticles can be synthesized.

Synthesis of semiconductor nanoparticles by colloidal route is done by WET CHEMICAL METHOD using appropriate salts.[45]

Sulphide semiconductors like CdS and ZnS can be synthesized by co precipitation.

For ex. To obtain Zns nanoparticles, any Zn salt is dissolved in aqueous (or non aqueous) medium and H_2S is added.

$$ZnCl_2 + H_2S \qquad\qquad ZnS + 2\ HCl$$

During synthesis process steric hindrance created by “chemical capping”. Chemical capping is done at high or low temperature depending on the reactants.

Sol gel method is used for the synthesis of nanoparticles by chemical method. Two types of materials or components- “sol” and “gel” are used. This process involve.

a. Low temperature - less energy consumption and less pollution
b. Generates highly pure, well controlled ceramics
c. Economical route, provided precursors are not expensive
d. Possible to synthesize nanoparticles, nanorods, nanotubes etc.

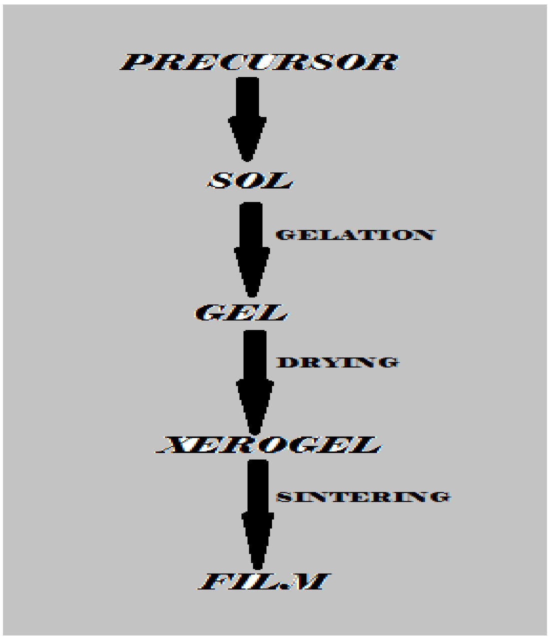


Fig. showing SOL GEL method for the nano particle synthesis by chemical method

Sols are solid particles in a liquid- subclass of colloids and Gels are polymers containing liquid. The process involves formation of ‘sols’ in a liquid and then connecting the sol particles to form a network. Liquid is dried to powders, thin films or even monolithic solid. This process is particularly useful to synthesize ceramics or metal oxides. Oxide ceramics are best synthesized by sol gel route. For ex: in SiO_4, Si is at the centre and 4 oxygen atoms at the axes of tetrahedron. Furthermore, chemicals reagents used normally for nano particles synthesis and stabilization are toxic and lead to by-products that are not eco-friendly.[46]

Biological Synthesis

Three types of biological synthetic methods have been used for the synthesis of for production of low-cost, energy-efficient, and nontoxic metallic nano particles [47].Following are the biological components used for the synthesis processor.

1. Use of microorganisms like fungi, yeasts (eukaryotes) or bacteria, actinomycetes (prokaryotes).
2. Use of plant extracts or enzymes.
3. Use of templates like DNA, membranes, viruses and diatoms.

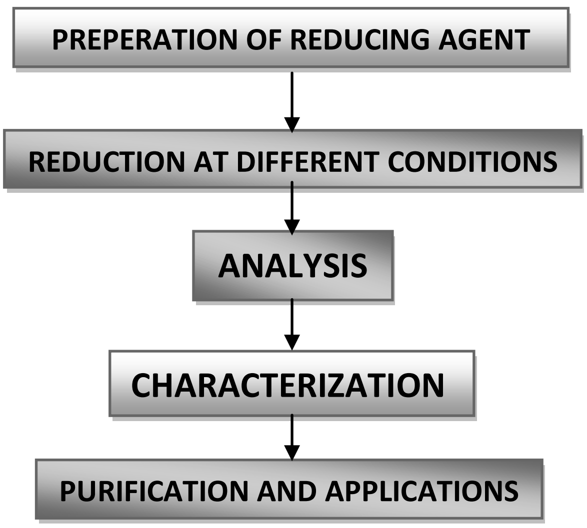


Figure: steps involved in biosynthesis of Nano particles.

