Review Article

Silver Nanoparticle in Pharmaceuticals as Advanced Drug Delivery System

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ABSTRACT

The term "nanotechnology" refers to the field of technology that has made it possible to create objects with dimensions in the "nanometres" range. In this, nanoparticles are the core components of nanotechnology. The development of nanomaterials, particularly inorganic nanoparticles (NPs) and nanorods, with unique uses and size-dependent physicochemical properties that differ significantly from their bulk counterpart, has led to the explosive growth of the nanotechnology industry. In particular, AgNPs are crucial to nanomedicine and other fields of nanoscience and nanotechnology. Physical, chemical, or biological mechanisms can all be used to produce AgNPs. In addition to being used as biosensors, vaccine adjuvants, anti-diabetic medicines, and in the promotion of bone and wound healing, AgNPs are principally used in antibacterial and anticancer treatment. Nanoparticles are advantageous delivery systems for the target-specific and controlled delivery of micro- and macromolecules in disease therapy due to the ability of both hydrophilic and hydrophobic substances to bind easily, the formation of stable interactions with ligands, variety in size and shape, high carrier capacity, and stable interactions with ligands. When therapeutic agents and nanoparticles are used together, problems with conventional therapy are overcome. Many scientists and researchers are currently concentrating their research on the use of silver nanoparticles in the treatment of psychiatric disorders, arthritis, hypertension, and PCOD.

Keywords: Nanotechnology, Silver nanoparticles, Particle size, Therapeutic drug delivery, Targeted delivery, Application.

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INTRODUCTION

Nanotechnology is a rapidly developing field with numerous uses in industries, environments, pharmaceuticals, and healthcare. The inorganic nanoparticles have special physical and chemical characteristics among nanosized particles. Therapeutics has advanced significantly since nanotechnology was developed. By creating a wide variety of nanoparticles that can penetrate even very impenetrable barriers like the blood-brain barrier, it has altered conventional approaches to medication design and delivery systems.[1] Nanotechnology is concerned with the analysis and control of substances at atomic or molecular scales that are almost 100 nm or smaller.[2] It entails exploring and creating various nanoscale materials (less than 100 nm). Due to its numerous applications in a variety of scientific disciplines, including nanoscale electronics, biomedical engineering, material science, and medicine, it is a more fascinating topic for scientists.[3]

Nanoparticles are essentially any particle with a size between 1 and 100 nm that is surrounded by an interfacial layer. Numerous applications of nanoparticles are found in the fields of health, biomedical technology, multicolour optical coding, manipulating biomolecules (proteins, DNA, cysteine), environmental cleanup, and cosmetics.[4] Due to their distinct physicochemical and biological features, Ag nanoparticles have attracted considerable interest. Nanoparticles are formed naturally, unintentionally, or artificially at the nanoscale in an aggregate and unbound condition with a dimension and size range of 1-100 nm.[5]

The nanoscale material has unique, superior physical and chemical properties in comparison to its Other structures because of an increase in the surface area ratio per material/particle volume.[6] Due to their simplicity in synthesis, metal nanoparticles have received the greatest attention from researchers. These materials can be used for a broad variety of purposes, including as detectors, catalysts, surface coating agents, antibacterial/ antimicrobials, and many more.[7] Gold, platinum, palladium, and silver are some of the most researched metallic nanoparticles (Ag, Au, Au, and Palladium). Ag NPs play a significant role in nanoparticle production and characterization due to their intrinsic ability to operate as an antibacterial agent even in a solid state.[8]

Table 1: Various characteristics and brief applications of nanosystem.[9]

