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A REVIEW ON NANOPARTICLES: SYNTHESIS, CHARACTERIZATION AND APPLICATIONS

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ABSTRACT

Generally nanoparticles size ranges from 1 to 100 nm with one (or) more dimensions. Generally nanoparticles classified into inorganic, organic and particles based on carbon in nanometric scale that has properties improved compared to larger size of respective materials. They show properties which are enhanced such as strength, sensitivity, high reactivity, stability, surface area etc., due to their smaller size. They were synthesized by various methods for research and commercial uses which are classified into three types-chemical, physical and mechanical processes which had sawn a vast improvement. We have prepared this paper to present a review on nanoparticles, their types, characterization, synthesis methods and applications in field of environment.

KEYWORDS: Nanoparticles, types, synthesis, characteristics and applications.

INTRODUCTION

Nanoparticles are the fundamental components of Nano technology. Nano particles size ranges from 1 to 100nm which are made up of metal, metal oxides, organic matter, carbon.[1] Nanoparticles differ from various dimensions, to shapes and sizes apart from their material.[2] Surface can be irregular with surface variations or a uniform. Among nanoparticles some are crystalline or amorphous with single or multi-crystal solids either agglomerated or loose.[3] In the process of synthesizing new drugs, most drug candidates are insoluble or poorly soluble in water which causes a huge downfall for the pharmaceutical industry. One of the main reasons for a drug's insolubility is its complex and large molecular structure. It has been reported that over 65% of new active pharmaceutical ingredients (APIs) are either poorly soluble in water or insoluble**.** Due to their low aqueous solubility properties and high permeability, they are categorized as class II of the Biopharmaceutics Classification System (BCS), where the dissolution step is the rate limiting factor in drug absorption. The pharmaceutical industries are now facing a challenge to improve the dissolution characteristic of poorly water-soluble drugs which is the key factor in enhancing drug bioavailability. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties. This review predominately focused on synthesis of different types of nanoparticles using chemical, physical and biological methods. However, chemical and physical methods are expensive and harmful but biological method is simple, non-toxic, rapid and eco- friendly. It also explains about the characteristics of nanoparticles and concluded with various applications.

Classification of Nanoparticles

The nanoparticles are generally classified into the organic, inorganic and carbon based.

1. Organic nanoparticles: micelles, Dendrimers, ferritin and liposomes etc. are commonly known polymers or organic nanoparticles. These nanoparticles are non-toxic, biodegradable, and some particles such as liposomes and micelles have a hollow core also known as nano capsules and are sensitive to thermal and electromagnetic radiation such as heat and light.[4] The organic nanoparticles are most widely used in the biomedical field for example drug delivery system as they are efficient and also can be injected on specific parts of the body which is also known as targeted drug delivery. Examples of organic nanoparticles are liposomes, dendrimers and micelles.

2. Inorganic nanoparticles: Inorganic nanoparticles are particles which are not made up of carbon. Metal and metal oxide-based nanoparticles are generally categorized as inorganic nanoparticles.

a. Metal NPs: Almost all the metals can be synthesised into their nanoparticles.[5] The commonly used metals for nanoparticle synthesis are aluminium (Al), cadmium (Cd), cobalt (Co), copper (Cu), gold (Au), iron (Fe), lead (Pb), silver (Ag) and zinc (Zn). These nanoparticles can be synthesized by chemical, electrochemical, or photochemical methods. In chemical methods, the metal

nanoparticles are obtained by reducing the metal-ion precursors in solution by chemical reducing agents. These have the ability to adsorb small molecules and have high surface energy. These nanoparticles have applications in research areas, detection and imaging of biomolecules and in environmental and bioanalytical applications. For example, gold nanoparticles are used to coat the sample before analyzing in SEM. This was usually done to enhance the electronic stream, which helps us to get high quality SEM images. Due to their advanced optical properties, metal NPs find applications in many research areas.

b. Ceramic NPs: Ceramic nanoparticles are inorganic solids made up of carbides, carbonates, oxides, carbides, carbonates and phosphates synthesized via heat and successive cooling. They can be found in polycrystalline, dense, amorphous, polycrystalline, dense, porous or hollow forms. Therefore, these NPs are getting great attention of researchers due to their use in applications such as catalysis, photocatalysis, photodegradation of dyes. By controlling some physical properties, these nanoparticles can be formulated in drug delivery system especially in targeting tumors, glaucoma, and some bacterial infections.

c. Semiconductor NPs: Semiconductor nanoparticles have properties like those of metals and non-metals. They are found in the periodic table in groups II-VI, III-V or IV-VI. These particles have wide bandgaps, which on tuning shows different properties. They are used in photocatalysis, electronics devices, photo-optics and water splitting applications. Semiconductor materials possess properties between metals and nonmetals and therefore they found various applications in the literature due to this property.

