MEDICAL APPLICATIONS IN NANOTECHNOLGOY

1. Introduction

- In the day today life various disease like diabetes, cancer, sparkinsen diseases, Alzheimer disease, cardiovascular disease and multiple sclerosis.
- As well as different kinds of serious inflammatory or infectious disease.
- Nanomedicine is an application of nanotechnology which works in the field of health and medicine
- Nanomedicine makes use of nanomaterials and nanoelectronic biosensor.
- Nanomedicine helps in earlier detection, prevention, ** and effective therapeutic regime.

Drug delivery

- Nanoparticles are used for site specific drug delivery.
- In this technique the required drug dose is used and side effects are lowered significantly as the active agents is deposited in the morbid region only.
- This highly selective approach can reduce cost and pain to the patients.
- There are variety of nanoparticles such as dendrimers, nanoporous material, are used for drug encapsulation.
- They transport small drug molecules to the desired location for the active release of the drug.
- In or gold nanoparticles are finding important application in the cancer treatment.
- The targeted medicine reduces the drug consumption and treatment expensive making a treatment of patient cost effective.

Protein / Peptide Delivey

- Nanoparticles were found useful in delivery the myclin antigen which induce immune tolerance in a mouse model with relapsing multiple sclerosis.
- In this technique biodegradable polyesterine microparticles coating with the myclin sheath peptide will reset the mouse immune system and this prevents the reoccurrence of disease and reduces the symptom.
- Protective myclin sheath forms protein on the nerve flues of the central nervous system.
- This method of treatment can potentially be used in the treatment of various other autoimmune disorder.

Oncology

- Due to the small size of nanoparticles, it can be great use in particularly in imaging
- Nanoparticles such as quantum dots with quantum confinement properties such as light emission can be used in conjunction with MRI to produce exceptional images tumor size.
- They also used in cancer therapy.
- Ex:

1.	Carbon nanotubes:	0.5 – 3 nm in diameter 20 – 1000 nm in length Used for detecting DNA mutastion. Detection of disease protein biomaker
2.	Dendrimers	Less than 10 nm in size Useful for release drug delivery Image contrast agent
3.	Nano crystals	2 – 9.5 nm in size It improves formulation for poorly soluble drugs. Labelling of breast cancer marker
4.	Nano particles	10 – 100 nm in size It is used in MRI Ultrasound images as a image contrast agents. Targetted drug delivery Reporters of apoptosis and angiogenesis.
5.	Nanoshells	Application in tumour specific imaging Deep tissue thermal ablation.
6.	Nanowires	Useful for disease protein biomarker detection DNA mutation detection Gene expression detection
7.	Quantum dots	2 – 9.5 nm in size Cell assays

Modified Medicated Textiles : tumor and lymphnode visualization

- Using nanotechnology newer antibacterial cotton has been developed and used for antibacterial textiles.
- Developmental works during nanotechnology new modified antibacterial textiles have been developed to inhibit the growth bacteria, fungi etc.

Nanopharmaceuticals

- Nanopharmaceuticals can be used to detect disease at much earlier stages and the diagnostic application could build upon convenient procedure using nanoparticles.
- Nanopharmaceuticals are an emerging field where the size of the drug particle or a therapeutic delivery system work at the nano scale.

- Delivering the appropriate dose of a particular active agent to specific disease still remains difficult in the pharmaceutical industry.

Antibiotic resistance

- Antibiotic resistance can be decreased by use of nanoparticle in combination therapy.
- Zinc oxide nanoparticle can decrease the antibiotic resistance and enhance the antibacterial activity of ciprofloxacin against microorganism by interfering with various protein that are interacting with antibiotic resistance.

Tissue engineering

- In tissue engineering, nanotechnology can be applied to reproduce or repair damaged tissue.
- By using suitable nanomaterial paste scaffolds and growth factor which artificially stimulant cell proliferation in organ transplant or artificial implant therapy.
- Nanotechnology can be useful which can lead to life extension

Synthesis of Nanomaterials

1. Introduction

There are a large number of techniques available to synthesize different types of nanomaterials in the form of colloids, clusters, powders, tubes, rods, wires, thin films etc. There are various physical, chemical, biological and hybrid techniques available to synthesize nanomaterials. The technique to be used depends upon the material of interest, type of nanostructure viz., zero dimensional, one dimensional, or two dimensional material size, quantity etc.

