



Synthetic Method of Controlling Shape and Size of Metallic Nanoparticles

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(Received: 16 September 2024

Revised: 11 October 2024

Accepted: 04 November 2024)

KEYWORDS

Metal
Nanoparticles,
Organic
Nanoparticles,
Inorganic
Nanoparticles,
Polyvinylpyrrolid
one, Nanoparticle
Biomedical
Applications,
Cytotoxicity,
Silver
Nanoparticles

ABSTRACT:

Metal nanoparticles are a new class of nanomaterials that possess remarkable optical, catalytic, and antibacterial properties. They are characterized by a wide range of morphological and electrical properties, such as elongation, morphology, and structure. Metallic nanoparticles have acquired considerable importance in several scientific disciplines and industry owing to their distinctive characteristics and multifaceted uses. The size and structure of metallic nanoparticles are crucial parameters that influence their characteristics and functionalities. This study offers a comprehensive examination of diverse synthetic techniques employed to meticulously control the form and size of metallic nanoparticles. The seed-mediated growth technique is a key way for controlling the shape and size of nanoparticles during synthesis. This technology employs pre-synthesized nanoparticles, commonly known as "seeds," which serve as templates to direct the production of certain forms. By meticulously modifying reaction parameters such as precursor concentration, temperature, and surfactant type, researchers may engineer nanoparticles with diverse geometries, including spheres, rods, cubes, and complex arrangements. This technique is very efficacious for noble metals. The polyol process is a versatile and widely employed technique known for its capacity to produce monodisperse nanoparticles with precise control over their dimensions and shapes. The appropriate capping agent combined with polyols functions as both a reducing agent and a solvent. Researchers may accurately manipulate the properties of nanoparticles by employing these concepts. The fabrication of metallic nanoparticles with meticulous regulation of their dimensions and architecture is essential to both nanoscience and nanotechnology. Scientists may produce nanoparticles for targeted applications in sectors such as catalysis, medicine, and environmental remediation, utilizing their expertise in various synthesis procedures, including seed-mediated growth and polyol processes. Ongoing advancements in this domain indicate significant promise for unlocking new opportunities in science and technology, driven by the increasing need for meticulously engineered nanoparticles. In this review, we also provide an overview of NPs and their potential applications in various biomedical applications, including diagnostics, anticancer therapies, antimicrobial properties, antiviral action, anti-inflammatory effects, and drug delivery in various malignancies.



INTRODUCTION

Nanomaterials represent an innovative class of materials with several prospective applications in daily life. One nanometer may be conceptualized as the length of five silicon atoms or ten hydrogen atoms arranged in a linear configuration. A substance is classified as a nanomaterial if its size or dimensions range from 1 to 100 nm. Determining the exact timing of human utilization of nanosized entities is tricky. [1] Nevertheless, utilizing nanomaterials has a lengthy and significant history, with humanity inadvertently employing nanoscale materials for various applications since prehistoric eras. Asbestos nanofibers were used by individuals around 4,500 years ago to enhance pottery compositions. Nearly 4,000 years ago, an ancient Egyptian hair-dyeing formulation incorporated PbS nanoparticles. The Lycurgus Cup is a fascinating relic from antiquity. In the fourth century A.D., the Romans crafted this dichroic cup. Under transmitted light, it seems ruby, yet in direct sunlight, it resembles jade more closely. It alters its hues according to the incident light. [2] The inclusion of Ag and Au nanoparticles renders these color shifts observable. In 1914, Richard Adolf Zsigmondy introduced the term nanoscale. In a 1959 speech at the annual meeting of the American Physical Society, Nobel laureate and American physicist Richard Feynman first articulated the concept of nanotechnology. This is purportedly the inaugural scholarly discourse about nanotechnology. A presentation entitled "There's Plenty of Room at the Bottom" was given by him. During our session, an individual proposed, "Why not condense all 24 volumes of the Encyclopaedia Britannica onto a pin?" The ultimate objective was to create a miniature, molecular-level machine. [3] Feynman contended in this lecture that our incapacity to function at atomic and molecular scales is primarily attributable to a deficiency in appropriate tools and methodologies rather than the constraints of nature. This marks the inception of contemporary technological concepts. This is why many see him as the originator of modern nanotechnology. Norio Taniguchi was likely the first to invent "nanotechnology" in 1974. Before the 1980s, nanotechnology was primarily a subject of discussion until Norio Taniguchi articulated: "Nanotechnology mainly consists of the processing, separation, consolidation, and deformation of materials at the atomic or molecular level." This statement enabled

researchers to start conceptualizing what would evolve into the discipline of nanotechnology. [4]

The advancement of nanotechnology was expedited by the emergence of several spectroscopic techniques. In 1982, researchers at IBM developed scanning tunneling microscopy (STM), enabling the visualization of individual atoms on flat surfaces. Since its inception in 1986, atomic force microscopy (AFM) has established itself as the benchmark for scanning probe microscopy. Driven by the necessity to develop high-density storage hard drives, researchers commenced the measurement of electrostatic and magnetic forces. [5] Electrostatic, Kelvin-probe, and magnetic force microscopy originated from this. The discipline of materials chemistry is rapidly integrating nanotechnology into almost all of its subfields. Advanced characterization and synthesis tools are now available for producing nanomaterials with precisely regulated dimensions, owing to the ever-advancing area of nanotechnology. Nanotechnology, a swiftly advancing technological domain, offers engineered nanomaterials that exhibit significant potential for creating products with greatly improved functionalities. Commercial uses of nanoparticles encompass scratch-resistant paints and coatings, electronics, cosmetics, sports equipment, sensors, and energy storage systems. They are also utilized in environmental restoration and remediation initiatives. [6]