Types of Nanosystem	Size (nm)	Characteristics and Material Used	Applications
Carbon nanotubes	0.5–3 diameter and 20–1000 length	Single-wall nanotubes (SWNTs), a third allotropic crystalline form of carbon sheets, or multiple-layer carbon sheets (multi-walled nanotube, MWNT). These crystals exhibit exceptional strength and distinct electrical characteristics (conducting, semi-conducting, or insulating) Materials used: metals, semiconductors	Functionalization increased solubility, access to the cytoplasm and nucleus of the cell, use as a vehicle for delivering genes, and delivery of peptides
Metallic nanoparticles	<100	Small size, the high surface area available for functionalization, and the stability of gold and silver colloids	Delivery of drugs and genes, highly sensitive diagnostic tests, thermal ablation, and improvement of radiotherapy
Nanocrystals Quantum dots	2–9.5	Synthesis of semi-conducting material using II-VI and III-V column elements; Size between 10 and 100; bright fluorescence, narrow emission, wide UV excitation, and high photostability	Long-term multicolour imaging of the liver cell; DNA hybridization; immunoassay; receptor-mediated endocytosis; and surface labelling of cancer cells with the breast cancer marker HeR 2.
Polymeric micelles	10–100	High drug entrapment, payload, and biostability in block amphiphilic copolymer micelles The material used: Amphiphilic block copolymers.	Target-specific active and passive drug delivery, long circulation, and diagnostic value
Polymeric nanoparticles	10–1000	Biocompatible and completely drug-protective, biodegradable. The material used: Biodegradable polymer.	Excellent carrier for delivering drugs in a controlled and sustained manner. Bio actives can be delivered actively or passively using stealthy and surface-modified nanoparticles.
Dendrimer	<10	A highly branched, nearly monodispersed polymer system created by controlled polymerization has three main parts: the core, the branch, and the surface.	Targeted bioactive delivery to macrophages, long circulation, controlled bioactive delivery, and liver targeting
Liposome	50–100	Phospholipids vesicles are biocompatible, adaptable, effective at entrapping molecules and provide simple	Long-circulatory, providing both passive and active gene, protein, peptide, and other types of delivery
Diamond	Below 50	They are particularly appealing for a variety of potential applications because they have excellent mechanical and optical properties, a large surface area, easy bioconjugation, and high biocompatibility.	Diamond nanoparticles may be used in a variety of biological applications, and because of their distinctive qualities, such as inertness and hardness, they may prove to be a more effective substitute for the conventional nanomaterials currently used to carry drugs and coat implantable devices.

SILVER NANOPARTICLES

Metal nanoparticles offer a wide range of applications in numerous industries. Particularly, technologies based on nanoscale materials have been utilized in several factors, from chemistry to medicine, because shapes, sizes, and compositions of metallic nanomaterials are significantly linked to their physical, chemical, and optical capabilities. Due to their instability, such as the potential for oxidation in a fluid containing oxygen, the use of silver-based nanomaterials has been constrained, although silver has exciting material characteristics and is a cheap and abundant natural resource.[10] Previous studies have demonstrated that AgNPs, size, distribution, morphology, and surface properties-all of which may be altered by a variety of synthetic techniques, reducing agents, and stabilizers-have a significant impact on their physical, optical, and catalytic capabilities. AgNPs can vary in size depending on the application; for instance, AgNPs designed for drug delivery are typically larger than 100 nm to account for the amount of drug to be supplied. AgNPs can also be shaped into a variety of shapes with diverse surface properties, such as rods, triangles, rounds, octahedral, polyhedral, etc. The application of AgNPs in the disciplines of nanomedicine, pharmacy, bio-sensing, and biomedical engineering has been made possible by their outstanding capabilities.[11]

SYNTHESIS OF SILVER NANOPARTICLES

Synthesis of AgNPs via Top-Down and Bottom-Up Methods

Ag nanoparticles can be created using a variety of techniques, including physical, chemical, biological, electrochemical, and radiation approaches. The green synthesis strategy is more dependable and preferable due to differences in particle size, size distribution, toxic effect, cost, scalability, environmental impact, and energy consumption. As a result, each method has some advantages and disadvantages. Currently, there are primarily two methods used to create nanoparticles. 1) A bottom-up strategy and 2) A top-down strategy.[12]

Bottom-up approaches

The production of Ag nanoparticles, which are the fundamental units of nanomaterials construction and which self-assemble and are controlled by chemical processes, begins with growing atoms or molecules. Under a specified sequence, structure, pattern, unique restriction, or external force, atoms or molecules can be assembled using a template or without a template. A method known as "Self Assembly Lithography," which is a practical method, is used to create nanoparticles smaller than 100 nm. But one of the specific difficulties of the Bottom-up Approach is the atoms' unpredictable mobility.[4]

Top-down approaches

In this method, bulk materials are decreased using some methods, which causes the development of nanostructures. Bulk material must be broken, cut, and etched throughout this process, and the entire process uses lithography, such as film machining, surface machining, mould machining, x-ray lithography, electron beam lithographing, x-ray lithography, electron beam lithography, etc.[4]

