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Review Article

A BRIEF REVIEW ON INORGANIC NANOPARTICLES

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ABSTRACT

For the past few years, there has been significant research in the area of nanotechnology using nanoparticles. In the field of modern material science, inorganic nanoparticles are emerging as novel drug delivery system due to their unique physical properties that mainly include size dependent optical, magnetic, electronic, and catalytic properties. These nanoparticles possess high stability, large surface area, tunable compositions, abundant physicochemical multifunctionality and specific biological behaviors. Biocompatible inorganic material-based nano systems provide a novel choice to surmount effectively the intrinsic drawbacks of traditional organic materials in biomedical applications, especially in overcoming the multidrug resistance. The aim of this article is to review the types, synthesis methods and characterization techniques related to inorganic nanoparticles.

Keywords: Carbon nanotube, Characterization, Fullerene, Gold, Iron, Silica, Silver, Synthesis, Quantum dot

INTRODUCTION

Size is the fundamental defining characteristic of all nanomaterials. While size is an easy concept to understand, it is more difficult to apply because there are no natural, physical or chemical boundaries that delineate the "nanoscale." By convention, 1-100 nm is the size range most commonly used in reference to nanomaterials, but there is no bright line that clearly demarks the nanoscale from a chemical or biological perspective [1]. Pharmaceutically important inorganic nanoparticles are discussed in this review.

Metallic inorganic nanoparticles

Metallic nanoparticles have fascinated scientists for over a century and are now heavily utilized in biomedical sciences and engineering. Today these materials can be synthesized and modified with various chemical functional groups which allow them to be conjugated with antibodies, ligands, and drugs of interest and thus opening a wide range of potential applications in biotechnology, magnetic separation, preconcentration of target analytes, targeted drug delivery, and vehicles for gene and drug delivery and more importantly diagnostic imaging. Moreover, various imaging modalities have been developed over the period of time such as magnetic resonance imaging, computed tomography, positron emission tomography, ultrasound, surface-enhanced Raman spectroscopy and optical imaging as an aid to image various disease states. These imaging modalities differ in both techniques and instrumentation and more importantly require a contrast agent with unique physiochemical properties. This led to the invention of various nanoparticulate contrast agents such as magnetic nanoparticles (Fe_3O_4), gold, and silver nanoparticles for their application in these imaging modalities. In addition, to use various imaging techniques in tandem newer multifunctional nanoshells and nanocages have been developed [2]. Over the years, nanoparticles such as gold, silver and magnetic nanoparticles (iron oxide), have been continuously used and modified to enable their use as a diagnostic and therapeutic agent [3].

Gold nanoparticles (GNPs)

GNPs occur in various size ranges from 2-100 nm; however 20-50 nm particle size ranges showed the most efficient cellular uptake. Specific cell toxicity has been shown by 40-50 nm particles. These 40-50 nm particles diffuse into tumors and easily recover it. In contrast, a larger particle, i.e., 80-100 nm does not diffuse into the tumor and stay near the blood vessels [4, 5]. The size can be controlled during their synthesis and functionalization with different groups. The size of the conjugated nanoparticles depends on upon the thiol/gold ratio [6]. When the amount of thiol is high, then the particle size will be small [7]. The GNPs have following advantages, it has unique physical and chemical properties which enhance the efficiency of drugs**,** drug loading, biocompatible, easily reach to the targeted site with blood flow, non-cytotoxic to the normal cells, and can be synthesized by various methods [8-10]. The gold nanorods, gold nanoshells, gold nanocages and gold nanospheres, are various types of GNPs [11].

The physical, chemical and biological methods can be employed for the synthesis of GNPs. The physical methods are initially used to give a low yield [12]. Chemical methods use various chemical agents to reduce metallic ions to nanoparticles. This comprises certain drawbacks as there will be the use of toxic chemicals and generation of hazardous by-products [13]. In the medical aspects, applications of nanoparticles increased tremendously only when the biological approach for nanoparticle synthesis came into focus. These methods are listed in (table 1) [14-16].

Table 1: Methods of synthesis of GNPs [17]

Chemical methods	Template method
	Electrochemical method
	PEGylation
	Turkevich method
	Brust method
	Perrault method
	Martin method
	Citrate thermo reduction method
	Solvent free photochemical method
	Oligonucleotide-functionalized nanoparticles
	Seed-mediated method
	Non-seed mediated method
	Hot injection technique
	Surfactant assisted method
	Two phase method
	Stober process
Physical methods	Sonolysis
	γ-irradiation method
Green methods	Green biosynthesis method
	Sunlight irradiation method
	New green chemistry method

The GNPs can be applied in diverse applications like *in vitro* assays, *in vivo* imaging, cell and phantom imaging, nucleic acid delivery, drug delivery, *in vivo* targeting and GNPs-clinical trials [18, 19].