Some examples of semiconductor nanoparticles are GaN, GaP, InP, InAs from group III-V; ZnO, ZnS, CdS, CdSe, CdTe are II-VI semiconductors and silicon and germanium are from group IV.[6]

d. Polymeric NPs: These are normally organic based NPs and in literature a special term polymer nanoparticle (PNP) is collectively used for it. Depending up on the preparation these are nanospheres or nano-capsular shaped. The former are matrix particles whose overall mass is generally solid and the other molecules are adsorbed at the outer boundary of the spherical surface. In the latter case the solid mass is encapsulated within the particle completely. The PNPs are readily functionalized and thus find bundles of applications in the literature.

Some of the merits of polymeric nanoparticles are controlled release, protection of drug molecules, ability to combine therapy and imaging, specific targeting and many more. They have applications in drug delivery and diagnostics. The drug deliveries with polymeric nanoparticles are highly biodegradable and biocompatible.

e. Lipid-based NPs: Lipid nanoparticles are generally spherical in shape with a diameter ranging from 10 to 100 nm. It consists of a solid core made of lipid and a matrix containing soluble lipophilic molecules. The external core of these nanoparticles is stabilized by surfactants and emulsifiers. These nanoparticles have application in the biomedical field as a drug carrier and delivery and RNA release in cancer therapy.

3. Carbon-based NPs: Carbon-based nanoparticles include two main materials, namely, carbon nanotubes (CNTs) and fullerenes. CNTs are nothing but graphene sheets rolled into a tube. These materials are mainly used for the structural reinforcement as they are 100 times stronger than steel. CNTs can be classified into single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). CNTs are unique in a way as they are thermally conductive along the length and non-conductive across the tube. Fullerenes are the allotropes of carbon having a structure of hollow cage of sixty or more carbon atoms. The structure of C-60 is called Buckminsterfullerene, and looks like a hollow football. The carbon units in these structures have a pentagonal and hexagonal arrangement.[7] These have commercial applications due to their electrical conductivity, structure, high strength, and electron affinity. The rolled sheets can be single, double or many walls and therefore they are named as single-walled (SWNTs), double-walled (DWNTs) or multi-walled carbon nanotubes (MWNTs), respectively. They are widely synthesized by deposition of carbon precursors especially the atomic carbons, vaporized from graphite by laser or by electric arc on to metal particles. Lately, they have been synthesized via chemical vapor deposition (CVD) technique. Due to their unique physical, chemical and mechanical characteristics, these materials are not only used in pristine form but also in nano-composites for many commercial applications such as fillers, efficient gas adsorbents for environmental remediation and as support medium for different inorganic and organic catalysts.[8]

Synthesis of Nanoparticles: The nanoparticles are synthesized by various methods that are categorized into bottom-up or top-down method. A simplified representation of the process is presented in synthesis process.

1. Bottom-up method: Bottom-up or constructive method is the build-up of material from atom to clusters to nanoparticles. Sol-gel, spinning, chemical vapour deposition (CVD), pyrolysis and biosynthesis are the most commonly used bottom-up methods for nanoparticle production.

- **Sol-gel:** The sol – a colloidal solution of solids suspended in a liquid phase. The gel – a solid macromolecule submerged in a solvent. Sol-gel is the most preferred bottom-up method due to its simplicity

and as most of the nanoparticles can be synthesized from this method. It is a wet-chemical process containing a chemical solution acting as a precursor for an integrated system of discrete particles. Metal oxides and chlorides are the typically used precursors in sol-gel process.[9] The precursor is then dispersed in a host liquid either by shaking, stirring or sonication and the resultant system contains a liquid and a solid phase. A phase separation is carried out to recover the nanoparticles by various methods such as sedimentation, filtration and centrifugation and the moisture is further removed by drying.