Significant advancements in nanotechnology pertain to the utilization of noble metals such as palladium, gold, and silver as nanoparticles. This has significant potential for the advancement of bioengineering materials that might evolve into cutting-edge diagnostic tools and therapeutic solutions for severe diseases. Silver and gold nanoparticles, due to their unique properties and numerous prospective applications, hold significant relevance in nanotechnology and materials science. The effective targeted drug delivery in various malignancies, together with their exceptional optical, catalytic, and antibacterial properties, distinguishes these noble metal nanoparticles. [7] Their distinctive plasmonic properties render them highly advantageous in domains such as photonics and sensor technologies due to their capacity to manipulate light at the nanoscale. Moreover, silver nanoparticles are renowned for their exceptional efficacy against microorganisms, resulting in their widespread application in several medical domains and as a



disinfectant.[8] Gold nanoparticles are utilized in drug delivery systems and many chemical processes owing to their remarkable catalytic activity. In terms of stability and changeable surface chemistry, silver and gold nanoparticles generally surpass nanoparticles of other metals or metal oxides. Their proficiency in transforming and manipulating matter and energy at the nanoscale is widely recognized. These characteristics are crucial tools for scientists across all fields, including health and environmental research, seeking innovative solutions to longstanding issues. Moreover, these nanoparticles are found in several everyday items, such as those utilized for personal cleanliness, food preservation, cosmetics, and bandages.[9]

CLASSIFICATION OF NPs

Nanomaterials are often classified as organic, inorganic, or carbon-based, depending on the synthesis method and the source of the materials employed in their production. This is a summary of the principal categories of nanoparticles that may be utilized in biomedicine, along with many noteworthy combinations of nanomaterials. [10]

ORGANIC NANOPARTICLES

The injection of medicinal substances into specific organs is a prevalent strategy for controlled release, and organic nanoparticles are widely utilized for this purpose in the pharmaceutical and biomedical sectors. Micelles, liposomes, dendrimers, nanogels, polymeric nanoparticles, and protein nanoparticles are the principal elements of this category. A hollow core region, sometimes referred to as a nanocapsule, is a prevalent characteristic of biodegradable nanoparticles such as micelles and liposomes. [11] Their distinctive characteristics provide them viable candidates for use as drug matrices. The bulk of water-insoluble pharmaceutical medicines are released into solution by micelles. They serve as a versatile delivery mechanism for active compounds since their hydrophilic shell protects them from physiological processes while their hydrophobic core accommodates water-insoluble molecules. [12] The malleability of liposomes, together with their ability to conjugate with diverse lipid molecules, results in significant variation in their shapes, sizes, and compositions. A significant advantage of liposomes is their potential to release active ingredients

upon fusion with cell membranes. A multilamellar liposome, characterized by several lipid layers interspersed with hydrophilic layers, may contain both hydrophilic and lipophilic molecules. Currently, researchers are investigating liposomes for several therapeutic applications, including antimicrobial therapy, targeted drug delivery, and cancer diagnosis and treatment. [13]

Polymeric nanoparticles, which may manifest as nanocapsules or nanospheres, might derive from natural or synthetic sources. The creation of these nanoparticles enables the targeted release of pharmaceuticals in substantial amounts. PMMA (poly (methyl methacrylate) dispersions) have been the focus of several research initiatives aimed at their advancement and possible applications. PMMA, a commonly utilized amorphous synthetic polymer, exhibits intriguing medical applications due to its low cost, non-toxicity, low inflammatory effects on tissues, and ease of processability. [14] Protein polymers, such as collagen, gelatin, albumin, or elastin—isolated proteins derived from plants or animals—can self-assemble to form protein nanoparticles. Utilizing polymer-based nanoparticles and genetic engineering, protein subunits autonomously assemble into effective drug-delivery systems. Abraxane®, an FDA-approved protein nanoparticle treatment, is a medication that facilitates the administration of paclitaxel via albumin in several breast cancer types. Another instance is Ontak, a protein engineered to amalgamate IL-2 with a formulation of diphtheria toxin nanoparticles. It is utilized for the treatment of cutaneous T-cell lymphomas that either recur or remain persistent. [15] The International Union of Pure and Applied Chemistry defines nanogels as "particles of gel of any shape with an equivalent diameter of approximately 1 to 100 nm." Nanogels provide several benefits over other nanocarrier systems, including decreased premature drug release, the capacity to encapsulate therapeutic agents inside a singular formulation, and straightforward delivery through parenteral or mucosal routes. The most promising use is nasal vaccination, however, studies have also examined the injection of cytokines, nucleic acids, and vaccines. [16]



INORGANIC NANOPARTICLES

Common instances of inorganic nanoparticles include quantum dots, silica-based nanoparticles, metal and metal oxide nanoparticles, and the metals themselves. Both top-down and bottom-up approaches can be employed to synthesize metal nanoparticles. Nanoparticles serve as an effective delivery mechanism for nearly all metals. The most prevalent metals employed in the fabrication of nanoparticles are gold, silver, iron, aluminum, cadmium, cobalt, copper, and zinc. Nanoparticles exhibit distinct general properties, including size, surface-to-volume ratio, pore size, electronic surface charge, surface density, crystalline or amorphous structure, spherical or cylindrical shape, color, reactivity, and sensitivity to environmental factors such as humidity, temperature, and light. [17] To synthesize metal oxide nanoparticles, it is necessary to modify the properties of the metal. For instance, when exposed to oxygen at room temperature, iron-based nanoparticles (FeNPs) undergo spontaneous oxidation to form iron oxide, rendering them more reactive than FeNPs in isolation. The bulk of metal oxide nanoparticles are synthesized by physical or chemical processes due to their increased chemical reactivity or their capacity to contract under physical stresses, such as those encountered in a spinning reactor. This technique is frequently employed to synthesize nanoparticles of iron oxide (Fe₂O₃), magnetite (Fe₃O₄), silicon dioxide (SiO₂), titanium oxide (TiO₂), and aluminum oxide (Al₂O₃). [18] These particles have superior features relative to the metals from which they are composed. A category of nanoscale particles, termed quantum dots, is minuscule and displays distinctive optical properties. Measuring between 2 and 10 nm, they consist of semiconductor materials, predominantly cadmium selenide (CdSe), cadmium telluride (CdTe), or lead sulfide (PbS). They serve several purposes, including as in bioimaging, solar cells, and displays. [19]

