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Contemporary approaches to the preparation of metal nanoparticles: methods and mechanistic insights

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ABSTRACT

Nanoparticles have transformed drug delivery systems to provide new approaches to increase the dissolution, absorption, and targeting properties of drug molecules. They have a nanoscale structure that gives them special characteristics such as high surface area, enhanced membrane permeability and enhanced physicochemical stability in comparison with the traditional drug delivery systems. Such properties render the nanoparticles especially useful in treatment of such complicated illness as cancer, neurodegenerative disorders, and chronic infectious diseases. This review paper focuses on the different ways of synthesizing metal nanoparticles and their pharmaceutical usage, as a way of overcoming the limitations of the conventional methods of delivery. Altogether, nanoparticles are characterized by enhanced stability and bioavailability, reduced toxicity, and a high possibility of benefiting therapeutic performance and safety in nanomedicine.

Keywords: Nanoparticles; Nanocomposites; Nanoarchitectures; Nanostructures; Nanomaterials.

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INTRODUCTION

The metal nanoparticles are nanoscale materials, which are normally of 1 to 100 nm sizes and are made of elemental metals or their compounds. Metals are very rich elements with varying physicochemical properties and their nano-scattered structures have special optical, electrical and biological properties. Metal nanoparticles are solid-state nanostructures of pure metals or metal compounds that are created by chemical, physical or biological methods, and are being pursued in tissue engineering, biomedical devices, and biomedical and therapeutic applications.[1] Silver and gold nanoparticles are the most widely investigated of these, with silver nanoparticles widely known as having good antimicrobial activity and gold nanoparticles receiving a lot of interest as bioimaging, diagnostics, and targeted drug delivery agents.[2-4] Plant extracts are also able to be used as natural reducing and stabilizing agents to synthesize metal nanoparticles through biosynthetic methods. Such green synthesis method provides better biocompatibility and can be less cytotoxic than nanoparticles synthesized conventionally, as well as develops other antimicrobial effects. In comparison to conventional drug delivery systems, nanomaterials have a number of benefits, namely, regulated particle size (1100 nm), high surface-volume ratio, high cellular uptake, and high permeability of biological membranes, which results in an increased systemic availability. Some of the most popular nanomaterials include gold, iron and silver nanoparticles as well as semiconductor nanomaterials like quantum dots and are easy to modify on the surface to increase bioavailability, therapeutic efficacy and site-specific drug targeting. Nanotechnology is a developing interdisciplinary research area that aims at designing, manipulating and putting materials into practice at the nanometer level.[5] Carbon nanotubes, nanoshells and nanofibers are nanomaterials with wide application in drug delivery and targeting systems in quick detection and treatment of diseases. In the recent past, nanomaterials have been a subject of a lot of research aimed at treating various diseases such as AIDS,

cancer, autoimmune diseases, cardiovascular diseases, and tuberculosis. Functionalization of nanoparticles with polymers, oligopeptides, enzymes, antibodies, antigens and DNA aptamers can be regularly used to enhance specificity and therapeutic activity.[6] Regardless of all the above benefits, metal nanoparticles have some limitations which are possible toxicity, immunological responses and unwanted molecular and cellular interactions in the biological systems. Thus, such crucial physicochemical parameters as the size of the particle, its shape, the surface charge, bioaccumulation, and toxicological behavior should be thoroughly considered before large-scale production and medical implementation.[7] This review has presented the different synthesis techniques that are used in the preparation of the nanoparticles.

Physical Methods of synthesizing nanoparticles

Thermal Evaporation: It is a top down approach used for the synthesis of metal nanoparticles. It is characterized by the thermal evaporation of the target materials through electronic beam evaporating machines or the Joule-heated refractory sources in controlled pressure (1-50 mbar). Ultra-fine nanoparticles are produced by gas-phase nucleation and growth processes as a result of repeated interactions of evaporated species at high residual gas pressures.[8] The most significant drawback of the technique is however non-uniform thermal flux within the evaporation source that may lead to uneven evaporation velocity and formation of nanoparticles with large distribution of size and low homogeneity in terms of compositions. Although it has the disadvantage, this is a beneficial process because it works under the conditions of high temperature and high pressure, which contributes to the increased mobility of atoms and the occurrence of thermodynamically favorable chemical reactions, which finally leads to the crystallization of nanoparticles. [10-13]