The above three biological component for the synthesis of nanoparticles are described here briefly as.

Use of microorganisms like fungi, yeasts (eukaryotes) or bacteria, actinomycetes (prokaryotes)

Microorganisms are capable of interacting with metals coming in contact with them through their cells and form nanoparticles.The cell- metal interactions are quite complex. Certain microorganisms are capable of separating metal ions, mechanism of nano particle biosynthesis is very important. It includes enzymatic reduction of the metal ions, sorption on the cell wall and, in some cases, subsequent chelating with extracellular peptides or polysaccharides has been developed, leading to their aggregation and the formation of nanoparticles.[48] The microbial cell reduces metal ions by use of specific reducing enzymes like NADH-dependent reductase or nitrate dependent reductase.[49] Metal ion resistance via transport and passive mechanisms leading to extracellular precipitation is more characteristic for prokaryotes.[50,51]

Biosynthesis of Metal Nanoparticles by Bacteria

This goal to cost effectively tailors the optical, electric and electronic property of NPs by controlling the configuration as well as monodispersity could be achieved using bacterial organisms in an organized manner.[52]

Synthesis of metal nanoparticles by microbes is due to their defence mechanism (resistance mechanism), the resistance caused by the bacterial cell for metal ions in the environment is responsible for its nanoparticles synthesis,[53] cell wall being negatively charged interacts electro statically with the positively charged metal ions. The enzymes present within the cell wall bio reduce the metal ions to nanoparticles, and finally the smaller sized nanoparticles get diffused of through the cell wall,[54] and this is how the nanoparticles produced are useful to us.

Many Bacterial cultures were used for different kinds of nanoparticles some are gold nanoparticles using Shewanella algae it's a kind of marine bacterium,[55] silver nanoparticles by Cyanobacteria Plectonema boryanum,[56] cadmium nanoparticles biosynthesis was done by Clostridium thermoaceticum,[57] magnetite nanoparticles by Actinobacter sp.[58] Shewanella oneidensis used for uranium nanoparticles[59] synthesis were reported.

For e.g.-The bio reduction of gold ions by bacteria was found to be initiated by the electron transfer from the NADH by NADH-dependent reductase as electron carrier.[60]

Biosynthesis of Metal Nanoparticles by Yeast

Among the eukaryotic microorganism, yeast has been exploited mainly for the synthesis of semiconductors.[61] The extracellular synthesis of nanoparticles in huge quantities, with straightforward downstream processing, has been reported.[62]

In an isolated report, Kowshik et al have demonstrated that MKY3, a silver-tolerant yeast species, when challenged with soluble silver in the log phase of growth, could precipitate a majority (N99%) of silver extracellular as elemental nanoparticles.[63]

In, baker's yeast, S. cerevisiae was also reported to biosorb and reduces Au+3 to elemental gold in the peptidoglycan layer of the cell wall in situ by the aldehyde group present in reducing sugars.[64]

Biosynthesis of Metal Nanoparticles by Algae

An alga is being explored for application in nanotechnology. Besides the production of NPs, algae are also being explored for determining its nutritional value, efficacy in bio-diesel improvement as well as its vast potential for therapeutic application.[65]

Elemental gold was mostly precipitated on the cell wall of Sargassum natans biomass and suggested that the carbonyl (C≡O) groups of the cellulosic materials were the main functional group in the gold binding with N-containing groups involved in a lesser degree.[66]

Biosynthesis of Metal Nanoparticles by Fungi

This includes easy and simple scale up method, economic viability, easy downstream processing and biomass handling, and recovery of large surface area with optimum growth of mycelia.[67]

It has been observed that most of the fungal genera are coupled with the synthesis of Ag-NPs either intracellular or extracellular showing the onset of deep brown coloration.[68] The proteins, polysaccharides and organic acids secreted by the fungus were believed to have facilitated the formation of different crystal shapes and directed the growth into spherical crystals.[69]