Silica-based nanoparticles are another type of inorganic nanomaterial, consisting of crystalline formations formed from silicon and oxygen atoms. Their minimal toxicity, chemical and thermal stability, and biocompatibility render them suitable for imaging, biosensing, and drug delivery, among other biomedical uses. Among the several categories of inorganic nanoparticles, semimetal nanoparticles emerge as a particularly fascinating subgroup. The optical and

electrical properties of these nanoparticles are intriguing, and they may possess therapeutic applications. [20] The many biological applications of nanoparticles derived from selenium, antimony, and bismuth are significant examples. Nevertheless, intriguing novel therapeutic applications for metal nanoparticles have arisen from their integration with other nanostructures. The synthesis of photothermal agents by the amalgamation of gold nanoparticles with silica nanoshells serves as a prominent illustration. Such particles can accumulate in tumor tissues with exceptional accuracy and subsequently kill cancer cells by emitting heat at their highest concentration upon exposure to near-infrared light. [21] Photothermal therapy is a technique that has promise in cancer treatment. An alternative for adaptable drug delivery systems is the integration of gold nanoparticles into liposomes. By directing these hybrid nanostructures to specific disease sites, such as tumors, they can release therapeutic agents in a controlled manner, enhancing the efficiency of chemotherapy while mitigating its adverse effects. Moreover, theranostic nanoplatforms including gold nanorods encased in mesoporous silica have been employed for standard radiation therapy and diagnostics. Hydrogel matrices infused with silver nanoparticles can be utilized to create antibacterial wound dressings. The gradual release of silver ions from these wound dressings eradicates pathogens and accelerates the healing process. [22]

CARBON-BASED NANOPARTICLES

Carbon-based nanoparticles are categorized into numerous types, including fullerenes, graphene, carbon nanotubes, nanofibers, and carbon black. Fullerenes are spherical molecules composed of up to 1500 carbon atoms interconnected by sp² hybridization. Carbonaceous nanoparticles are nanoparticles composed entirely of carbon. [23] Fullerenes has several prospective medicinal uses, including the transport of antibiotics and antiviral medications, X-ray imaging contrast agents, gene transfer, photodynamic treatment, and advanced magnetic resonance imaging (MRI) contrast agents. Graphene, an allotrope of carbon, consists of carbon atoms arranged in a two-dimensional hexagonal lattice. [24]

Carbon nanotubes are cylindrical carbon structures with lengths varying from one hundred nanometers to one millimeter in diameter. Due to their size and shape, they



serve as optimal carriers for active substances, facilitating entry into cells via endocytosis or direct membrane insertion. Graphene sheet-derived nanotubes can assume unconventional geometries, such as conical or cup-like forms when utilized in conjunction with carbon nanofibers. Carbon black, an amorphous carbon material, generally exhibits a spherical morphology with a diameter ranging from twenty to seventy nanometers. Particles aggregate into clusters around 500 nm in size due to their exceptionally strong interparticle interactions. [25]

METHODS OF METALLIC NANOPARTICLE PREPARATION

A) Top-down methods - These include the reduction of substantial quantities of material to nanoparticles. The reduction of the initial material's dimensions via several physical and chemical processes constitutes the basis of nanoparticle synthesis. Mechanical milling, thermal machining, and laser ablation constitute this group of technologies. Although top-down procedures are facile to implement, they are not the optimal method for producing irregularly shaped or minuscule particles. The modification of nanoparticle surface chemistry and physicochemical properties is the primary concern with this method. [26]

MECHANICAL MILLING

Ball milling - Ball milling is a form of mechanical milling that employs high-energy balls to diminish particle size. This method for reducing particle size was developed by John Benjamin in 1970. This method is responsible for modifying surface properties. Process variables and the characteristics of milling powders influence the efficacy of mechanical milling. Two categories of milling are differentiated by the quantity of mechanical energy imparted to the mixture: low-energy milling and high-energy milling. [27] A high-energy ball milling technique is frequently employed to produce nanosized particles. This method is frequently preferred for manufacturing intermetallic nanoparticles. A quantity of hefty spheres is positioned in a container containing bulk powder. A rapidly rotating ball is employed to impart significant mechanical energy to bulk powder material. Attrition ball mills, planetary ball mills, vibrating ball mills, low-energy tumble mills, and high-energy ball mills are many types of high-energy mills

capable of reducing particle size. In each of these methodologies, substantial, swiftly moving spheres with elevated specific energy either descend freely into the powder or traverse down a chamber's surface in successive parallel layers. [28]

MECHANOCHEMICAL SYNTHESIS

The mechanochemical synthesis process entails the repetitive deformation, welding, and fracture of the reactant mixture. Milling induces many chemical transformations at the interface of nanoscale particles. High temperatures are frequently essential in chemical reactions for several reasons, including the separation of reactant and product phases. The employment of a ball mill at reduced temperatures facilitates the synthesis of nanoparticles without external heating requirements. [29] The initial elements are combined stoichiometrically and processed using the mechanochemical synthesis method. Sodium carbonate and hexahydrate chloride are utilized in the manufacture of Fe₃O₂ nanoparticles. Milling results in the deformation, fragmentation, and welding of the reactants. A sequence of chemical reactions commences at the interface of the substrate and reagent surfaces; hence, the high-temperature reaction can transpire at a low temperature without further heat. Multiple displacement reactions occur throughout the process represented by $S_xC + yR = xS + RyC$. xS is the final product, RyC is the byproduct, while S_xC and yR serve as the reactants. The byproduct material surrounds the nanoparticles and is dispersed inside the soluble salt matrix. The subsequent step involves rinsing the particles with a suitable solvent to remove the byproduct. Subsequently, they are desiccated at 105 °C for 12 hours. [30]

LASER ABLATION

The laser ablation technique utilizes laser irradiation to accomplish nanoparticle size reduction. The solid target material undergoes pulsed laser irradiation after being positioned beneath a thin layer. Copper vapor lasers, Ti: Sapphire lasers, and Nd: YAG lasers, emitting at 106 μm, are predominantly employed. When a material is subjected to a laser, it disintegrates into nanoparticles. [31] The particles then deposit into the surrounding liquid, forming a colloidal solution. The number of atoms and particles ablated is contingent upon the duration and energy of the laser pulse. The efficacy of ablation and the



characteristics of the resultant metal particles are influenced by several factors, including wavelength, pulse duration, ablation duration, laser fluence, and the properties of the surrounding liquid medium, particularly its surfactant content.[32]