Silver nanoparticles (AgNPs)

Silver was known only as a metal until the recent advent of the nanotechnology era, when it became recognized that silver could be produced at the nanoscale. Metallic silver has been subjected to recent engineering technologies, resulting in ultrafine particles, the size of which is measured in nanometres (nm) and possess distinctive morphologies and characteristics. Silver nanoparticles are emerging as promising agents for cancer therapy. The anticancer activities of nano-sized silver particles have been evaluated against a variety of human cancer cells, including the breast cancer cells [20]. The AgNPs have following advantages like synthesized by various methods, used as biosensor materials; optical properties are exhibited by AgNPs, ability to enhance wound healing, utilized in the medical industry due to their antibacterial, antifungal, antiviral, anti-inflammatory and osteoinductive effect [21-23].

Synthesis of AgNPs

Silver nanoparticles can be synthesized by various physical, chemical and biological methods. These methods are listed in (table 2).

Table 2: Methods of synthesis of AgNPs [24]

Chemical methods	Chemical reduction Microemulsion technology UV initiated photoreduction Photoinduced reduction Electrochemical method Electrochemical synthetic method Irradiation Methods ➢ Microwave assisted synthesis ➢ Radiolysis ➢ γ-ray irradiation From polymers and polysaccharides Tollens method Pyrolysis
Physical methods	Physical vapor condensation Arc-discharge method Evaporation-condensation
Bio-based methods	From bacteria, fungi, yeast, algae and plants

Iron oxide nanoparticles (INPs)

Iron (III) oxide (Fe_2O_3) is a reddish brown, inorganic compound which is paramagnetic in nature and also one of the three main oxides of iron, while other two being FeO and Fe_3O_4. The Fe_3O_4, which also occurs naturally as the mineral magnetite, is super paramagnetic in nature. Due to their ultrafine size, magnetic properties, and biocompatibility, super paramagnetic iron oxide nanoparticles (SPIONs) have emerged as promising candidates for various biomedical applications, such as enhanced resolution contrast agents for magnetic resonance imaging (MRI), targeted drug delivery and imaging, hyperthermia, gene therapy, stem cell tracking, molecular/cellular tracking, magnetic separation technologies (e. g., rapid DNA sequencing) for early detection of inflammatory, cancer, diabetes, and atherosclerosis [25, 26].

Developing magnetic nanoparticles in the nanometer range is a complex process and various chemical routes for their synthesis have been proposed. These methods include micro emulsions, sol-gel synthesis, sonochemical reactions, and hydrothermal reactions, thermolysis of precursors, flow injection syntheses and electrospray synthesis [27, 28]. However, the most common method for the production of magnetite nanoparticles is the chemical co-precipitation technique of iron salts [29, 30]. The main advantage of the co-precipitation process is that a large amount of nanoparticles can be synthesized; however this method has limited control on size distribution. This is mainly due to that the kinetic factors are controlling the growth of the crystal. Thus, the particulate magnetic contrast agents synthesized using these methods include ultra-small particles of iron oxide (USPIO) (10-40 nm), small particles of iron oxide (SPIO) (60-150 nm). Besides, monocrystalline USPIOs are also called as monocrystalline iron oxide nanoparticles (MIONs), whereas MIONs when cross-linked with dextran they are called cross-linked iron oxide nanoparticles (10-30 nm) [31].

The particles synthesized with these methods tend to aggregate through non-covalent interactions. Many surfactants and other organic compounds with specific functional groups have been utilized for the stabilization of INPs [32]. The water soluble stabilizers like polyethylene glycol, polyvinyl alcohol, polyamides, etc., are especially useful for the synthesis of INPs for biomedical applications. The stabilizers can be incorporated at the time of synthesis of INPs, prevent particle coalescence during formation. The particle size can also be controlled by the varying stabilizer concentration [33]. Specific bio molecular ligands can be conjugated to INPs surface using the specific functionality of stabilizers, which in turn can be used for selective targeting of specific cells, tissues or organs.

INPs serve excellent contrast agent for MRI. The ability of INP as MRI contrast agent, together with the potential for selective targeting resulted in wide range potential applications in MRI-based imaging and diagnostics. Several antibodies and other ligands have been conjugated to INPs and tested for MRI imaging of tumours [34]. Using INPs conjugated with a cell surface receptor specific ligands, a modified cellular enzyme-linked immunosorbent assay (ELISA) called cellular magnetic linked immunosorbent assay (C-MALISA) has also been developed [35]. The magnetic property of INPs also holds potential for applications in drug and gene delivery [36]. Like GNPs and other metal nanoparticles, INPs shows hyperthermia. INPs targeted to tumors can be used for simultaneous MRI imaging and destruction by heating.