The enzyme nitrate reductase secreted by the fungi helps in the bio reduction of metal ions and synthesis of nanoparticles. A number of researchers supported nitrate reductase for extracellular synthesis of nanoparticles.[70-76]

Biosynthesis of Metal Nanoparticles from Actinomycetes

The possible mechanism of intracellular synthesis of metal nanoparticles by trapping of the Ag^+ ions on the surface of the actinomycete cells possibly via electrostatic interactions between the Ag^+ and negatively charged carboxylate groups in enzymes present in the cell wall of mycelia.[77]

1. Use of Plant Extracts or Enzymes

The synthesis processor and role of plant metabolites are described here as.

Biosynthesis of Metal Nanoparticles by Higher Angiosperm Plants

Use of plants for the fabrication of NPs has drawn attention of workers because of its rapid, economical, eco-friendly protocol and it provides a single step technique for the biosynthesis process.[78]

It is believed that the adsorption of bio reducing agents on the surface of metallic nanoparticles is attributable to the presence of **p-electrons and carbonyl groups** in their molecular structures.[79]

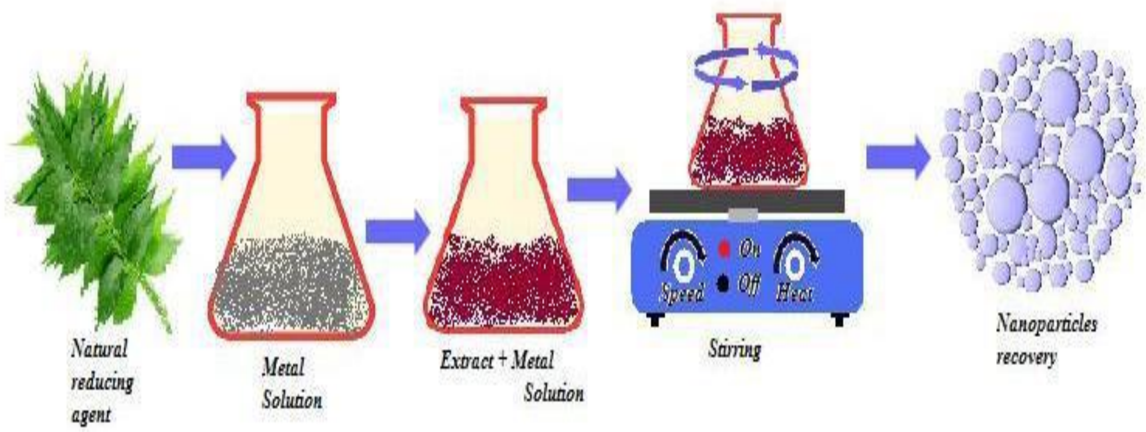


Fig. Synthesis of nanoparticle from plant extracts.[80]

Various plant metabolites, play an important role in the bio reduction of metal ions, yielding nanoparticles.

a) Using FTIR spectroscopy of nanoparticles synthesized in plants/plant extracts, it has been demonstrated that terpenoids are often associated with nanoparticles.[81]

b) Flavonoids are a large group of polyphenolic compounds that comprise several classes: anthocyanins, isoflavonoids, flavonols, chalcones, flavones, and flavanones, which can actively chelate and reduce metal ions into nanoparticles.

c) Glucose was also noted to be a stronger reducing agent than fructose, because the antioxidant potential of fructose is limited by the kinetics of tautomeric shifts.[82]

d) Instead of bio reduction, it was proposed by some researchers that proteins could act as stabilizing agents as well.[83]

Fabrication of Nanoparticles Using Weeds

Recently the bio reduction property of three aquatic weed leaves extracts such as Ipomoea aquatic (Convolvulaceae), Enhydra fluctuans (Asteraceae) and Ludwigia adscendens (Onagraceae) in the synthesis of silver nanoparticles has been investigated by Roy et al.[84]

2. Use of templates like dna, membranes, viruses and diatoms

CdS or other sulphide nanoparticles can be synthesized using DNA. DNA can bind to the surface of growing nanoparticles. Cadmium acetate is added to a desired medium like water, ethanol, propanol etc.[85] Various inorganic materials such as carbonates, phosphates, silicates etc are found in parts of bones, teeth, shells etc.