ION SPUTTERING

Ion sputtering is utilized for the vaporization of solids through a beam of ions generated from inert gases. Magnetron sputtering of metallic targets is a novel technology employed to produce nanoparticles from diverse metals. This process involves the application of mass nanostructured films onto silicon substrates following the generation of collimated nanoparticle beams. Throughout the whole operation, low pressures of 1 mTorr are used. In a vacuum chamber, sputtering gas is injected, and operating pressures of 0.05 and 0.1 mbar are sustained during the deposition process. [33] Gas ionization transpires when a substantial voltage is provided to the target or cathode, subsequently directing free electrons down a helical trajectory via a magnetic system. Along this trajectory, they collide with atoms of sputtering gas, specifically argon. This process produces a plasma glow discharge to ignite materials. The target is continuously assailed by positively charged gas ions attracted to it. When this occurs repeatedly, and the energy approaches the target's surface, it is sufficiently proximate to release a single atom. In a vacuum container, metallic atoms incessantly clash with gas molecules, resulting in the dispersion of the atoms and the eventual formation of a diffuse cloud. [34]

B) Bottom-up methods - This method involves the synthesis of nanoparticles from smaller entities, such as atoms, molecules, or particles, rather than from bigger structures. This technology synthesizes nanoparticles by initially fabricating their nanostructured constituents and subsequently assembling them. [35]

SOLID STATE METHODS

Physical vapor deposition method. Nanoparticles or thin films can be placed as subsurface material via the physical deposition process. The material is evaporated and subsequently concentrated on a substrate by meticulously controlled vacuum procedures, including sputtering deposition and thermal evaporation. The fabrication of lanthanum strontium cobalt thin films frequently employs physical vapor deposition methods, such as pulsed vapor deposition. Pulsed laser deposition

involves the ablation of a solid target by a laser, resulting in the formation of a plasma composed of ablated species. Subsequently, this plasma is applied to a substrate to create a film. This process is frequently employed to deposit metal nanoparticles and thin coatings onto carbon nanotubes.[36]

CHEMICAL VAPOR DEPOSITION METHOD

Carbon fiber filaments and electric lamp color pigments were synthesized using chemical vapor deposition, a process first recorded and patented in the late 19th century. Gaseous molecules containing atoms essential for film formation engage in a chemical reaction during this deposition process, leading to the deposition of a thin film of the target material onto a surface. [37] A thin film is formed by a series of chemical interactions among the precursor fragment, the precursor, and the substrate surface. The reactions commence with the emission of the target substance as a volatile molecule, serving as a precursor. This method is frequently employed to produce atomic layer deposition (ALD) thin films by a chemical reaction at the surface. Thermally active chemical vapor deposition (TACVD), plasma-enhanced chemical vapor deposition (PECVD), and photo-initiated chemical vapor deposition (PICVD) are three techniques capable of depositing the requisite material. [38] Polymers and other heat-sensitive substrates are unsuitable for thermally triggered chemical vapor deposition. The scalability of plasma-enhanced chemical vapor deposition technique is hindered by its specific operating requirements. Photo-initiated procedures, including photo-initiated CVD, provide a wide array of possible variants and low-energy treatment alternatives. At ambient temperature and pressure, the photo-initiated process does not require any specialized equipment. [39]

LIQUID STATE SYNTHESIS METHODS

Sol-gel method - The sol-gel method was first examined about the sol-gel chemistry of transition metal oxides by Livage et al. (1988). Nanoparticles can be synthesized via the sol-gel technique in two primary methods: (a) by directly amalgamating metal and metal oxide or nanoparticles within a pre-hydrolyzed silica sol, or (b) by blending prepared colloids of metal (oxide) with a sol containing the matrix-forming species, subsequently permitting gel formation. c) Hydrolysis after metal-silicon complexation and ensuing metal reduction. This approach forms a network in the continuous liquid phase



(gel) by amalgamating a colloidal suspension (sol) with gelatin. The ion of a metal alkoxide or alkoxy silane serves as a precursor for colloid formation. Silica gel is predominantly synthesized using tetraethoxysilane (TEOS). Metal alkoxides are water-insoluble and function as organo-metallic precursors for several metals, including silica, aluminum, titanium, and many more. Common solvents frequently encompass alcohol. The four fundamental steps in sol-gel formation are hydrolysis, condensation, particle development, and agglomeration. This method initiates with the formulation of a homogeneous solution containing selected alkoxides, followed by the incorporation of a catalyst to trigger a reaction at a controlled pH. Metal oxide particles are frequently precipitated from silica sol through the direct precipitation of metal or metal oxide process, generally involving low-temperature thermal treatment. The principal use is in the fabrication of thin films. [37,40]

Chemical reduction method - One method is the chemical reduction technique, which entails decreasing ionic salt in an appropriate medium with a surfactant and other reducing agents. Aqueous solutions of reducing agents, such as sodium borohydride, are employed to synthesize metal nanoparticles. Upon preparation, metal nanoparticles are coated with either sodium lauryl sulfate (SLS) or trisodium citrate (TSC). Combining a reducing agent with a stabilizing agent is not unusual. Absorbance analysis was employed to evaluate the stability of the metal nanoparticles in the dispersion. The synthesis of silver nanoparticles employs reducing agents such as sodium borohydride (NaBH₄), glucose, ethylene glycol, ethanol, sodium citrate, and hydrazine hydrate, among others. [41]

Hydrothermal method - The deposition of fine particles is accomplished by the hydrothermal process, which depends on the interaction of vapors from an aqueous solution with solid materials at high pressure and temperature. The process starts with the precipitation of cations as polymeric hydroxides; the subsequent dehydration of these hydroxides accelerates the crystallization of metal oxides. Restricting the synthesis of complex hydroxide facilitates the use of the second metal cation in regulating the particle formation process upon the introduction of a base to a metal salt solution. [38,40]

Solvothermal method - The solvothermal method for nanophase synthesis entails incorporating a solvent, such as water, or an organic molecule like methanol, ethanol, or polyol, into the mixture. The reaction occurs in a pressure cooker, where the solvents (alcohol and water) are cooked to temperatures beyond their boiling points. Microwave-assisted techniques can enhance the kinetics of crystallization by a factor of one to two. [42]

Laser pyrolysis - Laser pyrolysis refers to the method of synthesizing nanoparticles by laser light. This method entails subjecting the precursor to laser illumination to initiate homogenous nucleation processes. This is caused by localized heating and cooling, as opposed to heating gas in a furnace. Infrared carbon dioxide lasers are the most prevalent for heating applications due to the absorption of the laser's energy by sulfur hexafluoride, an inert photosensitizer. Nanoparticle formation in CO₂ pyrolysis commences immediately upon attaining a suitably supersaturated condensable product in the vapor phase. [43]