The INPs shows wide applications like tumor targeting, protein separation and purification, drug delivery, MRI contrast agents, bio sensing, diagnostics and imaging [37, 38].

Quantum dots (QDs)

When a solid exhibits a distinct variation of optical and electronic properties with a variation of particle size<100 nm, it can be called a nanostructure, and is categorized as (1) two-dimensional, e. g., thin films or quantum wells, (2) one-dimensional, e. g., quantum wires, or (3) zero-dimensional or dots [39]. Nanometer-sized crystals often referred to as quantum dots. Typical QD sizes range between 2-20 nm [40]. However, their diameter should be strictly below 10 nm [41, 42]. The dimensions of QDs depend mainly on the material used to prepare them [43].

The main advantage in using quantum dots is that because of controlled size, it is possible to have very precise control over the conductive properties of the material. QDs are particularly significant for optical applications due to their high extinction coefficient. The ability to tune the size of quantum dots is advantageous for many applications. For instance, larger quantum dots have a greater spectrum-shift towards red compared to smaller dots and exhibit less pronounced quantum properties. Conversely, the smaller particles allow one to take advantage of more subtle quantum effects. Being zero-dimensional, quantum dots have a sharper density of states than higher-dimensional structures. As a result, they have superior transport and optical properties [44].

Properties of quantum dots

- Extremely high brightness when excited.
- Highly resistant to photobleaching.
- Emission spectra can be tuned by the size (called "size quantization effect"), the composition of their cores and shells.
- Broad excitation and narrow symmetric emission spectra, which make it feasible to perform simultaneous detection of multiple signals using a single excitation source.

Synthesis processes

Several routes have been used to synthesize QD. Generally, the techniques for synthesis of QD are categorized either as a top-down or bottom-up approach [45, 46].

Top-down synthesis process

In the top-down approach, a bulk semiconductor is thinned to form the QDs. Electron beam lithography, reactive ion etching and/or wet chemical etching are commonly used to achieve QD of diameter ~30 nm. Controlled shapes and sizes with the desired packing geometries are achievable for systematic experiments on quantum confinement effect. Alternatively, focused ion or laser beams have also been used to fabricate arrays of zero-dimension dots. Major drawbacks with these processes include incorporation of impurities into the QD and structural imperfections by patterning.

Bottom-Up approach

A number of different self-assembly techniques have been used to synthesize the QD, and they may be broadly subdivided into wet-chemical and vapor-phase methods. A microemulsion, sol-gel, competitive reaction chemistry, hot-solution decomposition and electrochemistry are generally placed in the category of wet-chemical methods. Self-assembly of nanostructures in material grown by molecular beam epitaxy, sputtering, liquid metal ion sources, or aggregation of gaseous monomers are generally categorized under vapor-phase methods. There are various applications like DNA sensors, protein sensors, drug delivery, photodynamic therapy, real-time detection of intracellular events, sugar sensors, immunoassays, live cell imaging, *in vitro* imaging, single molecule tracking, *in vivo* and animal imaging, MRI contrast agent, functionalized with different bio-active agents and multiple QD can be used in the same assay with minimal interference with each other [47].

Silica nanoparticles

Silica NPs used for biomedical applications can be categorized as mesoporous or nonporous (solid) NPs, both of which bear amorphous silica structure. Mesoporous silica NPs characterized by the mesopores (2-50 nm pore size) are widely used for delivery of active payloads based on physical or chemical adsorption [48, 49]. In contrast, nonporous silica NPs deliver through encapsulation or conjugation.

Silica NPs are also promising candidates for improved drug delivery systems. Drug molecules have been loaded into silica NPs, and surface modification of the NPs with bio recognition entities can allow specific cells or receptors in the body to be located [50]. Upon target recognition, NPs can release their drug payload at a rate that can be precisely controlled by tailoring the internal structure of the particles for a desired diffusion/release profile. It is also possible to make multifunctional silica NPs with the aim of developing nanoscale composites with innovative optical, chemical, and magnetic properties, all combined in one single nanostructure [51, 52]. There are various methods of preparation of silica nanoparticles such as stober method, reverse micro emulsion, sol-gel method, spray drying, template method, heating degradation, laser ablation, thermal annealing, thermal vaporization, hydrolysis, polycondensation, hard templating and soft templating which includes single micelle-templating, vesicle-templating, micro-emulsion-templating, polymer beads-templating [53, 54].

There are a number of applications used in silica nanoparticles are as stimuli-responsive drug delivery, photodynamic therapy, drug delivery, gene delivery, protein delivery, for imaging and diagnosis, DNA and microarray detection, as radio carrier/radio sensitizer, improve molecule transport especially for larger molecules (such as biodiesel, biomolecules), ultrasensitive single bacterium detection and bar-coding tags.