Microwave/ Gamma Radiation: Microwave or gamma irradiation is used to heat the reaction system quickly and volumetrically avoiding a significant heating of the environment around it and thus creating a uniform distribution of energy and the creation of homogeneous nanoparticles. These irradiation methods are also utilized in the heating and evaporation of the precursor or target materials and provide a quick and efficient solution to the synthesis of metal nanoparticles. In the microwave-assisted synthesis, the heating process is the reaction of electromagnetic fields and polar molecules and ionic species in the reaction medium, leading to the increase of the rate of molecular rotation and ionic conduction. It results in fast nucleation and growth mechanism and majorly lowers the reaction time with respect to traditional thermal heating. [14-19]

Plasma Method: The technique used is a bottom-up synthesis technique of nanoparticles in which a metal is heated to temperatures higher than its own evaporation temperature in an empty chamber with the use of high-temperature plasma. The ionizing gas is normally an inert gas like helium that has been excited with radio-frequency (RF) energy in the form of induction coils to produce very high thermal energy.[20] The atomic particles of the evaporated metals are nucleated when they collide with the atoms of helium and subsequently form nanoparticle and are then transported and collected on a cooler collector rod. The obtained nanoparticles could be passivated through controlled exposure to oxygen and inhibit oxidation and agglomeration. Thermal plasma, plasma-enhanced chemical vapor deposition (PECVD) and in-liquid plasma are common plasma-based methods that are used to synthesize nanoparticles.[21] Some of the benefits of this method include purity of the product, control of particle size and morphology, high synthesis rate, and noble and non-noble metals can be synthesized as well, the process can be used to make thin-film, and it may be a green process (environmentally friendly) because unlike traditional methods, minimal chemical reactants are used.

Mechanical Method: This technique entails reduction of bulk solid material into nanoparticles by high-energy mechanical milling with hardened steel, silicon carbide or tungsten carbide grinding media.[22] Repeated impact, compression, shear forces are used to impart mechanical energy to the material, which allows transfer of kinetic energy to the solid material that is subject to comminution by the milling media. Extensive milling times (typically, between 100 and 150 hours) are used to achieve fine and relatively homogenous Nano powders with particle sizes of the order of 210 nm. Even though, this is a simple, cost-effective, solvent-free, and scalable method to produce nanoparticles, it has some limitations like lack of control over the shape of the particles, a wide size distribution, and a possible contamination of the product by the milling media and thus impacts on the purity of the product.

Nano lithographic Method: Nanolithography is a top-down process of nanoparticle fabrication also normally utilized together with thin-film deposition, in which case focused beams of electrons, ions, electromagnetic radiation, and so forth, can be used to pattern nanoscale features on a substrate. Photolithography is a typical illustration of nanolithographic method, as is electron-beam lithography, ion-beam lithography, ion-track lithography, X-ray lithography and nanoimprint lithography.[24-28] One conventional technology that is utilized at very high rates during fabrication of integrated circuits is photolithography, which entails the utilization of a source of light, masking substance, optical projection devices and radiation reactive photoresists to transfer designs onto samples. Ion-

beam lithography, particularly focused ion beam (FIB) milling can be used to perform nanoscale etching, especially in modifying devices, repairing features on masks, and failure analysis. X-ray lithography is a method where short wavelength X-rays are used to transfer high-resolution and the least impacts of diffraction pattern, but requires special masks and it can be damaged by vibrations and deformations. [29]

Wire explosion method: It is a Joule heated, top-down nanoparticle synthesis methodology which is also known as the wire explosion method. During this process, a high-density current of electricity is swiftly introduced into a metallic wire, which leads to intensive resistive heating, melting, vaporization and further explosion of the metallic wire and subsequent development of metallic nanoparticles. A feeding unit constantly feeds the metallic wire into a chamber or wire explosion chamber and directs this wire laterally by a pneumatic cylinder in such a way that a fixed length of wire is precisely placed between two electrodes.[30] After placing the required length, the wire feed is stopped and the wire is cut and then clamped between the electrodes. An electric pulse is then introduced across the electrodes with a large amount of power and the energy is rapidly deposited, the wire is disintegrated, and the metal vapor is condensed into nanoparticles, collected later within the chamber.