- **Spinning:** The synthesis of nanoparticles by spinning is carried out by a spinning disc reactor (SDR). It contains a rotating disc inside a chamber/reactor where the physical parameters such as temperature can be controlled. The reactor is generally filled with nitrogen or other inert gases to remove oxygen inside and avoid chemical reactions. The disc is rotated at different speeds where the liquid i.e., precursor and water are pumped in. The spinning causes the atoms or molecules to fuse together and is precipitated, collected and dried[10]. The various operating parameters such as the liquid flow rate, disc rotation speed, liquid/precursor ratio, location of feed, disc surface, etc. determines the characteristics nanoparticles synthesized from SDR.
- **Chemical Vapor Deposition (CVD):** Chemical vapour deposition is the deposition of a thin film of gaseous reactants onto a substrate. The deposition is carried out in a reaction chamber at ambient temperature by combining gas molecules. A chemical reaction occurs when a heated substrate comes in contact with the combined gas.[8,11] This reaction produces a thin film of product on the substrate surface that is recovered and used. Substrate temperature is the influencing factor in CVD. The advantages of CVD are highly pure, uniform, hard and strong nanoparticles. The disadvantages of CVD are the requirement of special equipment and the gaseous by-products are highly toxic.
- **Pyrolysis:** Pyrolysis is the most commonly used process in industries for large-scale production of nanoparticle. It involves burning a precursor with flame.[12] The precursor is either liquid or vapour that is fed into the furnace at high pressure through a small hole where it burns.[13] The combustion or by-product gases are then air classified to recover the nanoparticles. Some of the furnaces use laser instead of flame to produce high temperature for easy evaporation. The advantages of pyrolysis are simple, efficient, cost effective and continuous process with high yield.

Biological synthesis of Nanoparticles

- The synthesis of nanoparticles by biological synthesis carried by the following methods

Synthesis by plant extract: The synthesis by plant extract is free from toxicity and the plants tender the superior option for the synthesis of nanoparticles. The gold and silver nanoparticles can be produced from the plant extracts like Geranium, aloe vera, sun dried cinnamon camphora, azadiracta indica etc.[14]

Synthesis by bacteria: The synthesis of NPs in previous years has enlarged comprehensively due to its immense applications. Bacillus species are widely used in the production of metal nanoparticles, since this bacterium has ability to fabricate extracellularly. The size ranges from 10 to 20 nm. Gold nanoparticles can also be produced.[15]

Synthesis by fungi: The nanoparticles can be produced by using various species of fungi like aspergillus niger, aspergillus orizae, fusarium solani. Phoma globerta has been traced to produce silver nanoparticles and its efficacy against *E.coli*, *S.aureus*, *P.aeruginosa* has been assessed.[16]

Synthesis by yeast: This uses *candida glabarta* and *schizosaccharomyce pombe* for the synthesis of cadmium nanoparticles. The silver and gold nanoparticles are also investigated using extremophilic yeast strain isolated from the acid mine drainage. The marine yeast *rodosporidium diobovatum* has been explored for the synthesis of stable lead sulphide nanoparticles.[17]

Synthesis by biological particles: The biological particles like proteins, peptides, virus, enzymes are used as biological particles in the synthesis of nanoparticles.[18] Tobacco mosaic virus helps in the mineralization of sulphides. Cowpea chlorotic mottle virus, cowpea mosaic virus have also been employed and these can be demonstrated on the surface of M13 bacteriophage.

2. Top-down methods

Top-down or destructive method is the reduction of a bulk material to nanometric scale particles. Mechanical milling, nanolithography, laser ablation, sputtering and thermal decomposition are some of the most widely used nanoparticle synthesis methods.

- **Mechanical milling:** Among the various top-down methods, mechanical milling is the most extensively used to produce various nanoparticles. The mechanical milling is used for milling and post annealing of nanoparticles during synthesis where different elements are milled in an inert atmosphere.[19] The influencing factors in mechanical milling is plastic deformation that leads to particle shape; fracture leads to decrease in particle size and cold-welding leads to increase in particle size.
- **Nanolithography:** Nanolithography is the study of fabricating nanometric scale structures with a minimum of one dimension in the size range of 1 to 100 nm. There are various nanolithographic processes for instance optical, electron-beam, multiphoton, nanoimprint and scanning probe lithography.[20] Generally, lithography is the process of printing a required shape or structure on a light sensitive material that selectively removes a portion of material to create the desired shape and structure. The main advantage of nanolithography is to produce from a single nanoparticle to a cluster with desired shape and size. The disadvantages are the requirement of complex equipment and the cost associated.[21]
- **Laser ablation:** Laser Ablation Synthesis in Solution (LASiS) is a common method for nanoparticle

production from various solvents. The irradiation of a metal submerged in a liquid solution by a laser beam condenses a plasma plume that produces nanoparticles.[22] It is a reliable top-down method that provides an alternative solution to conventional chemical reduction of metals to synthesis metal-based nanoparticles. As LASiS provides a stable synthesis of nanoparticles in organic solvents and water that does not require any stabilizing agent or chemicals, it is a 'green' process.