Fullerenes

A fullerene is a pure carbon molecule composed of at least 60 atoms of carbon. A fullerene takes a shape similar to a soccer ball or a geodesic dome; it is sometimes referred to as a buck ball after the inventor of the geodesic dome, Buckminster Fuller, for whom the fullerene is more formally named. Fullerenes are seen as promising components of future micro-electromechanical systems and in nanotechnology. Compounds of fullerenes may be classed according to two different categories: exohedral (inside the cage) and endohedral (outside the cage). Examples of the former include metals such as lanthanum enclosed in a C82 cage, and examples of the latter include transition metal complexes [55].

Fullerenes consist of 20 hexagonal and 12 pentagonal rings as the basis of icosohedral symmetry closed cage structure. Each carbon atom is bonded to three others and is sp^2 hybridized. The C_{60} molecule has two bonds lengths-the 6:6 ring bonds can be considered "double bonds" and are shorter than the 6:5 bonds. C_{60} is not "super aromatic" as it tends to avoid double bonds in the pentagonal rings, resulting in poor electron delocalisation. As a result, C60 behaves like an electron deficient alkenes and reacts readily with electron rich species. The geodesic and electronic bonding factors in the structure account for the stability of the molecule. In theory, an infinite number of fullerenes can exist, their structure based on pentagonal and hexagonal rings [56]. The advantages of fullerenes are an as high tensile strength, high electrical conductivity, high ductility, high resistance to heat, relative chemical inactivity [57].

Physical properties of C_{60} (fullerene) [58]

- Density: 1.65 g cm^{-3}
- Standard heat of formation: 9.08 k cal mol^{-1}
- Index of refraction: 2.2 (600 nm)
- Boiling point: sublimes at 800K
- Resistivity: 1014 ohm m^{-1}
- Vapour density: N/A
- Crystal form: Hexagonal cubic
- Vapour pressure: 5 x 10^{-6} torr at room temperature

Organoleptic properties

- Color: Black solid
- Odour: Odorless
- Buckyball soot: Very finely divided black powder
- Fullerite: Brown/black powder

The fullerenes are also found to be soluble in common solvents such as benzene, toluene or chloroform. If one shakes up some fullerene soot with toluene and filter the mixture, one obtains a red solution. As the solvent evaporates, crystals of pure carbon appear.

Production/synthesis of fullerenes [59]

- Laser vaporization of carbon in an inert atmosphere
- Resistive heating of graphite
- Inductive heating of graphite or another source (acetylene, etc.)
- Pyrolysis of hydrocarbon (naphthalene)
- Total synthesis of fullerene

There are various applications like as photosensitizers, in drug and gene delivery, organic photovoltaics, antioxidants and biopharmaceuticals, endohedral fullerenes, diagnostic application.

Carbon nanotubes

Carbon nanotubes (CNTs) are nanostructures derived from rolled graphene planes, possesses various interesting chemical and physical properties and have been extensively used in biomedicine. The discovery of CNTs by using high-resolution electron microscopy (HREM) has stimulated intense experimental and theoretical studies on carbon nanotubes. CNTs are allotropes of carbon with a nanostructure that can have a length-to-diameter ratio greater than 1,000,000 [60, 61].

CNTs can be conjugated with various biological molecules including drugs, proteins and nucleic acid to afford bio-functionalities [62, 63]. Moreover, the aromatic network existing on the CNT surface allows efficient loading of aromatic molecules such as chemotherapeutic

drugs via stacking [64]. CNTs exist as single-walled (SWCNTs) and multiple-walled (MWCNTs) structures. They present several interesting properties, such as high-aspect-ratio, ultra-light weight, tremendous strength [65], high thermal conductivity and remarkable electronic properties ranging from metallic to semiconducting [66].

SWCNTs offers the additional photoluminescence property that could be proficiently applied in diagnostics, while MWCNTs present a wider surface that allows a more efficient internal encapsulation and external functionalization with active molecules. They have been both used for diversified roles including biosensors, field-effect transistors, and scanning probe elements [67]. The CNTs offers various advantages like, biocompatible, non-biodegradable and non-immunogenic nature, highly elastic nature and have the possibility of intracellular delivery, may exhibit minimum cytotoxicity, excreted by urine 96% and remaining 4% by faeces, ultra-light weight and do not break down during processing, able to enter cells by spontaneous mechanism due to its, tubular and nanoneedle shape, and distinct inner and outer surface, which can be differentially modified for chemical biochemical functionalization [68].

Single-walled carbon nanotubes (SWCNTs)

SWCNTs consist of a single cylindrical carbon layer with a diameter in the range of 0.4-2 nm, depending on the temperature at which they have been synthesized. It was found that higher the temperature larger is the diameter of CNTs [69]. The structure of SWCNTs may be armed chair, zigzag, chiral or helical arrangements [70]. In drug delivery, SWCNTs are known to be more efficient than MWCNTs because SWCNTs have ultra-high surface area and efficient drug-loading capacity [71].