Chemical Methods of synthesizing nanoparticles

Polyol Method: Polyol technique is a commonly used and accepted soft chemical approach to the production of nanoparticles. It is a chemical approach of reduction where non-aqueous polyol solvent performs the role of a reaction medium and reducing agent at the same time. Non-aqueous polyols have the benefits of reduced surface oxidation and less agglomeration of the particles resulting in enhanced stability of the particles. It is a cost-effective, easy-to-use method appropriate in the production of nanoparticles on a large scale. The polyol process may also be modified to produce oxide nanoparticles with controlled nucleation and particle growth at high temperatures similar to solgel-type processes.[31] The most frequently used solvent in the polyol method of metal and metal oxide nanoparticles synthesis is ethylene glycol because it has good reducing capacity, high dielectric constant, and high boiling point that enhances easy reduction and growth control of these nanoparticles.

Microemulsion: Polyol method is widely adopted and acceptable soft-chemical method of nanoparticles production. It is a type of chemical reduction that utilizes non-aqueous polyol solvent simultaneous as a reaction medium and reducing agent. The advantages of the non-aqueous polyols include lower oxidation of the surface and reduced agglomeration of the particles of the non-aqueous polyols leading to the increased stability of the particles.[32] It is a relatively cheap and simple technique that can be applicable in the large-scale production of nanoparticles. The polyol process can also be adjusted to result in oxide nanoparticles that are controlled in their nucleation and particle growth at high temperatures such as solgel-type processes. Ethylene glycol is the most commonly used solvent in polyol method of production of metal and metal oxide nanoparticles due to its good reducing capacity, good dielectric constant and high boiling point that brings in easy reduction and control of growth of these nanoparticles.

Sol-Gel Method: Sol-gel is a wet-chemical process, which is employed in the synthesis of the nanostructured metal oxides, with the hydrolysis and condensation of the molecular precursors to create a sol of nanometric particles that subsequently polymerize into a three-dimensional metal oxide network (wet gel).[33] The process is carried out at room temperature and hence the process has to be followed by heat treatment in order to get crystallinity. The preparation of TiO_2 nanopowders can be done through the use of titanium (IV) butoxide as a precursor, alcohols as solvents, diethanolamine as a stabilizer, hydrochloric acid as a catalyst, and deionized water as a hydrolysis medium. The sol is then prepared by mixing titanium butoxide with diethanolamine and then adding alcohol and finally drop wise addition of water alcohol mixture and allowing the mixture to age after a period of 24 hours. The gel is burnt to 500°C and kept approximately 90 minutes to produce crystalline TiO_2 nanoparticles, and then subjected to fine grinding into fine powder. [34]

Thermal Decomposition method: Due to the high temperature thermal decomposition of organometallic precursors in organic solvents in the presence of surfactants, highly monodispersed metal oxide nanoparticles of controlled size can be prepared. In this method the precursors of cupferron are prepared by the precipitation of metal ions in an aqueous solution at controlled pH with the help of cupferron (ammonium salt of N-nitrosophenylhydroxylhydroxylamine). Heated in the presence of nitrogen, dried metal cupferronates decomposed at normal temperatures (approximately 180°C $FeCup_3$), (230°C MnCup 2) and (205°C CuCup 2) to produce 7-Fe_2O_3, MnO, and Cu, respectively. Trioctylamine is dried in the presence of nitrogen and under vacuum to dry it and eliminate moisture and oxygen. This is analyzed by means of the rapid injection of the precursor solution into hot trioctylamine (approximately 300°C) and vigorously stirred with inert conditions as indicated by the color change and the formation of gases. [35-38]

Biological Methods: Green synthesis is a technology and process of biocompatibility, low cost and eco-friendly synthesis of nanoparticles through the use of plant extracts and microorganisms. It is also better than chemical and physical methods in that it is easy,

inexpensive, produces minimal waste and is not poisonous. Plants are particularly favorable sources because leaf, root, seed, stem, bark, fruit and shoot are sources of primary and secondary metabolites - flavonoids phenolics, enzymes and alkaloids - reducing and stabilizing agents. This is synthesized in three steps whereby in the reduction step, the phytoactive compounds de-metalize the metal ions to produce the zero-valent atoms; in the growth stage, the phytoactive compounds reform the metal atoms into a nanoparticle of various shapes; and in the termination, antioxidants and other phytochemicals are adsorbed onto the nanoparticle surface, to prevent oxidation and stabilize the nanoparticle. Silver nanoparticles are functionalized with flavonoids, tannins, phenolic compounds etc. and enhance their stability and biocompatibility. [39-42]

Plants: Under plant-mediated synthesis of nanoparticles, leaves, roots, and bark of plants are washed, chopped and boiled to obtain the extract which is purified through filtration and centrifugation.[43] Metal salt solution and water are put into the extract in appropriate proportions and the mixture is incubated until the reduction of the metal ions is seen by changing the color of the visible color. Nanoparticles are then collected using standard isolation techniques and to achieve monodispersity a number of key points of the reaction should be regulated.