- **Sputtering:** Sputtering is the deposition of nanoparticles on a surface by ejecting particles from it by colliding with ions.[23] Sputtering is usually a deposition of thin layer of nanoparticles followed by annealing. The thickness of the layer, temperature and duration of annealing, substrate type, etc. determines the shape and size of the nanoparticles.[23]
- **Thermal decomposition:** Thermal decomposition is an endothermic chemical decomposition produced by heat that breaks the chemical bonds in the compound. The specific temperature at which an element chemically decomposes is the decomposition temperature.[24] The nanoparticles are produced by decomposing the metal at specific temperatures undergoing a chemical reaction producing secondary products.

Characterization of Nanoparticles

Zeta potential: The zeta potential of a nanoparticle is commonly used to characterise the surface charge property of nanoparticles. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential between −10 and +10 mV are considered approximately neutral, while nanoparticles with zeta potentials of greater than +30 mV or less than −30 mV are considered strongly cationic and anionic, respectively.[26] The zeta potential can also be used to determine whether a charged active material is encapsulated within the centre of the nanocapsule or adsorbed onto the surface. The magnitude of the Zeta Potential provides information about particle stability, with higher magnitude potentials exhibiting increased electrostatic repulsion and therefore increased stability.

- 0-5 mV: Particles tend to agglomerate or aggregate
- 5-20 mV: Particles are minimally stable
- 20-40 mV: Particles are moderately stable
- 40+ mV: Particles are highly stable

It is important to consider that the magnitude of the charge on the nanoparticle surface depends on the solution pH.

The Henry equation is then used to calculate the zeta potential, z:

$$Ue = \frac{2\varepsilon z f(ka)}{3\eta}$$

Where Ue is the electrophoretic mobility, e is the dielectric constant, η is the absolute zero-shear viscosity of the medium, f(ka) is the Henry function, and ka is a measure of the ratio of the particle radius to the Debye length.

UV-visible absorption spectroscopy: Absorbance spectroscopy is used to determine the optical properties of a solution. A Light is sent through the sample solution and the amount of absorbed light is measured. When the wavelength is varied and the absorbance is measured at each wavelength. The absorbance can be used to measure the concentration of a solution by using Beer-Lamberts Law.[27] The optical measurement of UV-visible spectrophotometer has different absorbance peak like 410 nm.

X-ray diffraction (XRD) analysis: X-ray diffraction is a conventional technique for determination of crystallographic structure and morphology. There is increase or decrease in intensity with the amount of constituent. This technique is used to establish the metallic nature of particles, gives information on translational symmetry size and shape of the unit cell from peak positions and information on electron density inside the unit cell, namely, where the atoms are located from peak intensities.[28] XRD patterns were calculated using X per Rota flex diffraction meter using Cu K radiation and =1.5406 Å. Crystallite size is calculated using Scherrer equation:

$$CS = K / \cos$$

Where CS is the crystallite size Constant [K] = 0.94 is the full width at half maximum [FWHM] in radius

$$[\beta] = FWHM \times \pi / 180\lambda$$

Cos = Bragg angle. X-ray diffraction analysis with various nanoparticles has been studied by various research workers to find the high crystallinity of the prepared sample.

Fourier Transform Infrared [FTIR] spectroscopy: It measures infrared intensity vs. wavelength of light, it is used to determine the nature of associated functional groups and structural features of biological extracts with nanoparticles. The calculated spectra clearly reflect the well-known dependence of nanoparticle optical properties. The green synthesized silver nanoparticle by employing various leaf extract was analysed using Fourier Transform Infrared [FTIR] Spectroscopy showed characteristic peaks.

Microscopic techniques: These techniques namely SEM and TEM mainly used for morphological studies of nanoparticles.[29] Many researchers used these techniques to show that the synthesized nanoparticles were more or less uniform in size and shape.

Transmission electron microscopy (TEM): Transmission electron microscopy is a microscopy technique in which a beam of electrons is transmitted through an ultra-thin specimen, interacting with the specimen as it passes through. An image is formed from

the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device, such as a fluorescent screen, on a layer of photographic film, or to be detected by a sensor such as a CCD camera.[29] TEM forms a major analysis method in a range of scientific fields, in both physical and biological sciences. TEMs find application in cancer research, virology, materials science as well as pollution, nanotechnology, and semiconductors.