- **Physical methods:** *(a) mechanical:* ball milling, melt mixing

  (b) Vapor: physical vapor deposition, laser ablation, sputter deposition, electric arc deposition, ion implantation
- **Chemical methods:** colloids, sol-gel, L-B films, inverse micelles.
- **Biological methods:** biomembranes, DNA, enzymes, microorganisms.

2. Physical methods

(a) Ball milling: It is used in making of nanoparticles of some metals and alloys in the form of powder. Usually the mill contains one or more containers are used at a time to make fine particles. Size of container depends upon the quantity of interest. Hardened steel or tungsten carbide balls are put in containers along with powder or flakes (<50 um) of a material of interest. Initial material can be of arbitrary size and shape. Container is closed with tight lids. The containers are rotated at high speed (a few hundreds of rpm) around their own axis. Additionally they may rotate around some central axis and are therefore called as 'planetary ball mill'. When the containers are rotating around the central axis, the material is forced to the walls and is pressed against the walls. But due to the motion of the containers around their own axis, the material is forced to other region of the container. By controlling the speed of rotation of the central axis and container as well as duration of milling, it is possible to ground the material to fine powder whose size can be quite uniform. Some of the materials like Co, Cr, W, Ni-Ti, Al-Fe, Ag-Fe etc. are made nanocrystalline using ball mill.

Large balls, used for milling, produce smaller grain size and larger defects in the particles. The process may add some impurities from balls. The container may be filled with air or inert gas. However, this can be an additional source of impurity. A temperature rise in the range of 100 to 1100 C is expected to take place during the collisions. Cryo-cooling is used to dissipate the generated heat.

(b) Melt Mixing: It is possible to form or arrest the nanoparticles in glass. Structurally, glass is an amorphous solid, lacking long range periodic arrangement as well as symmetry arrangement of atoms/molecules. When a liquid is cooled below certain temperature, it forms either a crystalline or amorphous solid (glass). Nuclei are formed spontaneously with homogenous (in the melt) or inhomogeneous (on the surface of other materials) nucleation, which can grow to form ordered, crystalline solid. Usually, metals form crystalline solids but, if cooled at very high cooling rate, they can form amorphous solids. Such solids are known as metallic glasses. Even in such cases the atoms try to reorganize themselves into crystalline solids. Addition of elements like B, P, Si etc. helps to keep the metallic glasses in amorphous state. It is possible to form nanocrystals within metallic glasses. It is also possible to form some nanoparticles by mixing the molten streams of metals at high velocity with turbulence. On mixing thoroughly, nanoparticles are formed.

(c) Physical Vapor Deposition: It involves material for evaporation, an inert gas or reactive gas for collosion of material vapor, a cold finger on which clusters or nanoparticles can condense, a scraper to scrape the nanoparticles and piston- anvil (an arrangement in which nanoparticle powder can be compacted). All the processes are carried out in a vacuum chamber so that the desired purity of the end product can be obtained.

Metals or high vapor pressure metal oxides are evaporated or sublimated from filaments or boats of refractory metals like W, Ta, Mo in which materials to be evaporated are held. Size, shape and even the phase of evaporated material can depend upon the gas pressure in deposition chamber. Clusters or nanoparticles condensed on the cold finger (water or liquid nitrogen cooled) can be scraped off inside the vacuum system. The process of evaporation and condensation can be repeated several times until enough quantity of material falls through a funnel in which a piston-anvil arrangement has been provided.

(d) Ionized Cluster Beam Deposition: It is useful to obtain adherent and high quality single crystalline thin films. The set up consists of a source of evaporation, a nozzle through which material can expand into the chamber, an electron beam to ionize the clusters, an arrangement to accelerate the clusters and a substrate on which nanoparticle film can be deposited, all housed in a suitable vacuum chamber. Small clusters from molten material are expanded through the fine nozzle. The vapor pressure, ~10 torr to 10-2 torr needs to be created in the source and the nozzle needs to have a diameter larger than the mean free path of atoms or molecules in vapor form in the source to form the clusters. On collision with electron beam clusters get ionized. Due to applied accelerating voltage, the clusters are directed towards the substrate. By controlling the accelerating voltage, it is possible to control the energy with which the clusters hit the substrate. Thus it is possible to obtain the films of nanocrystalline material using ionized cluster beam.