Microorganisms: On the intracellular and extracellular adsorption and reduction of metal ions, nanoparticles may also be obtained. In intracellular synthesis, Nanoparticle production is by association of the metal salts dissolved in a solution with the microbial biomolecules to form nanoparticles; and by association of the metal ions with the negatively charged microbial proteins or enzymes and reduction of the metal salts with cytoplasmic enzymes.[44] The microbial production minimizes the chemical receptor use, and it is possible to produce nanoparticle of various shapes and compositions, and extracellular pathways are more likely to be widespread as nanoparticles can be easily recovered.

Fungi: Fungi are also popular in the production of nanoparticle because they are easy to grow, do not need complex media, and can be produced in bulk. Fungal enzymes and extracellular metabolites, including proteins, polysaccharides, phenolic compounds, flavonoids, anthraquinones, and hydroxyquinoline are reducing and stabilizing agents, which facilitate efficient production of stable and low-toxicity nanoparticles. Preferred since it is more efficient, readily scalable, and easier to recover, extracellular synthesis is observed in Fusarium oxysporum where it produces 15 to 30 nm nanoparticles at 37°C. The NADH-dependent nitrate reductase is important as it transfers electrons to reduce the metal ions (e.g., Ag^{+}, Au^{3+}) to their neutral metallic state, whereas other metabolites stabilize the nanoparticles.[45] During intracellular synthesis, the metal ions are bound to the negatively charged surfaces on the cell wall of a fungus and are reduced enzymatically in the cytoplasm producing nanoparticles under the cell membrane. In general, fungi offer an inexpensive, scalable and controlled nanoparticle factory, both by reduction and stabilization.

Bacteria: There are extracellular and intracellular methods through which bacteria can synthesize nanoparticles. The extracellular synthesis is also preferred since it is quicker and it does not involve a complicated downstream extraction, wherein metal ions are decreased by biomolecules on the cell surface or in the medium. Intracellular synthesis is a process of reducing the metal ions in the bacterial cytoplasm by enzymes and proteins found in the cytoplasm to form nanoparticles.[46] On nanoparticle formation, the factors include pH, temperature, incubation time and concentration of bacterial cells or metal salts. Specifically, some species, including Deinococcus radiodurans, have a high potential of making stable gold nanoparticles with higher antimicrobial effects because of their high antioxidant and radiation-resistant characteristics.

Algae: The algae serve as efficient agents in the synthesis of green nanoparticles because they contain acids, bases, and neutral molecules (e.g., a glycosidesulfate group), which accumulate and reduce metal ions, so bioactive molecules (e.g., proteins, enzymes, pigments, and polysaccharides (e.g., fucoidans)) serve as reducing and stabilizing factors. Algal biomass (living and dead) can be utilized, providing high carbon sequestration, rapid growth, use of low-energy and production of non-toxic sub-products, i.e. the process is sustainable and environmentally friendly.[47] Several other algal strains such as Sargassum muticum, Acanthophora spicifera, Laminaria japonica, Tetraelmis kochinensis and Turbanaria conides have been demonstrated to have potential to produce gold nanoparticles and composites of Chlorella vulgaris have proven to have antibacterial properties against multidrug-resistant Staphylococcus aureus. Altogether, algae offer an ecologically friendly and versatile basis to fabricate nanoparticles.[48]

Virus: Viruses are also found to be useful as templates in synthesis of nanocrystals of cadmium sulfide, zinc sulfide, silicon dioxide, iron oxide, and semiconductor nanoparticles are of particular interest with regards to green chemistry and electronic devices. Viral protein shells offer surfaces of metal ion binding facilitating the formation of nanoparticles in controlled ways as well as enabling three-dimensional structures applicable in biomedical systems. As an example, the tobacco mosaic virus (TMV) has 2,130 capsid proteins, which provides several sites of nanoparticle nucleation. It has also been demonstrated that the presence of TMV

together with gold or silver salts and plant extracts (e.g. Nicotiana benthamiana or Hordeum vulgare) result in smaller, better-dispersed nanoparticles, and the higher the TMV concentration, the better the yield and quality.[49] In general, the efficiency and the control of the nanoparticle synthesis are enhanced by the presence of viruses over the virus-free system.