BIOLOGICAL METHOD/BIOMIMETIC METHOD/GREEN SYNTHESIS METHOD

Nanotechnology is experiencing a transition towards the environmentally sustainable production of nanoparticles. Concerns regarding response difficulties, elevated costs, and safety are among the issues that these novel ideas seek to address. To mitigate the adverse impacts on human and environmental health, "green chemistry" approaches included innovative techniques in chemical manufacturing and many applications of chemical products. The four fundamental approaches are clean chemistry, atomic economy, ecologically benign chemistry, and benign by-design chemistry. Biological methods for nanoparticle manufacturing utilize diverse microorganisms, enzymes, and plant derivatives, including extracts and isolates. These technologies are cost-effective, ecologically benign, and readily scalable for extensive manufacturing, providing several advantages over conventional physical and chemical methods. Furthermore, green synthesis does not utilize any deleterious chemicals, elevated temperatures, or pressure. [42,44]

SIZE CONTROL OF METAL NANOPARTICLES TO THE SUB-NANOMETER SCALE

Chemical reduction has demonstrated significant efficacy in the creation of metal nanoparticles. This



process entails the reduction of a metal salt precursor in solution using a reducing agent or polyalcohol to yield zero-valent metal nanoparticles. Multiple experimental variables must be adjusted to influence nucleation and growth kinetics to control nanoparticle size. The concentrations of the precursors, the ratio of precursors to surfactants, and the reduction temperature attained by selecting a suitable solvent are deemed essential. [45] Teranishi et al. delineated a method for synthesizing Pt nanoparticles measuring between 1.5 and 5.0 nm. Chloroplatinic acid was utilized as the platinum precursor in a blend of alcohols, including polyvinylpyrrolidone (PVP). The study indicated that smaller Pt nanoparticles were achievable with alcohols possessing higher boiling points, emphasizing the significance of nucleation rate in determining particle size. A larger particle size arises from an increased reduction rate at lower temperatures, leading to a decreased number of nuclei. The absence of PVP-protecting groups results in diminished development, increasing the size of Pt nanoparticles as the ratio of PVP to Pt⁴⁺ drops. Seed-mediated growth is a technique for augmenting nanoparticle size, wherein premade nanoparticles are introduced into the precursor solution during the second stage of the process. [46] The upper limit for Pt nanoparticle size is 10 nm. This section will focus on seed-mediated development for shape control. Integrating two precursors with varying oxidation states

is an alternative method to regulate the nuclei concentration during nucleation. Tsung et al. synthesized Pt nanocubes of controlled dimensions by incorporating two Pt salts comprising Pt²⁺ and Pt⁴⁺. The final dimensions of the nanocubes were augmented by generating fewer nuclei when the relative concentration of Pt⁴⁺, which diminishes at a far slower rate than Pt²⁺, in the mixed precursor was increased. Metal nanoparticles of Rh, Pd, Ru, and Pt, with controlled dimensions in the 1-10 nm range, have been produced utilizing the same techniques. Metal nanoclusters were first reported by Wang et al., who omitted the use of an organic capping agent. Utilizing a polyol reduction, they successfully synthesized Pt, Rh, and Ru nanoclusters in organic solvents. Ethylene glycol and sodium hydroxide are essential elements in this process since they facilitate the formation of nanoclusters and maintain their colloidal stability. Consequently, by using various surfactants after the reaction, this synthetic method is employed to produce metal nanoparticles with diverse capping agents. A diverse array of surfactants, including sodium polyacrylate, allylamine, oleic acid, ascorbic acid, trioctylphosphine, isopropylacrylamide, and tetradecyl-trimethyl ammonium bromide, among others, has been utilized in the formulation of various synthetic methodologies for the production of monodispersed platinum nanoparticles in different media. [44,45]

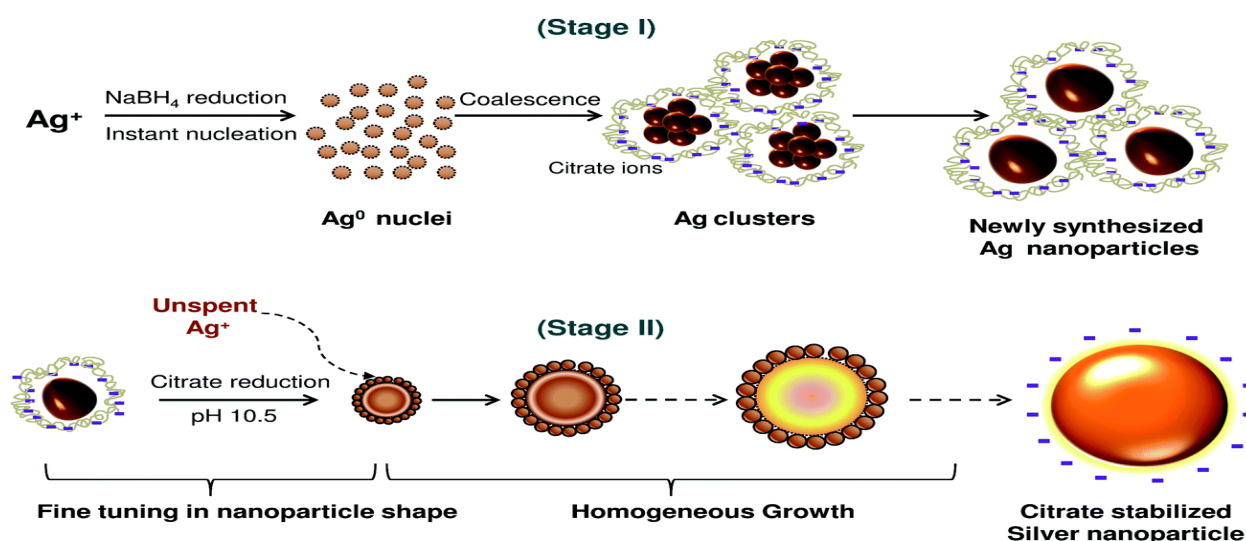


FIGURE 1: Schematic representation of size-controlled silver nanoparticles synthesized employing the co-reduction approach. [57]