Scanning electron microscope: The characterization of Scanning electron microscopic analysis is employed to determine the size, shape & morphologies of formed nanoparticles. SEM gives high resolution images of the surface of a sample as desired. The scanning electron microscope works with same principle as an optical microscope, but it measures the electrons scattered from the sample rather than photon. Because electrons can be accelerated by an electric potential, the wavelength can be made shorter than the one of photons.[29] This makes the SEM capable of magnifying images up to 200,000 times. Measures the particle size and characterization, Conductive or sputter coated sample is involved and the sensitivity down to 1nm.

Applications of Nanoparticles

General applications of organic nanoparticles

Micelles

- In treatment of malignant tumours
- Reduces enzymatic degradation and inactivation of drugs
- Improves stability of the drugs
- Reduces critical micellar concentration

Liposomes: Liposomes have also been used to fortify dairy products with vitamins to increase their nutritional value as well as to aid in digestion of constituents inherent to dairy products. Usually phospholipids are used to form the bilayer, and frequently used phospholipids are phosphatidyl choline (neutral charge), and the negatively charged phosphatidic acid, phosphatidyl glycerol, phosphatidyl serine, and phosphatidyl ethanolamine. Archaeosomes are liposomes made from one or more of the polar ether lipids extracted from the Archaeobacteria. As compared with liposomes (which is made from ester phospholipid), archaeosomes are relatively more thermostable and more resistant to oxidation, chemicals and enzymatic hydrolysis. They are also more resistant to low pH and bile salts that would be encountered in the gastrointestinal tract.[30]

Dendrimers: Dendrimers can also be used in various fields like gene delivery, conjugate systems, boron neutron capture therapy, molecular recognition, and for drug delivery.[31] It includes use as contrast agents, such as for magnetic resonance imaging (MRI), but more significantly, as a carrier for drug delivery in cancer treatment. Enzymatic degradation and inactivation is hindered, improving drug stability. In the treatment of malignant tumor, mostly polymeric micelles are used. Enzymatic degradation and inactivation is hindered, improving drug stability. In the treatment of malignant tumor, mostly polymeric micelles are used. Enzymatic degradation and inactivation is hindered, improving drug stability. In the treatment of malignant tumor, mostly polymeric micelles are used.

General Applications of Inorganic Nanoparticles

Therapeutic applications of metallic nanoparticles

As anti-Infective Agents: Metallic nanoparticles have been described as a HIV preventative therapeutic. In a couple of studies, it has been shown that as virucidal agent silver acts directly on the virus by binding to the glycoprotein gp120. This binding in turn prevents the CD4 dependent virion binding which effectively decreases HIV1's infectivity.[32] and it has also been reported that metallic nanoparticles have been effective antiviral agents against herpes simplex virus, influenza, respiratory syncytial viruses.

As anti-Angiogenic: Angiogenesis is the development of new blood vessels and occurs during normal development and in some disease states. It plays a main role in number of diseases such as cancer, rheumatoid arthritis. In normal conditions, angiogenesis is tightly regulated between various pro-angiogenic growth factors (VEGF, PDGF, and TGF-B) and anti-angiogenic factors (platelet factor 4, TSP-1). Under diseased conditions, angiogenic is turned on. Some reviews have reported that these agents have serious toxicities such as fatal haemorrhage, thrombosis, and hypertension. It may be overcome if these nanoparticles alone can be efficacious as an anti-angiogenic agent.[33]

In Tumour Therapy: It has been studied that naked gold nanoparticles inhibited the activity of heparin-binding proteins such as VEGF165 and bFGF *in vitro* and VEGF induced angiogenesis *in vivo*. Further work in this area has been reported that onto the surface of AuNPs heparin binding proteins are absorbed and were subsequently denatured.[34] The researchers also showed that surface size plays a main role in the therapeutic effect of AuNPs. Mukherjee and colleagues also experimented the effect of gold nanoparticles on VEGF mediated angiogenesis using a mouse ear model injected with an adrenoviral vector of VEGF. A week later, the AdVEGF administration, mice treated with AuNPs developed lesser edema than the same treated mice. Eom and Colleagues revealed the anti-tumour effects of 50 nm AgNps In vitro and In vivo.

In Multiple Myeloma: Researchers have designed a nanoparticle based therapy that is effective in treating mice with multiple myeloma. Multiple myeloma is a cancer that affects plasma cells.