Yeast: There is a high degree of control of nanoparticle size and shape in biological systems. Indicatively, (Schizosaccharomyces) pombe makes semiconductor nanocrystals in the log phase, usually extracellularly, and particles are directed by proteins. Ascomycote fungi, and in particular yeasts, have been extensively employed in nanoparticle production including gold nanoparticles, by them either intracellularly or through fungal cell mediated mechanisms as in Verticillium luteoalbum.[50] The properties and yield of nanoparticles are controllable, e.g. pH and temperature. Yeasts also endure and remove heavy metals via the absorption and concentration of metal ions with the help of extracellular polysaccharides and peptides that create protective shells or ion efflux or ion efflux facilitation. This ability allows yeasts to dissolve metal ions into nanoparticles in a controlled and biocompatible fashion and they could be useful in the generation of green nanoparticles.

Applications of Metal Nanoparticles

Biodetection of pathogens: Bacteria (e.g., Campylobacter, Salmonella, Listeria, E. coli), viruses, parasites, and mycotoxins are a threat to food safety, causing digestive disorders, neurological complications, cancer, or death, especially in children. Quick screening of spoilage and pathogenic materials in standard foods like meat, dairy and juices is of high priority but the traditional systems take long before testing. Bio-functionalized nanomaterials targeting pathogens through antibody-antigen, adhesin-receptor, antibiotic or DNA interactions, can be used to detect, within minutes, liquids, solids, or biofilms at the single-cell level (rapid), at the sensitive level (single cells), and with the specificity of the interaction (multiplex). The peculiarities of nanomaterials, such as physical, chemical, magnetic, electrical, and optical properties allow the creation of portable, easy, and efficient biosensors, improving the existing technologies in detecting pathogens.[51]

Detection of proteins: The expanding biomedical presence of nanomaterials and their possible toxicity have led to the need to have diverse methods of investigating protein-nanoparticle (NP) interactions. An affinity, ratio and mechanism of binding is determined by spectroscopy techniques whereas chromatography, electrophoresis and MALDI-TOF-MS identify NP-bound proteins. Surface plasmon resonance (SPR) and quartz crystal microbalance (QCM) are used in the study of dynamic binding kinetics. To employ the protein detection, six non-covalent gold nanoparticle- fluorescent polymer conjugates sensor array has been made: gold nanoparticles quench polymer fluorescence, and protein binding interferes with this interaction to produce characteristic fluorescence patterns. A pattern-based analysis with linear discriminant analysis (LDA) of these patterns allowed the successful identification of 52 unknown protein samples in seven different proteins with an accuracy of 94.2% that showed the possibility of nanomaterial-based protein detector arrays in medical diagnostics. [52]

Biomarker mapping: The low molecular weight blood fraction contains useful proteomic data in early diagnosis of disease ailments, including cancer. High surface area nanoparticles due to their adjustable physicochemical characteristics can be designed to target biomarkers to facilitate high-sensitivity proteomic analysis. Although applications of nanoparticles have been mainly through imaging and drug delivery, biomarker harvesting is not very well explored. Nanoplasmonic systems take advantage of an enhanced light-matter interaction as a biomolecular detection system. In this case, a bright-field plasmonic biosensor based on gold nanohole arrays (Au-NHAs) allows the visualization of single subwavelength gold nanoparticles as high-contrast heatmaps upon the detection of NP-labeled molecules.[53] This platform was implemented on a sandwich immunoassay and could identify 10 pg/mL of biotinylated bovine serum albumin (bBSA) and 27 pg/mL of human C-reactive protein (CRP) within 2 hours -at least 4 orders of magnitude below clinically relevant concentrations. The biomedical and diagnostic uses of large-area Au-NHA chips with sensitive, multiplexed, and rapid detection of multiple biomarkers can be realized through scalable and low-cost large-area fabrication based on biomarker detection.