Multiple-walled carbon nanotubes (MWCNTs)

MWCNTs consist of several coaxial cylinders, each made of a single graphene sheet surrounding a hollow cone. The outer diameter of MWCNTs ranges from 2-100 nm, while the inner diameter is in the range of 1-3 nm, and their length is one to several micrometres [72]. MWCNTs structures can be split into two categories based on their arrangements of graphite layers: one has a parchment-like structure which consists of a graphene sheet rolled up around it and the other is known as the Russian doll model where a layer of the graphene sheet is arranged within a concentric structure [73].

Methods of CNTs synthesis [74-76]

- Plasma based synthesis method or arc discharge evaporation method
- Laser ablation method
- Thermal synthesis process
- Gas-phase methods
- Chemical vapor deposition (CVD)
- Plasma enhanced CVD (PECVD)

There are various applications of CNTs such as drug delivery in blood cancer, breast cancer, brain cancer, lymph node metastasis, liver cancer, cervical cancer, gene therapy, immune therapy, biomedical imaging, biosensors and tissue engineering.

6. Characterization of nanoparticles

Nanoparticles are generally characterized by their size, morphology and surface charge, using such advanced microscopic techniques as scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM). The average particle diameter, their size distribution, and charge affect the physical stability and the *in vivo* distribution of the nanoparticles. Electron microscopy techniques are very useful in ascertaining the overall shape of polymeric nanoparticles, which may determine their toxicity. The surface charge of the nanoparticles affects the physical stability and dispersibility of the polymer dispersion as well as their *in vivo* performance [77].

Particle Size is determined by various techniques like nuclear magnetic resonance, optical microscopy, electron microscopy, dynamic light scattering and atomic force microscopy.

Nuclear magnetic resonance (NMR)

Nuclear magnetic resonance (NMR) can be used to determine both the size and the qualitative nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle [78].

Optical microscopy

Most nanoparticles are below the resolution limit of direct optical imaging, though microscopy is still useful to get an estimate of the size and crystallinity of starting materials, as might be desirable in the instance of commination or homogenization processing or other larger particles. However, the dark field techniques, in which particles are observed indirectly as bright spots on a dark background because of their scattering under oblique illumination is extremely valuable in assessing the presence and numbers of nanoparticles.

Electron microscopy

Scanning and transmission electron microscopy (SEM and TEM), respectively, provide a way to observe nanoparticles directly, with the former method being better for morphological examination. TEM has a smaller size limit of detection, is a good validation of other methods, and affords structural information via electron diffraction, but staining is usually required, and one must be cognizant of the statistically small size and the effect that vacuum can have on the particles. Very detailed image data can result from freeze-fracture approaches in which a cast is made of the original sample. Sample corruption resulting from the extensive sample preparation is always a possibility; though lower vacuum (environmental-or E-SEM) instrumentation reduces this manipulation, at the loss of some resolution [79, 80].

Dynamic light scattering (DLS)

Currently, the fastest and most popular method of determining particle size is photon correlation spectroscopy (PCS) or dynamic light scattering (DLS). DLS is widely used to determine the size of Brownian nanoparticles in colloidal suspensions in the nano and submicron ranges. Shining monochromatic light (laser) onto a solution of spherical particles in Brownian motion causes a Doppler shift when the light hits the moving particle, changing the wavelength of the incoming light. This change is related to the size of the particle. It is possible to extract the size distribution and give a description of the particle's motion in the medium, measuring the diffusion coefficient of the particle and using the autocorrelation function. The photon correlation spectroscopy (PCS) represents the most frequently used technique for accurate estimation of the particle size and size distribution based on DLS [81].

Atomic force microscopy (AFM)

Atomic force microscopy (AFM) offers a ultra-high resolution in particle size measurement and is based on a physical scanning of samples at sub-micron level using a probe tip of atomic scale [82]. The instrument provides a topographical map of the sample based on forces between the tip and the sample surface. Samples are usually scanned in contact or non-contact mode depending on their properties. In contact mode, the topographical map is generated by tapping the probe onto the surface across the sample and probe hovers over the conducting surface in non-contact mode. The prime advantage of AFM is its ability to image non-conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and microstructures [83]. AFM provides the most accurate description of size and size distribution and requires no mathematical treatment. Moreover, particle size obtained by the AFM technique provides a real picture which helps understand the effect of various biological conditions [84, 85].