In Leukaemia: B-chronic Lymphocytic Leukaemia (CLL) is an incurable disease predominantly characterized by apoptosis resistance, by co-culture with an anti-VEGF antibody, found induction of more

apoptosis in CCL B cells. In CLL therapy, gold nanoparticles were used to increase the efficacy of these agents. Gold nanoparticles were chosen based on their biocompatibility, very high surface area, surface functionalization and ease of characterization. To the gold nanoparticles, VEGF antibodies were attached and determined their ability to kill CLL B cells.[35]

In Rheumatoid Arthritis: Scientists from the University of Wollongong (Australia) have built a new class of anti-arthritic drug which could be used by gold nanoparticles and it has fewer side effects. Rheumatoid arthritis is an autoimmune disease that occurs when the immune system does not function properly and attacks a patient's joints. New research has shown that gold particles can invade macrophages, and stop them from producing inflammation without killing them. In the Journal of inorganic biochemistry it has been published that by reducing the size of gold into smaller nanoparticles (50 nm), it was able to cause more gold to immune cells with lesser toxicity.[36]

In Photo Thermal Therapy: Gold nanoparticles absorb light strongly as they convert photon energy into heat quickly and efficiently. Photo-thermal therapy (PTT) is an invasive therapy in which photon energy is converted into heat to kill cancer. In Radiotherapy Tumours are loaded with gold, this absorbs more X-rays as gold is an excellent absorber of X-rays. Thus, deposition of more beam energy and resulting in a local dose which increases specifically to tumour cells. Gold nanoparticles have been more useful to treat cancer.[37]

Therapeutic applications of ceramic nanoparticles: Ceramic nanoparticles like titania have also been added into polymer matrices to adjust composite surface chemistry, topography, and wettability (surface energetics) of the polymer matrix, aiming at the promotion of osteogenic responses on the material surfaces.[38]

- Functionalized magnesium oxide, zirconia, sulfate, and calcium carbonate are added to polymethylmethacrylate (PMMA) bone cement to reduce the exothermic effect of PMMA while increasing its cytocompatibility, X-ray radiopacity, as well as antibacterial potential.
- Antibacterial effects of $BaSO_4$ nanoparticles against *Staphylococcus aureus* and *Pseudomonas aeruginosa* have been discovered, suggesting their potential applications as anti-infective additives to bone cement, implant coating, and medical tubing.
- Therefore, these NPs are used by researchers across the globe in wide applications, such as catalysis, photocatalysis, photo degradation of dyes, and imaging applications. Medical technologies use nanoceramics for bone repair.[39]
- Ceramic NPs are also used in energy supply and storage, communication, transportation systems, construction, and medical technology.
- One of the main uses of nanoceramics has been in biomedicine and medical technology, particularly in bone repair. Bioactive ceramics closely match the properties of bone and can act as a nanoscaffold to help support bone regrowth.
- It has also been suggested that nanoceramics might find uses in energy supply and storage, communications, transportation systems, aerospace and construction. They have also found use in electronics as insulators, semiconductors, conductors and magnets.[38,39]
- Nanoceramics might also find a use in armor to replace the stiff, tough layers of woven fiber which absorbs impact. A hard body armor is under development that includes ceramic inserts and steel or titanium panels that could offer greater protection against blunt trauma and high velocity ammunition. The inserts could absorb kinetic energy of the projectile and dissipate it in a localized shattering of the ceramic insert.

Therapeutic applications of Polymeric nanoparticles

- They develop innovative drug delivery system in the treatment of neurodegenerative and brain associated diseases.
- Polymeric NPs provide protection to the drugs via encapsulating, entrapping them inside the core, conjugating, or adsorbing them on to the particle surface.
- Polymeric NPs deliver cargo-loaded molecules across the BBB by following endocytosis and transcytosis pathways.
- This polymeric coating is thought to reduce immunogenicity, and limit the phagocytosis of nanoparticles by the reticulo-endothelial system, resulting in increased blood levels of drug in organs such as the brain, intestines, and kidneys.
- These have been applied in gene therapy to breast cancer cells, resulting in anti-proliferative effects.

Therapeutic applications of lipid based nanoparticles

- These are mainly used to various types of cancer like GIT cancer, lung cancer, breast cancer, pancreatic cancer, prostate cancer.[40]
- It significantly enhances transdermal penetration of phytomedicines inside skin.
- SLNs increase the therapeutic potential of eugenol and efficiently inhibited the growth of Candida infection during oral candidiasis.
- It has enhanced antimicrobial activity.