DNA Probing: Semiconductor nanoparticles Semiconductor nanoparticles (quantum dots) are biologically finding use as a result of their photoluminescence, which has allowed them to be used as sensors and fluorescent probes. Electronic crosstalk and selective recognition of DNA structures can be achieved using hybrid nanocomposites of base pairs of TiO_2 nanoparticles and DNA oligonucleotides through enediol ligands, including dopamine. These photoactive TiO_2 /DA/DNA systems produce photogenerated charges that can report DNA hybridization as well as allow biomolecules to be manipulated by light. Also, scanometric arrays utilizing gold nanoparticle-modified oligonucleotide probes enhance the detection of DNA improving selectivity of single-nucleotide mismatches over fluorophore-labeled probes by up to two orders of magnitude.[54] Quantum dots therefore offer versatile model systems on sensing structure and sequence of DNA with high selectivity and sensitivity.

Tissue Engineering: Natural-based biomaterials in combination with nanoparticles have a high level of benefits in the fields of biomedical science, especially wound healing, tissue engineering (TE), and regenerative medicine. TE is proposed to heal or replace injured tissues yet they have issues of biomaterials, poor cell growth, low replication of architecture and lack of delivery of growth factors. Polymer is commonly used in the scaffolds and has poor mechanical properties. These characteristics encompass the incorporation of nanoparticles in polymeric scaffolds that increase mechanical strength and cell adhesion, viability, proliferation, and migration. Other functions of nanoparticles include control of delivery of growth factors, tuning of scaffold properties, and imaging contrast. In spite of all the advancement that had been made, nanoparticles have not reached their full potential in TE.[46] Altogether, nanoparticle-based systems are becoming the versatile tools to overcome the existing limitations of TE and enhance the scaffold operation in cardiovascular, neural, bone, and skin tissue engineering.

Antitumor activity: The problem of cancer is one of the top causes of morbidity and mortality, and the traditional forms of treatment have restricted capabilities due to low specificity, toxicity, and resistance to multiple drugs. In comparison to conventional treatments, nanoparticles (1100 nm) have a number of advantages: biocompatibility, stability, targeted therapy, permeability and retention. They are also under investigation in delivery of drugs, imaging and combination therapy and tumor heterogeneity and multidrug resistance. Different types of nanoparticles, targeting methods and approved nanotherapeutic nanoparticles have demonstrated potential in preclinical research. Even with advances, clinical translation is still in the dark ages, there are not many approved nanodrugs and there are still safety, efficacy, and regulatory approval issues.[41]

MRI Contrasting agents: MRI is a non-invasive imaging method, which has outstanding soft tissue contrast, boosted by contrast substances which minimize relaxation time. The traditional chelate-based therapies present toxicity issues and thus efforts have been made towards nanoparticles-based therapies that are more stable and exhibited longer circulation times and tunable surface characteristics. The paramagnetism of lanthanide- and iron-oxide-based nanoparticles is a promising nanoparticles and size and shape as well as surface functionalization of nanoparticles affect stability. Polymers are used to modify surfaces and inhibit aggregation and maximize imaging efficiency. MRI guided radiotherapy using nanoparticles is currently under investigation to allow tumor-specific imaging, local radiation increase, and minimal off-target effects.[38] Some of the strategies involve exploiting the augmented permeability and retention impact and targeted ligands of the tumor uptake. The research is currently in the preclinical and clinical stage of research, and it is based on safety, efficacy, and multifunctional diagnostic-therapeutic.

CONCLUSION

Nanotechnology has gained popularity in treating different diseases and the use of nanoparticles is important in prevention, diagnosis and treatment of diseases. Their extraordinary properties including biocompatibility, size, shape and surface alterations facilitated them in different therapeutic uses which are gene and drug delivery, diagnostics, radiotherapy, vaccine development, controlled release systems, and targeted therapy to increase the therapeutic efficacy and compliance of patients. The biopolymer-functionalized nanoparticles can be used as an instrument in a number of biological applications with lesser toxicological impact. The above review presents several effective techniques used in the synthesis of nanoparticles that can address the shortcomings of the conventional drug delivery systems which include being unstable, degrading and non-targeted therapy. They however require preclinical and clinical trials to determine the safety, efficacy, long term stability, and scaling up. Nevertheless, their unique rights in the management of diseases to provide a fast, less costly and less invasive to the patient.

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