Zeta potential analysis

It is a technique for determining the surface charge of nanoparticles in solution (colloids). Nanoparticles have a surface charge that attracts a thin layer of ions of opposite charge to the nanoparticle surface. This double layer of ions travels with the nanoparticle as it

diffuses throughout the solution. The electric potential at the boundary of the double layer is known as the zeta potential of the particles and has values that typically range from+100 mV to-100 mV. The magnitude of the zeta potential is predictive of the colloidal stability. Nanoparticles with zeta potential values greater than+25 mV or less than-25 mV typically have high degrees of stability [86].

Differential scanning calorimetry (DSC)

DSC can be used to determine the nature of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies. A complement to X-ray diffraction, this method is regularly used to determine the extent to which multiple phases exist in the interior or to which the various constituents, including the drug. DSC is calibrated using indium as standard. Samples should be placed in sealed aluminum pans and should be heated from 30 ºC to 300 ºC at a rate of 10 ºC/min under a nitrogen atmosphere (60 ml/min), with the empty pan as reference [87, 88].

X-Ray diffraction analysis

The geometric scattering of radiation from crystal planes in the presence or absence of the former to be determined the degree of crystallinity be assessed. In one example, the crystallization of interior lipids could be tracked. Application of the method is little different from that for bulk powders, through the broadening of the diffraction pattern's peaks is observed for particles less than 100 nm in diameter [89].

X-ray photoelectron spectroscopy (XPS)

It is a surface-sensitive quantitative spectroscopic technique that measures the elemental composition at the parts per thousand range, empirical formula, chemical state and electronic state of the elements that exist within a material. XPS spectra are obtained by irradiating a material with a beam of X-rays while simultaneously measuring the kinetic energy and number of electrons that escape from the top 0-10 nm of the material being analyzed. XPS requires a high vacuum (P ~ 10^{-8} millibar) or ultra-high vacuum (P<10^{-9}millibar) conditions, although a current area of development is ambient pressure XPS, in which samples are analyzed at pressures of a few tens of millibar [90].

Drug loading and entrapment [91]

A high drug-loading capacity is the measure of the successful nanoparticulate system because it reduces the amount of matrix material for the administration. Drug loading can be done by two methods:

Incorporation method

In this method, the drug is incorporated during the formation of the nanoparticles.

Adsorption/absorption method

In this method, the drug is made to be adsorbed on nanoparticles. Nanoparticles are kept in a concentrated solution of the drug and adsorption phenomenon take place.

The incorporation efficiency, drug loading and % yield are calculated according to the following equation [92];

$$\text{Loading Capacity (\%)} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of nanoparticles recovered}} \times 100 \text{ eq (1)}$$

$$\text{Incorporation Efficiency (\%)} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in formulation}} \times 100 \text{ eq (2)}$$

$$\text{Percentage yield (\%)} = \frac{\text{Total nanoparticles weight}}{\text{Total solid weight}} \times 100 \text{ eq (3)}$$

***In vitro* drug release studies**

A central reason for pursuing nanotechnology is to deliver drugs, hence understanding the manner and extent to which the drug molecules are released is important. In order to obtain such information, most release methods require that the drug and its delivery vehicle be separated. The nanoparticles equivalent to 20 mg of drug are placed in a dialysis membrane, tied from both the sides with the thread. The dialysis membrane is immersed in a beaker containing 900 ml buffer solution. Aliquots of dissolution fluid (10 ml) are withdrawn at specified time intervals. The fresh buffer is added to the beaker at the same rate, in order to keep the volume constant. The technique used for this analysis is classical analytical methods like UV spectroscopy or high-performance liquid chromatography (HPLC) after ultracentrifugation, ultrafiltration, gel filtration, or centrifugal ultrafiltration. Quantification is performed with the UV spectroscopy or HPLC. Drug release assays are also similar to drug loading assay which is assessed for a period of time to analyze the mechanism of drug release [93, 94].

Ultraviolet-visible (UV-Vis) spectroscopy

Gold nanoparticles exhibit a distinct optical feature commonly referred to as localized surface plasmon resonance (LSPR), that is, the collective oscillation of electrons in the conduction band of gold nanoparticles in resonance with a specific wavelength of incident light. LSPR of gold nanoparticles results in a strong absorbance band in the visible region (500-600 nm), which can be measured by UV-Vis spectroscopy. The LSPR spectrum is dependent both on the size and shape of gold nanoparticles. The peak absorbance wavelength increases with particle diameter and for uneven shaped particles such as gold nano-urchins, the absorbance spectrum shifts significantly into the far-red region of the spectrum when compared to a spherical particle of the same diameter. The peak optical density, or absorbance of the sample, correlates linearly to the concentration of nanoparticles in solution.