Characterization of Nanoparticles

In order to investigate various properties of the prepared sample, it has to goes under a number of characterisation techniques.

A. Structural Characterisation

In order to get exact information about the crystal structure, surface morphology, particle size etc. the following characterisation techniques are applicable:

XRD (X-ray Diffraction)

SEM (Scanning electron microscope)

Transmission electron microscope (TEM).

B. Optical characterisation

On putting the sample to following characterisation techniques gives information related to optical properties

UV-Visible Spectroscopy

Fourier Transform Infrared Spectroscopy (IR).

C. Thermal analysis

DSC&TG.

XRD (X-ray Diffraction)

Unique characteristic X-ray diffraction pattern of each crystalline solid gives the designation of “fingerprint technique” to XRD for its identification. XRD may be used to determine its structure, i.e. how the atoms pack together in the crystalline state and what the interatomic distance and angle are etc.

SEM (Scanning Electron Microscope)

The scanning electron microscope (SEM) uses a focused beam of high-energy electrons to generate a variety of signals at the surface of solid specimens. The signals that derive from electron reveal information about the sample including external morphology (texture), chemical composition, and crystalline structure and orientation of materials making up the sample.

TEM (Transmission Electron Microscope)

The main use of this technique is to examine the specimen structure, composition or properties in sub microscopic details so that this microscopy technique is significantly involved in numerous fields.

UV-Visible Spectroscopy

Absorption of radiation by a sample is measured at various wavelengths and plotted by a recorder to give the spectrum which is a plot of the wavelength of the entire region versus the absorption (A) of light at each wavelength**.**

FTIR (Fourier Transform Infrared Spectroscopy)

In the region of longer wavelength or low frequency the identification of different types of chemicals is possible by this technique of infrared spectroscopy and the instrument requires for its execution is Fourier transform infrared (FTIR) spectrometer.

DSC (Differential Scanning Calorimetry)

Thermal Analysis (STA) generally refers to the simultaneous application of Thermo gravimetry (TGA) and Differential scanning calorimetry (DSC) to one and the same sample in a single instrument.

Applications of Nanoparticles

Nanoparticles have been found to be relevant to numerous emerging technologies [86]. Some examples are: cosmetics and sunscreens, water filtrations, glare filters, ink, stain-resistant clothing, more durable tennis balls, more lightweight tennis rackets, dressings for burns or injuries [87], where the potential applications of nano particles include.

Potential Applications of Nano Particles

A list of some of the applications of nano materials to biology or medicine is given below

1) Antimicrobial assay.[88]
2) Fluorescent biological labels.[89-91]
3) Drug and gene delivery.[92, 93]
4) Bio detection of pathogens.[94]
5) Detection of proteins.[95]
6) Probing of DNA structure.[96]
7) Tissue engineering.[97, 98]
8) Tumour destruction via heating (hyperthermia).[99]
9) Separation and purification of biological molecules and cells.[100]
10) MRI contrast enhancement.[101]
11) Phagokinetic studies.[102]

DISCUSSION

The synthesis of nanoparticles has received importance and has been a focus of researchers due to their high chemical and thermal stability, fascinating optical, electronic properties, and promising applications such as nanoelectronics, biomedicine, sensing, and catalysis. Different physical and chemical methods for nanoparticles synthesis have been discussed in this paper but these methods are either expensive or are not eco-friendly due to use of hazardous chemicals, stringent protocol used during the process. These drawbacks necessitate the development of nonhazardous and biological methods for nanoparticles synthesis. This review provide the insight of comparative analysis of synthesis of nanoparticles by various route and their potential application in various fields.

CONCLUSION AND OUTLOOK

The study indicates the need of development of environmentally benign procedures for synthesis of nano particles. A promising moves toward to reach this objective is to develop the array of biological resources in nature which have great advantages over classical methods, so it may be used in biomedical applications.

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