Therapeutic applications of semiconductor nanoparticles: It has significant attention in research and applications in emerging technologies such as nanoelectronics, nanophotonics, energy conversion, non-linear optics, miniaturized sensors and imaging devices, solar cells, catalysis, detectors, photography biomedicine etc.[41]

Therapeutic applications of carbon based nanoparticles

Drug and gene delivery: The application as drug delivery is very common in carbon-based nanoparticles, especially, the graphene-based nanoparticles. The π-conjugated structure of six-atom rings of carbon can be conceptually considered as a planar aromatic macromolecule. This unique structure offers a large loading capability to a variety of fluorescent probes and drugs. The chemical modification of graphene can allow the conjugation with targeting ligands, therefore, achieve the targeted delivery of the drug. Both *in vitro* and *in vivo* studies have provided the evidence of the graphene for delivering anti-cancer drugs to the desired location of tumor cells, rather than the normal and healthy cells.

Bioimaging: Carbon-based materials have long been investigated in many imaging applications. For example, fluorescence imaging (FL), two-photon FL, Raman imaging, magnetic resonance imaging (MRI), tomography (CT), photoacoustic imaging (PAI), computed positron emission tomography/single photon emission computed tomography (PET/SPECT), and multimodal imaging. Recently, a new form of carbon-based nanomaterials, carbon quantum dots, has attracted tremendous interests in its bioimaging applications.

Energy sources: Carbon-based nanomaterials have been widely investigated as the catalysts and key components of hydrogen storage systems. Due to their intrinsic characteristics, carbon-based materials are a desired material as electrodes in capacitors and batteries. CNTs have shown a high reversible capacity for use in lithium-ion batteries and also in a variety of fuel cell components. The high electrical conductivity also allows the CNT be used in current collectors and gas diffusion layers. The high surface area and thermal conductivity make CNT and graphene very useful as electrode catalyst supports in fuel cells.

Common Applications of Nanoparticles

Tumor targeting using nanoparticulate delivery systems

The rationale of using nanoparticles for tumor targeting is based on

1) Nanoparticles will be able to deliver a concentrated dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles.
2) Nanoparticles will reduce the drug exposure of healthy tissues by limiting drug distribution to target organ.

When conventional nanoparticles are used as carriers in chemotherapy, some cytotoxicity against the Kupffer cells can be expected, which would result in deficiency of Kupffer cells and naturally lead to reduced liver uptake and decreased therapeutic effect with intervals of less than 2 weeks administration. Moreover, conventional nanoparticles can also target bone marrow (MPS tissue), which is an important but unfavorable site of action for most anticancer drugs because chemotherapy with such carriers may increase myelo suppresive effect. Therefore, the ability of conventional nanoparticles to enhance anticancer drugs' efficacy is limited to targeting tumors at the level of MPS-rich organs. Also, directing anticancer drug-loaded nanoparticles to other tumoral sites is not feasible if a rapid clearance of nanoparticles occurs shortly after intravenous administration.

Long circulating nanoparticles: To be successful as a drug delivery system, nanoparticles must be able to target tumors which are localized outside MPS-rich organs. In the past decade, a great deal of work has been devoted to developing so-called "stealth" particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes [42]. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the MPS. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins [43]. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production of nanoparticles. Efforts have been devoted to achieving "active targeting" of nanoparticles in order to deliver drugs to the right targets, based on molecular recognition processes such as ligand-receptor or antigen-antibody interaction. Considering the fact that folate receptors are over expressed on the surface of some human malignant cells and the cell adhesion molecules such as selectins and integrins are involved in metastatic events, nanoparticles bearing specific ligands such as folate may be used to target ovarian carcinoma while specific peptides or carbohydrates may be used to target integrins and selectins. Oyewumi et al demonstrated that the benefits of folate ligand coating were to facilitate tumor cell internalization and retention of Gd-nanoparticles in the tumor tissue. Targeting with small ligands appears more likely to succeed since they are easier to handle and manufacture. Furthermore, it could be advantageous when the active targeting ligands are used in combination with the long-circulating nanoparticles to maximize the likelihood of the success in active targeting of nanoparticles.