Silver nanoparticles exhibit yellowish brown color in aqueous solution due to excitation of surface plasmon resonance band in the UV-visible region. When aniline solution is mixed with an aqueous solution of the silver nitrate and cetyltrimethylammonium bromide, pale-yellow color appears due to the reduction of the silver ion; which indicates the formation of silver nanoparticles. It is generally accepted that UV-Vis spectroscopy could be used to examine the size and shape-controlled nanoparticles in aqueous solution. The absorption spectra of silver sol consists a single sharp surface plasmon resonance band at 400 nm. The most characteristic part of the silver sol is a narrow plasmon absorption band observable in the 350-600 nm regions. A broad surface plasmon resonance band is due to aggregation and/or adsorption of aniline onto the surface of Ag nanocrystals [95].

Antimicrobial activity

The antimicrobial susceptibility of the synthesized Ag nanoparticles can be investigated against the Gram-positive bacteria *B. subtilis* and Gram-negative *E. coli*, *S. typhi* and *V. cholerae* through disc diffusion method. In the antimicrobial activity, initially, AgNPs attach to the surface of the bacterial cell membrane and then penetrate into the bacteria. After penetration, they inactivate the enzymes of the microbes, generating hydrogen peroxide and causing bacterial cell death. The antibacterial properties of these green-synthesized AgNPs suggest their usage in medical devices as an antimicrobial coater [96].

Gel electrophoresis

Gel electrophoresis is a common analytical technique that separates macromolecules or particles based on their size, shape and charge. It is a powerful tool for analyzing gold nanoparticles and their surface modification. The distinct color of gold nanoparticles and other noble metal nanoparticles enables direct observation of the sample and its migrations within the gel. Modification of the gold surface with charged ligands or molecules such as amine-PEG, carboxyl-PEG oligonucleotides or proteins generally result in a change in the surface charge, which can be seen by an altered migration pattern (direction or migration distance) in agarose gel electrophoresis. Also, surface coating of biomolecules such as protein increase the size of the nanoparticles thereby slowing down their electrophoretic speed when compared to unmodified gold nanoparticles. Gel electrophoresis can thus be effectively used in optimizing the conjugation conditions of molecules onto gold nanoparticles, by revealing the point of saturation beyond which increased loading of molecules causes no further migration shift of the band. Agarose gel electrophoresis can also be used for separation followed by isolation and purification of individual components after functionalization.

Bio-functionality testing

Gold nanoparticles are often conjugated with biomolecules to serve as probes in various bioassays. It is not only important to ensure the proper conjugation and stability using aforementioned methods such as UV-Vis measurement, but it is also essential to confirm the functionality of the conjugate, i.e., specific binding of target analytes. One simple method to evaluate the functionality of gold conjugate is through immunoblotting. Briefly, a serial dilution of the analyte to be detected is spotted on a nitrocellulose membrane followed by the addition of the conjugate of interest. If the gold conjugate is functional, binding to the spotted analyte will occur, which is conveniently visualized by a bright red color [97].

Magnetization measurements

The saturation of magnetization should be evaluated using a vibrating sample magnetometer. Vibrating sample magnetometer (VSM) is based on Faraday's law which states that an electromagnetic force is generated in a coil when there is a change in flux linking the coil. In the measurement setup, a magnetic sample is moving in the proximity of two pickup coils [98]. When a sample material is placed in the uniform magnetic field, a dipole moment proportional to the product of sample susceptibility and applied field is induced in the sample. If the sample is made to undergo sinusoidal motion as well, an electrical signal will be induced in suitable located stationary pick-coils. This signal, which is at the vibration frequency, is proportional to the magnetic moment, vibration amplitude and vibration frequency. The instrument displays the magnetic moment in electromagnetic units [99]. The magnetic moment should be recorded at the corresponding magnetic field. On the basis of this data, the hysteresis loop of magnetic nanoparticles can be plotted.

Scanning tunneling microscopy (STM)

It is used to examine the morphologies of self-assembled quantum dots. In order to induce the self-assembly, spatial thermal modulations in nanoscale may be created *in-situ* on strained-but-flat surfaces in a molecular beam epitaxy growth reactor by applying interferential irradiations of laser pulses. Examination of irradiated surfaces should be done using an attached ultra-high vacuum STM. Using a STM tip as an engineering or analytical tool, artificial atomic-scale structures can be fabricated; novel quantum phenomena can be probed, and properties of single atoms and molecules can be studied at an atomic level. The STM manipulations can be performed by precisely controlling tip–sample interactions, by using tunneling electrons, or electric field between the tip and sample [100].

Small-angle neutron scattering (SANS)

It is an appropriate technique for the structural characterization of fullerenes in solvents, with strong SANS contrast (e. g., CS_2). Deuterated solvents (e. g., toluene-d_8) have a high scattering length density (SLD), which is close to that of C60, so there is virtually no SANS contrast with the solvent. Hence, these particles are practically "invisible" in such media, though the negative scattering length of hydrogen means that SLD of H^1-containing materials is much lower, so they have a strong contrast with toluene-d_8. Thus, SANS makes it possible to study the size and shapes of modified buck balls [101].