Nanoclusters with particle sizes under 1 nm have attracted the attention of several catalysis researchers due to their exceptionally high surface-to-volume ratio. When a metal's particle size is below 1 nm, its surface characteristics, including melting temperature, ionization potential, and nearest-neighbor distance, become predominant, unlike in bulk metal. Recently, dendrimers composed of hyperbranched polymers have been effectively utilized to synthesize various nanoparticles, including metallic and bimetallic types, with dimensions under 1 nm. The formation of dendrimers is dictated by the quantity and nature of the repeating units. The terminal functional groups of each branch decrease to produce metal clusters by coordinating with complex metal species. [47] Nanocluster synthesis frequently utilizes polyamidoamine (PAMAM) or poly (propylene imine) (PPI), two prevalent dendrimers. An instance is the synthesis of dendrimer-encapsulated platinum nanoparticles containing 20 and 40 platinum atoms, respectively, measuring 0.8 and 1.0 nm in size, achieved by modulating the concentration of platinum metal ions relative to the PAMAM dendrimer. A recent study illustrates the development of Pt clusters in the sub-nanometer range into ordered Pt nanocrystals with polyhedral geometries, facilitated by PAMAM dendrimers, as observed through high-resolution transmission electron microscopy (TEM), although the morphology of nanoclusters remains challenging to discern using TEM due to their diminutive size. Recent studies illustrate the boundless potential for regulating particle size, namely the capacity to modify the diameter of Pt nanoparticles from 1 to 100 nm with precise size distributions by a multistep seed-mediated approach. This encompasses the dendrimer-templating methodology. [48]

SHAPE CONTROL OF METAL NANOPARTICLES

The production of metal nanoparticles is characterized by the multiplication of nuclei within a colloidal solution. Nonetheless, new methodologies exist to shape their final manifestations beyond the simple development process. To understand the development of metal nanoparticles with progressively intricate shapes, one must study a nanoparticle seed, which is a cluster with distinctly defined structures formed during the last step of nucleation. The morphology of the final metal nanoparticle is influenced in several syntheses by the incorporation of nanoparticle seeds, shape-directing

agents, or additional ions. The seed form exhibiting the minimal surface free energy (γ), which is the energy required to generate a new surface area, is the most stable during the nucleation phase of a free-conducting quantum well (fcc) structure of metal nanoparticles. [49] According to the thermodynamic stability of surface free energies, the $\{111\}$ surfaces of face-centered cubic (fcc) crystals exhibit the highest stability, succeeded by the $\{100\}$ and $\{110\}$ surfaces. To reduce surface energy, it is advisable to employ octahedral or tetrahedral seeds with $\{111\}$ facets in low-index faceted face-centered cubic crystals. According to Wulff's hypothesis, the most efficient shape for a single crystal seed to reduce surface area and interfacial free energy is a truncated octahedron, referred to as a Wulff polyhedron. [41] This is because octahedrons and tetrahedrons possess greater surface areas than cubes relative to their unit volume. Based on the development behavior during reactions, this Wulff polyhedron seed can evolve into one of three polyhedral forms: octahedron, cuboctahedron, or cube. Numerous instances of metal nanoparticle production have been observed. The formation of flaws might result in the production of seeds that are either singly or multiple-twisted. An instance of a single twinned seed is commonly encountered in metal nanoparticle syntheses, whereby one of the twin flaws possesses a (111) mirror plane. This single twinned seed, characterized by a random-HCP structure akin to a plate, is encircled by $\{111\}$ and $\{100\}$ facets to minimize interfacial free energy. The nucleation stage is a common site for the production of decahedral seeds, which are multiply-twinned structures composed of five interconnected single-crystal tetrahedral seeds. [27] A little gap will remain at the border to accommodate defect planes and elongated bond lengths, despite each tetrahedral seed sharing two planes with adjacent seeds to form a decahedron. Interestingly, one-dimensional structures including a bipyramid or pentagon plane may be produced by the intrinsic properties of singly or multiple twinned seeds, which may manifest as elongated rods or wires. The Xia group has proposed oxidative etching as a way for regulating the distribution of single crystal and twinned seeds. The reaction solution's oxygen and ligand create an oxidative etchant that selectively diminishes the concentration of twinned seeds. The addition of tiny quantities of halogen ions (e.g., Cl and Br) or iron-containing species, in conjunction with oxygen gas,



greatly decreased the number of twinned seeds and enhanced the concentration of more resilient single-crystal seeds. [50]

The morphology of nanoparticles in colloidal syntheses is influenced by many additives. Metal ions (Ag^+ , Fe^{3+} , Co^+), complexes ($\text{W}(\text{CO})_6$), and reactive gaseous molecules (H_2 , O_2 , CO , NO) constitute many categories of structure-directing agents. Platinum nanoparticles transition from cubic, cuboctahedral, and octahedral geometries to augmented Ag^+ ions with the introduction of Ag^+ ions. Recent study indicates that the preferential adsorption of Ag^+ ions on the more active $\{1\ 0\ 0\}$ surfaces of Pt enhances the crystal growth rate in that direction. Triangular and hexagonal palladium nanoplates may be selectively synthesized by slow reduction by modulating the reduction kinetics of a polyol method and including FeCl_3/HCl . Another method to produce isotropic Pd nanobars with $\{1\ 0\ 0\}$ facets involves disrupting cubic symmetry in a regulated kinetic environment with KBr . [51]

A prominent strategy for regulating nanoparticle morphology and enhancing crystal size is seed-mediated growth. The technique of seed formation has been previously characterized as a method for manipulating structure; moreover, synthesized nanoparticles may act

as a nucleus for the development of a secondary crystal. Epitaxial growth on the seed surface produces single metal nanoparticles with enhanced size and morphology when the extra metal atoms are identical to the preformed seed component. This procedure transpires throughout growth. The multifaceted seed may be utilized to produce core/shell bimetallic nanoparticles upon the addition of additional atoms. [38] Heteroepitaxial growth occurs only when the seed and supplementary precursors exhibit a precise lattice match. Habas et al. fabricated Pt/Pd core/shell nanocrystals by controlling the epitaxial overgrowth of a secondary metal on cubic Pt seeds. This article delineates a technique for meticulously regulating the morphology of Pt/Pd core/shell nanocrystals, transitioning from a cube to a cuboctahedron and ultimately to an octahedron with increasing NO_2 concentration. Complex nanostructures such as concave cubes, multi-pods, and highly-branched dendrites may be synthesized by the integration of seeded growth, kinetically controlled overgrowth, and selective etching. In a pressure reaction vessel, the ratio of oleylamine to oleic acid, an organic surfactant, may regulate growth rates, enabling the manipulation of Pd nanoparticle morphologies from isotropic polyhedrons under thermodynamic circumstances to anisotropic multi-pods in kinetic regimes. [28,47]