(e) Laser Vaporization: In this method, vaporization of the material is effected using pulses of laser beam of high power. The set up is a ultra high vacuum or high vacuum system equipped with inert or reactive gas introduction facility, laser beam, solid target and cooled substrate. Clusters of any material of which solid target can be made are possible to synthesize. Usually laser giving UV wavelength such as excimer laser is necessary because other wavelengths like IR or visible are often reflected by some of the metal surface. A powerful beam of laser evaporates the atoms from a solid source, atoms collide with inert gas atoms (or reactive gases) and cool on them forming clusters. They condense on the cooled substrate. The method is often known as laser ablation. Gas pressure is very critical in determining the particle size and distribution. Simultaneous evaporation of another material and mixing the two evaporated materials in inert gas leads to the formation of alloys or compounds.

(f) Laser Pyrolysis or Laser Assisted Depositon: Here a mixture of reactant gases is decomposed using a powerful laser beam in presence of some inert gas like helium or argon. Atoms or molecules of decomposed reactant gases collide with inert gas atoms and interact with each other, grow and are then get deposited on cooled substrate. Many materials like Al_2O_3, WC, Si_3Ni_4 etc. are synthesized in nanocrystalline form by this method. Here too, gas pressure plays an important role in deciding the particle size and their distribution.

(g) Sputter Deposition: In sputter deposition, some inert gas ions like Ar are incident on a target at a high energy. The ions become neutral at the surface but due to their energy, incident ions may get implanted, get bounded back, create collision cascades in target atoms, displace some of the atoms in the target creating vacancies, interstitials and other defects, desorb some adsorbents, create photons while loosing energy to target atoms or even sputter out some target atoms/molecules, clusters, ions and secondary electrons. Sputter deposition is a widely used thin film deposition technique, specially to obtain stoichiometric thin films from target material. Target material may be some alloy, ceramic or compound. It is a very good technique to deposit multilayer films for mirrors or magnetic films for spintronic applications. Sputter deposition can be carried out using Direct Current (DC) sputtering, Radio Frequency (RF) sputtering or magnetron sputtering. In all these methods, one uses discharge or plasma of some inert gas atoms or reactive gases. The deposition is carried out in a required gas pressurized high vacuum or ultra high vacuum system equipped with electrodes, one of which is a sputter target and the other is a substrate, gas introduction facility etc.

In DC sputtering, the target is held at high negative voltage and substrate may be at positive, ground or floating potential. Substrates may be simultaneously heated or cooled depending upon the requirement. Once the required base pressure is attained in the vacuum system, usually argon gas introduced at a low pressure. A visible glow is observed and current flows between anode and cathode indicating the deposition onset. When sufficiently high voltage is applied between anode and cathode with a gas in it, a glow discharge is set up with different regions as cathode glow, Crooke's dark space, negative glow, Faraday dark space, positive column, anode dark space and anode glow. These regions are the result of plasma. Plasma is a mixture of free electrons, ions and photons. Plasma is overall neutral but there can be regions, which are predominantly of positive or negative charge. The density of various particles and the length over which they are spread and distributed depends upon the gas pressure.

In RF sputtering 5-30 MHz frequency is used and the electrodes can be insulating. However, 13.56 MHz is a commonly used frequency for deposition. Target itself biases to negative potential becoming cathode.

RF and DC sputtering efficiency can be further increased using magnetic field. When both electric and magnetic fields act simultaneously on a charged particle, force is acted upon it. Electrons moves in a helical path and is able to ionize more atoms in the gas. In practice, both parallel and magnetic fields to the direction of electric field are used to further increase the ionization of the gas, increasing the efficiency of sputtering. By introducing gases like O2, N2, NH3, CH4, H2S etc. while metal targets are sputtered, one can obtain metal oxides like Al2O3, nitrides, carbides etc., This is known as reactive sputtering.

The plasma density can be further enhanced using microwave frequency and coupling the resonance frequency of electrons in magnetic field. Ionization density using Electron Cyclotron Resonance plasma is about 2-3 orders of magnitude larger. Thin films and nanoparticles of Si2O3, SiN, GaN etc. have been obtained using this technique.

(h) Chemical Vapour Deposition (CVD): It is a hybrid method using chemicals in vapour phase. Basic CVD process can be considered as a transport of reactant vapour or reactant gas towards the substrate kept at some high temperature where the reactant cracks into different products which diffuse on the surface, undergo some chemical reaction at appropriate site, nucleate and grow to form the desired material film. The by-products created on the substrate have to be transported back to the gaseous phase removing them from the substrate. Vapours of desired material may be often pumped into reaction chamber using some carrier gas. In some cases the reactions may occur through aerosol formation in gas phase. There are various processes such as reduction of gas, chemical reaction between different source gases, oxidation or some disproportionate reaction by which CVD can proceed. However, it is preferable that the reaction occurs at the substrate rather than in the gas phase. Usually temperature ~ 300 to 1200 C is used at the substrate. There are two ways viz., hot wall and cold wall by which substrates are heated. In hot wall set up the deposition can take place even on reactor walls. This is avoided in cold wall design. Besides this, the reaction can take place in gas phase with hot wall design,which is suppressed in cold wall set up. Further, coupling of plasma with chemical reaction in cold wall set up is feasible. Usually gas pressures in the range of 0.1 torr to 1.0 torr are used. Growth rate and film quality depend upon the gas pressure and the substrate temperature. When the growth takes place at low temperature, it is limited by the kinetics of surface tension.