Raman spectroscopy

Raman spectroscopy is one of the most powerful tools for characterization of carbon nanotubes. Without sample preparation, a fast and non-destructive analysis is possible. All allotropic forms of carbon are active in Raman spectra. The position, width and relative intensity of bands are modified according to the carbon forms. [102].

Advantages of inorganic nanoparticle systems for drug delivery and targeting

The use of inorganic nanoparticles for applications in drug delivery presents a wide array of advantages, which are as follows:

1. Ease of functionality with a range of surface and conjugation chemistries which can be carefully selected based on the base material used, allowing attachment of various structures and cytotoxic drugs.

2. High payload loadings, which are determined by the porosity and pore size of the material, the payload properties and the surface chemistry chosen.

3. Tunable degradation rates, which are controlled by the chosen surface chemistry and the base material properties, and controlled release kinetics based on the material/payload interaction and/or capping mechanism selected.

4. Payload protection, controlled by the ability of the porous material to house the payload inside an inaccessible porous network until release, hence improving the *in vivo* half-life.

5. Localized and targeted delivery, magnetically or antibody-targeted nanoparticles to specific tissue/disease sites.

6. Enhanced penetration into tissue and certain nanomaterials can be designed so that they can effectively transverse specific tissue barriers.

7. Exploitation of the enhanced permeation and retention effect, where certain sized nanoparticles naturally accumulate in tumor tissue due to the lack of a lymphatic system, and hence, the ability to filter particles [103].

8. Mesoporous silica nanoparticles are relatively biocompatible, making them suitable for administration to patients, although they are not bioresorbable.

9. Carbon-based materials, such as nano graphene, have modifiable surface chemistries, can be produced with ultra-high surface areas for drug loading, and also have unique electrical and optical properties. Commonly used in positron emission tomography.

10. Iron oxide nanoparticles have near neutral zeta-potential, is large enough to avoid renal clearance, and is stable. Superparamagnetism is an important property of metal oxide nanoparticles as it allows the targeting of SPIONs to be visualized by MRI contrast agents. Magnetic nanoparticles are used for targeting of drugs by means of magnetic field gradients. Magnetic nanoparticles are guided or held in place by means of a magnetic field. The whole body is not exposed to the harmful effect of anticancer drugs. Commonly used as hyperthermia agents.

11. Near-IR absorbing gold nanoparticles (including gold nanoshells and nanorods) produce heat when excited by light at wavelengths from 700-800 nm. This enables these nanoparticles to eradicate targeted tumors. When light is applied to a tumor containing gold nanoparticles, the particles rapidly heat up, killing tumor cells. Gold nanoparticles also scatter light and can produce an array of interesting colors under dark-field microscopy. The scattered colors of gold nanoparticles are currently used for biological imaging applications. Also, gold nanoparticles are relatively dense, making them useful as probes for transmission electron microscopy.

12. Gold nanoparticles are also used to detect biomarkers in the diagnosis of heart diseases, cancers, and infectious agents. They are also common in lateral flow immunoassays, a common household example being the home pregnancy test [104].

13. Silver nanoparticles are used in biosensors and numerous assays where the silver nanoparticle materials can be used as biological tags for quantitative detection.

14. Silver nanoparticles are incorporated in apparel, footwear, paints, wound dressings, appliances, cosmetics, and plastics for their antibacterial properties [105]. Used as thermal sources for hyperthermia and thermally modulated release from particle surface coatings. Silver nanoparticles can also be incorporated into core/shell constructs, in which an amorphous silica shell is grown uniformly onto silver nanoparticle seeds.

15. The shells can have a variety of functional groups conjugated within, allowing fluorophores, drug molecules or other high molecular weight organic molecules to be integrated within the shell for labeling or drug delivery applications [106].

CONCLUSION

Availability of various types of inorganic nanoparticles and various synthesis methods have provided the opportunity to formulate novel drug delivery systems. Several significant issues should be considered before translating these inorganic nanosystems into the clinical stage. The first important issue is the biocompatibility regarding the selection of inorganic nanosystems. Compared with the well-developed organic nanomaterials, the clinical translation of inorganic nanosystems for drug delivery are still under strong debate due to the lack of enough evidence and data regarding the bio-safety, especially the biodegradation behavior, excretion routes and long-term toxicity assessments, to support theirs *in vivo* biosafety. Elaborately designed biocompatible inorganic materials-based nanosystems offer an unprecedented opportunity and show the encouraging bright future of personalized medicine for many diseases.

CONFLICT OF INTERESTS

The authors do not have any conflict of interest to declare.

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