BIOMEDICAL APPLICATIONS OF METAL NPs

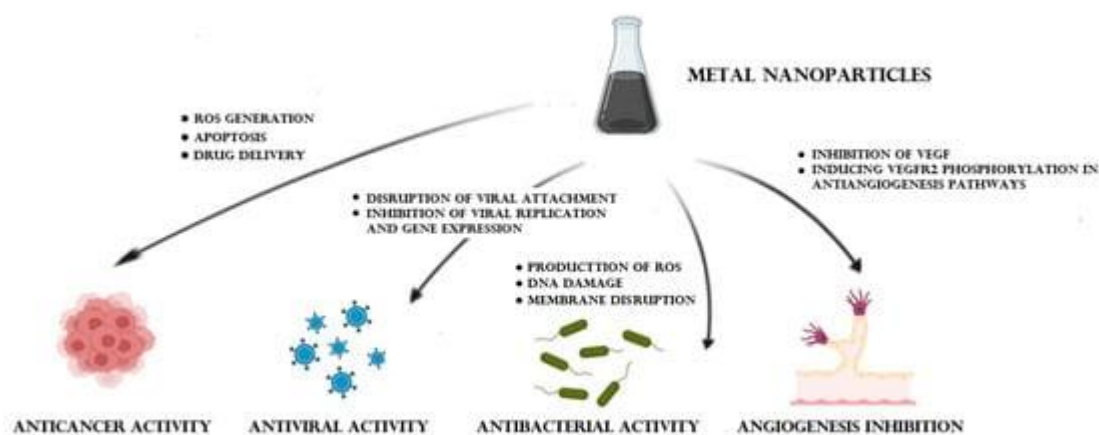


Figure 2: Biological activities of metal NPs and their potential mechanisms (VEGF—vascular endothelial growth factor; VEGFR—vascular endothelial growth factor receptor). [28]

Diagnostics - While the majority of nanoparticles exhibit biocompatibility and stability, many possess distinctive features, including magnetic properties. Thus, magnetic nanoparticles may be directed to a specific site within the

body by an externally generated magnetic field. Their magnetic susceptibility, defined by the relationship between the applied field and the resultant magnetization, is a crucial attribute in their medical use.



For instance, super-paramagnetic iron oxide nanoparticles (SPIONs) are often employed as MRI contrast agents in medical institutions.[24]

Anticancer Activity - Nanoparticles (NPs) possess anticancer characteristics and are utilized as therapeutic agents, diagnostic tools, and hydrophobic drug carriers. A key use is the targeted delivery of antineoplastic agents to malignant tissues, as nanoparticles may infiltrate these tissues and transport the drug to a specific site. Moreover, NPs are receiving considerable interest as prospective vehicles for gene and drug delivery systems, as well as biosensors that directly interact with blood. Jagtap et al. validated a significant anticancer effect, particularly against A549 lung cancer cells, in their in vitro study of embelin-derived AgNPs. Metal nanoparticles are more efficient in eliminating cancer cells than healthy ones. Several mechanisms have been postulated for the cytotoxicity of metal nanoparticles. This encompasses ROS production, mitochondrial outer membrane permeabilization, and targeted DNA breakage, which subsequently induce cancer cell death by autophagy, necrosis, and apoptosis. [52]

Angiogenesis Inhibition - Gold nanoparticles have significant promise in cancer therapy by obstructing the formation of new blood vessels. Antibodies and small compounds, among other therapeutic agents, can be utilized by targeting nanoparticles. Mukherjee et al. discovered that AuNPs inhibit angiogenesis through a dose-dependent mechanism by obstructing protein phosphorylation; dosages between 335 and 670 nM resulted in virtually complete suppression. A potential mechanism of suppression involves the direct binding of heparin-binding growth factors to AuNPs. [53] Recent studies on apigenin-biosynthesized AuNPs have emphasized their dual role, indicating a potential to diminish angiogenesis and facilitate the anti-proliferative effects against cholangiocarcinoma. Furthermore, an original study established the in vitro inhibition of angiogenesis, tumor migration, and mesenchymal-epithelial transition by the use of sorafenib derivatives-capped AuNPs. A notable study using AgNPs was conducted by Kalishwaralal et al., which demonstrated that nanoparticles synthesized from *Bacillus licheniformis* on BRECs reduced angiogenesis. Utilizing BRECs as an in vitro model, another study showed that AgNPs inhibited VEGF-induced cell proliferation,

migration, and tube formation. The impact of ecologically sustainable AgNPs synthesized from an extract of the brown alga *Dicotyota ciliolata* was the focus of another study. The NPs exhibited antiangiogenic characteristics, suppressing the development of tertiary blood vessels, alongside enhanced cytotoxicity against a lung cancer cell line. [54]

Antimicrobial Properties - The antibacterial characteristics of metal nanoparticles (NPs) encompass minimal bacterial resistance, several mechanisms for bacterial inhibition and eradication, and a substantial surface-to-volume ratio. The metal nanoparticles that exhibited the most promising outcomes were zinc, titanium, copper, gold, and silver. Complex nanoparticles, such as Ag/Cu₂MoO₄ NPs, exhibited inhibitory effects against *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*, along with glucose detection capabilities. Meanwhile, LaNiO₃/SrCeO₃ and NiV₂O₆/CeO₂ nanocomposites demonstrated significant activity against *Klebsiella pneumoniae* and *Bacillus cereus*, as well as against *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Legionella pneumophila*, respectively, in addition to photocatalytic properties. *Mycobacterium tuberculosis* and *Helicobacter pylori* were investigated utilizing bimetallic metal-organic frameworks composed of iron and nickel, demonstrating promising efficacy. [55] Nanostructures of silver indium sulfide and nickel molybdenum sulfide enhanced peroxidase-like activity for uric acid detection and exhibited antibacterial properties against *Escherichia coli* and *Staphylococcus aureus* during light exposure. Nanocomposites of NiCo₂O₄-Bi₂O₃ and Ag₂ZrO₃ showed significant bactericidal activity against *P. aeruginosa* and *S. Aureus*. *Pneumonia* corroborates the assertion that these nanoparticles possess several roles. Due to their small size and extensive surface area, metal nanoparticles interact with microorganisms more efficiently than bulk metals. The antimicrobial activity results from several mechanisms, including oxidative stress, DNA damage, and membrane disruption.[52]