CVD is widely used in industry because of relatively simple instrumentation, ease of processing, possibility of depositing different types of materials and economic viability. Under certain deposition conditions nanocrystalline films or single crystalline films are possible. There are many variants of CVD like metallo organic CVD (MOCVD), atomic layer epitaxy (ALE), vapor phase epitaxy (VPE), plasma enhanced CVD (PECVD) etc. They differ in source gas pressure, geometrical layout, temperature used etc.

(i) Electric Arc Deposition: This is one of the simplest and useful methods, which leads to mass scale production of fullerenes and carbon nanotubes. It requires water cooled vacuum chamber and electrodes to strike an arc between them. The positive electrode itself acts as the source of material. If some catalyst are to be used, there can be some additional thermal source of evaporation. Inert gas or reactive gas introduction is necessary. Usually the gap between the electrodes is ~1mm and high current ~50 to 100 amperes is passed from a low voltage power supply (~12-15 volts). Inert gas pressure is maintained in the vacuum system. When an arc is set up, anode material evaporates. This is possible as along as the discharge can be maintained. By striking the arc between the two graphite electrodes, it is possible to get fullerenes in large quantity. In case of fullerenes, the formation occurs at low helium pressure as compared to that used for nanotube formation. Also, fullerenes are obtained by purification of soot collected from inner walls of vacuum chamber, whereas nanotubes are found to be formed only at high He gas pressure and in the central portion of the cathode. No carbon nanotubes are found on the chamber walls

(j) Ion Implantation: In this method high energy (few keV to hundereds of keV) or low energy (<200 eV) ions are used to obtain nanoparticles. Ions of interest are usually formed using an ion gun specially designed to produce metal ions, which are accelerated to high or low energy towards the substrate heated to few hundered of C. Depending upon the energy f the incident ions, various other processes like sputtering and generation of electromagnetic radiation may take place. It is possible to obtain single element nanoparticles or compounds and alloys of more than one element. In some experiments it has been possible to even obtain doped nanoparticles using ion implantation. There is possibility of making nanoparticles using swift heavy ions (few MeV energy) employing ion accelerators like a pelletron.

(k) Molecular beam epitaxy (MBE): This technique of deposition can be used to deposit elemental or compound quantum dots, quantum wells, quantum wires in a very controlled manner. High degree of purity in materials is achievable using ultra high vacuum (better than torr). Special sources of deposition known as Kundsen cell (K-cell) or effusion cell are employed to obtain molecular beams of the constituent elements. The rate of deposition is kept very low and substrate temperature is rather high in order to achieve sufficient mobility of the elements on the substrate and layer by layer growth to obtain nanostructures.

(l) Thermolysis: Nanoparticles can be made by decomposing solids at high temperature having metal cations, and molecular anions or metal organic compounds. The process is called thermolysis. For example, small lithium particles can be made by decomposing lithium azide, LiN3. The material is placed in an evacuated quartz tube and heated to 400 C. At but 370 C LiN3 decomposes, releasing N2 gas, which is observed by an increase in the pressure on the vacuum gauge. In a few minutes the pressure drops back to its original low value, indicating that all the N2 has been removed. The remaining lithium atoms coalesce to form small colloidal metal particles. Particles less than 5nm can be made by this method. Passivation can be achieved by introducing an appropriate gas.

(m) Pulsed laser method: Pulsed lasers have been used in the synthesis of nanoparticles of silver. Silver nitrate solution and a reducing agent are flowed through a blenderlike device. In the blender there is a solid disk, which rotates in the solution. The solid disk is subjected to pulses from a laser beam creating hot spots on the surface of the disk. Silver nitrate and the reducing agent react at these hot spots, resulting in the formation of small silver particles, which can be separated from the solution using a centrifuge. The size of particles is controlled by the energy of the laser and rotation speed of the disk. This method is capable of a high rate of production.