Reversion of multi-drug resistance in tumour cells: Anticancer drugs, even if they are located in the tumour interstitium, can turn out to be of limited efficacy against numerous solid tumour types, because cancer cells are able to develop mechanisms of resistance.[44] These mechanisms allow tumours to evade chemotherapy. Multi-drug resistance (MDR) is one of the most serious

problems in chemotherapy. MDR occurs mainly due to the over expression of the plasma membrane p-glycoprotein (Pgp), which is capable of extruding various positively charged xenobiotics, including some anticancer drugs, out of cells. In order to restore the tumoral cells' sensitivity to anticancer drugs by circumventing Pgp-mediated MDR, several strategies including the use of colloidal carriers have been applied. The rationale behind the association of drugs with colloidal carriers, such as nanoparticles, against drug resistance derives from the fact that Pgp probably recognizes the drug to be effluxed out of the tumoral cells only when this drug is present in the plasma membrane, and not when it is located in the cytoplasm or lysosomes after endocytosis.[45]

Nanoparticles for oral delivery of peptides and proteins: Significant advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of suitable carriers remains a challenge due to the fact that bioavailability of these molecules is limited by the epithelial barriers of the gastrointestinal tract and their susceptibility to gastrointestinal degradation by digestive enzymes.[46] Polymeric nanoparticles allow encapsulation of bioactive molecules and protect them against enzymatic and hydrolytic degradation. The gastrointestinal tract provides a variety of physiological and morphological barriers against protein or peptide delivery, e.g., (a) proteolytic enzymes in the gut lumen like pepsin, trypsin and chymotrypsin; (b) proteolytic enzymes at the brush border membrane (endopeptidases); (c) bacterial gut flora; and (d) mucus layer and epithelial cell lining itself.[47] The histological architecture of the mucosa is designed to efficiently prevent uptake of particulate matter from the environment. One important strategy to overcome the gastrointestinal barrier is to deliver the drug in a colloidal carrier system, such as nanoparticles, which is capable of enhancing the interaction mechanisms of the drug delivery system and the epithelial cells in the GI tract.

Targeting of nanoparticles to epithelial cells in the GI tract using ligands: Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be classified into those utilizing specific binding to ligands or receptors and those based on non-Specific adsorptive mechanism. The surface of enterocytes and M cells display cell-specific carbohydrates, which may serve as binding sites to colloidal drug carriers containing appropriate ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure by specific receptor-mediated mechanism. Different lectins, such as bean lectin and tomato lectin, have been studied to enhance oral peptide adsorption.[48] Vitamin B-12 absorption from the gut under physiological conditions occurs via receptor-mediated endocytosis. The ability to increase oral bioavailability of various peptides (e.g., granulocyte colony stimulating factor, erythropoietin) and particles by covalent coupling to vitamin B-12 has been studied.[49] For this intrinsic process, mucoprotein is required, which is prepared by the mucus membrane in the stomach and binds specifically to cobalamin. The mucoprotein completely reaches the ileum where resorption is mediated by specific receptors.

Nanoparticles for gene delivery: Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral and cell-mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system.[50] The key ingredient of polynucleotide vaccines, DNA, can be produced cheaply and has much better storage and handling properties than the ingredients of the majority of protein-based vaccines. Nanoparticles loaded with plasmid DNA could also serve as an efficient sustained release gene delivery system due to their rapid escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment.[56] This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morphogenic proteins.

Nanoparticles for drug delivery into the brain: The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water-soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid-soluble molecules by the function of enzymes or efflux pumps.[51] Consequently, the BBB only permits selective transport of molecules that are essential for brain function.

Nanoparticles in food products: Amorphous silica nanoparticles are used as anti-caking agent to maintain the flow properties in powder products (*e.g.*, instant soups) and to thicken pastes. The conventional form of amorphous silica is known as food additive E551**.** It is also used in cosmetics, especially in sunscreens. Sunscreens contain titanium dioxide and zinc oxide nanoparticles, because they are colorless and reflect/scatter ultraviolet light more efficiently than larger particles. The small size of nanoparticles provides the benefit of making them transparent, which results in better consumer acceptance and thus improves the protection of human skin against UV-induced damage. To improve the appearance of materials is still a major application of nanoparticles, just as in ancient times. A prominent example is automotive coatings, which consist of several layers. The timeline from the discovery in the

laboratory to a commercial product is typically very long. For example, from the first report on the use of titanium dioxide nanoparticles in a dye-sensitized solar cell it took more than 20 years to develop a commercially available product.

CONCLUSION

The foregoing discussion shows that nanoparticulate systems have great potentials, being able to convert poorly soluble, poorly absorbed and labile biologically active substance into promising deliverable drugs. The core of this system can enclose a variety of drugs, enzymes, genes and is characterized by a long circulation time due to the hydrophilic shell which prevents recognition by the reticular-endothelial system. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and particle engineering, is still required. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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