Antiviral Action - metal nanoparticles, are characterized by their diminutive size, extensive surface area, and catalytic activity. These distinctive physicochemical properties provide them with a compelling option for this position. Their capacity to attach to and modify the



structure or function of viral components (including proteins and membranes) renders them useful in inhibiting the replication and dissemination of viruses. Numerous viruses, such as herpes simplex virus (HSV), HIV-1, and influenza virus, have been evaluated for the antiviral capabilities of AgNPs. Studies have shown that AgNPs can obstruct viral entry, replication, and release by engaging with viral envelope proteins or RNA. [53] Furthermore, AgNPs can augment the immune response by promoting the production of chemokines and cytokines, therefore activating antiviral defenses. Determining the precise mechanism of action of these nanoparticles is particularly tough due to the considerable variability in their sizes and production methods. Their inhibitory efficacy improves when size diminishes, as per the research conducted by Gaikwad et al. AgNPs appear to interact with viral surface proteins, either eliminating them or restricting their penetration, so altering the virion's structure and integrity; yet, the precise antiviral mechanism remains incompletely elucidated. In vitro testing demonstrated that AgNPs effectively inhibited the entrance of SARS-CoV-2 into cells, hence preventing infection. [54]

Anti-Inflammatory Activity - The immune system sustains inflammation by the release of chemotactic substances, including complement cells, interleukin-1 (IL-1), TNF- α , and TGF- β , alongside the production of pro-inflammatory cytokines. The anti-inflammatory properties of metal nanoparticles render them a potentially valuable class of materials. Numerous studies indicate that these nanomaterials can impede the production of chemokines, reactive oxygen species, and pro-inflammatory cytokines, hence reducing inflammation. Consequently, they are regarded as prospective therapeutic alternatives for the treatment of many inflammatory conditions. The potent anti-inflammatory properties of AgNPs are believed to underlie their ability to inhibit the synthesis of pro-inflammatory cytokines, such as TNF- α and IL-1, in macrophages. Moreover, the production of the inducible nitric oxide synthase (iNOS) enzyme, a crucial element of the inflammatory response, is diminished by AgNPs. Numerous studies have demonstrated that AuNPs can reduce the synthesis of pro-inflammatory cytokines and chemokines in human endothelial cells. These encompass IL-6, IL-8, and MCP-1.

Zinc oxide nanoparticles (ZnO NPs) inhibit the activation of nuclear factor-kappa B (NF- κ B), whereas copper nanoparticles (NPs) exhibit anti-inflammatory properties by diminishing the production of pro-inflammatory cytokines such as IL-1, TNF- α , and IL-6 in macrophages activated by lipopolysaccharide (LPS). [49,50]

CYTOTOXICITY OF METAL NPs

It is increasingly evident that nanomaterials may adversely impact human organs, potentially influencing their utilization in biomedicine. Due to their dimensions, comparable to those of protein molecules, metal-based nanoparticles may easily traverse cell membranes. This indicates their potential to induce neurotoxicity, immunotoxicity, and genotoxicity via interactions with proteins or components of subcellular organelles. The widespread use of these materials and technologies has made their biosafety a significant area of investigation. AgNPs have several delivery routes, including oral, intravenous, and transdermal. Upon absorption, AgNPs are distributed across several human systems and organs, including the respiratory, digestive, urinary, neurological, immunological, and reproductive systems. [55] The bulk of these nanoparticles are predominantly located in the spleen, liver, kidneys, and lungs, with lesser quantities deposited in the teeth and bones. The non-specific dispersion of AgNPs restricts their utility due to toxic effects on the skin, eyes, respiratory system, reproductive system, and neurological system. The potential cytotoxicity of AgNPs is influenced by factors like size, shape, concentration, and delivery techniques. Wang et al. employed TEM with synchrotron radiation beam transmission X-ray microscopy (SR-TXM) and 3D tomographic imaging to examine the cellular uptake, accumulation, degradation, chemical alteration, and removal of AgNPs. Researchers determined that the chemical transformation of AgNPs into Ag⁺, Ag-O-, and Ag-S-species, which may induce biological alterations, was the primary source of cytotoxicity. [56]

CONCLUSION

Nanomaterials, with dimensions ranging from 1 to 100 nanometers, have a rich historical context and significant potential across various applications, particularly in biomedicine and technology. Their unique properties, especially those of noble metal nanoparticles like silver



and gold, enable advancements in drug delivery, diagnostics, and environmental solutions, highlighting the transformative impact of nanotechnology on modern science and everyday life. Inorganic and carbon-based nanoparticles exhibit unique properties and versatile applications in fields such as medicine, electronics, and materials science. Their synthesis methods, including top-down and bottom-up approaches, enable the development of advanced nanostructures that enhance therapeutic efficacy and improve delivery mechanisms in various biomedical applications. There are various methods for synthesizing nanoparticles, emphasizing the significance of both bottom-up and top-down approaches, including physical and chemical vapor deposition, sol-gel techniques, and green synthesis methods. The key takeaway is that advancements in nanoparticle synthesis techniques enable precise control over particle size and properties, which is crucial for their applications in nanotechnology. The production and morphology of metal nanoparticles can be significantly influenced by the use of nanoparticle seeds, shape-directing agents, and specific synthesis conditions, allowing for the creation of complex structures with tailored properties. Understanding these factors is essential for advancing applications in nanotechnology and materials science. Metal nanoparticles (NPs) demonstrate significant potential in various biomedical applications, including diagnostics, anticancer therapies, antimicrobial properties, antiviral action, and anti-inflammatory effects. However, their cytotoxicity and potential adverse effects on human health necessitate careful consideration and further research to ensure their safe and effective use in medical settings.

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