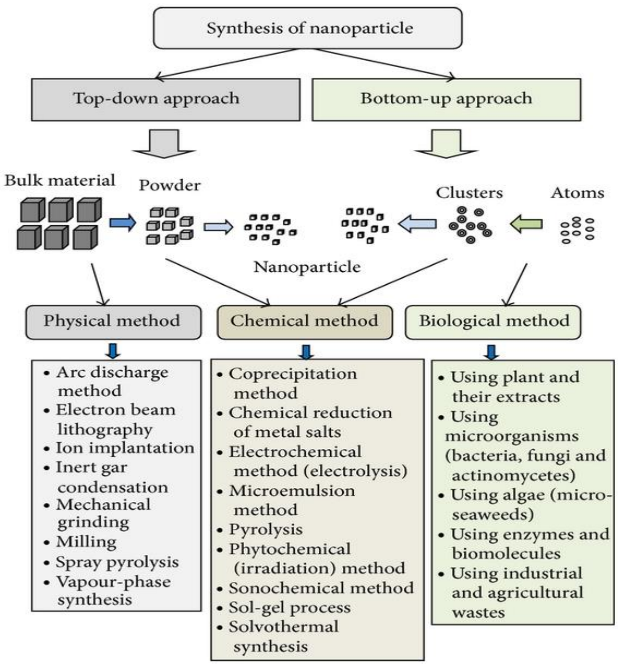

Figure 1. Synthesis of nanoparticles.[13]

PHYSICAL METHOD

The evaporation-condensation method and the laser ablation technique are both used in the physical synthesis of AgNPs.[14] Those methods may produce huge amounts of high-purity AgNPs without the use of hazardous chemicals that endanger human health and the environment and create harmful byproducts. But since capping agents are rarely employed, agglomeration is frequently a significant difficulty. Both strategies also use more power and necessitate specialized equipment and a rather lengthy synthesis period, all of which raise the running costs of each method. When creating nanospheres via the evaporation-condensation method, a tube furnace is commonly used for the gas phase pathway. Through the use of several materials, including Au, Ag, and PbS, different nanospheres have been created utilizing this method.[15] The ultimate synthesis of NPs is made possible by an evaporated base metal source that is contained in a vessel in the centre of the tube furnace. The design of the reaction facilities can be altered to regulate the size, shape, and yield of the NPs. However, the evaporation-condensation method of making AgNPs in the tube furnace has a lot of disadvantages. The tube furnace takes up a lot of room, uses a lot of energy to raise the temperature around the metal source, and needs more time to maintain its thermal stability.[16]

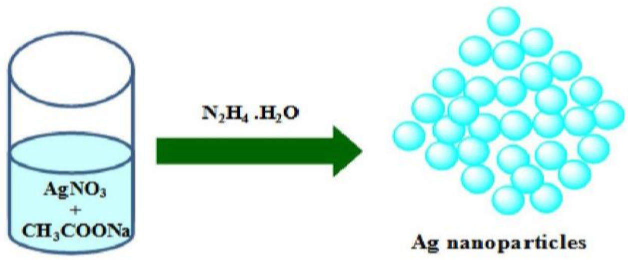

Figure 2. Synthesis of Silver Nanoparticles by Evaporation-condensation method.[17]

Laser ablation is another method of physical synthesis. By laser ablation of a bulk metal source positioned in a liquid environment, the AgNPs can be created. Only the base metal source's AgNPs remain in the liquid environment following pulsed laser irradiation because all other ions, compounds, and reducing agents have been removed.[18] The features of metal NPs created are influenced by several factors, including the laser's strength, the radiation's duration, the type of base metal source, and the characteristics of the liquid medium. The synthesis of NPs by laser ablation is pure and uncontaminated in contrast to chemical synthesis because it only employs mild surfactants in the solvent and no other chemical reagents.[19]

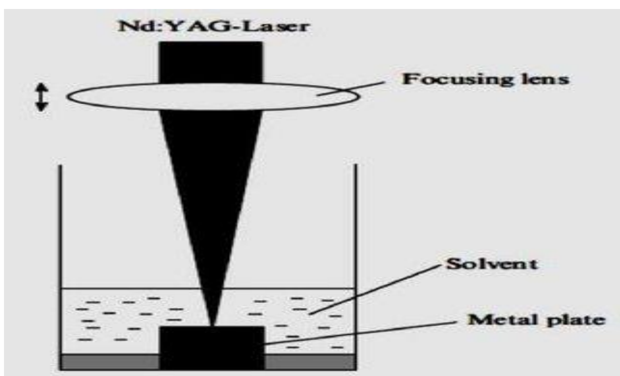

Figure 3. Laser ablation method.[4]

CHEMICAL METHODS

Chemical Reduction Methods

Chemical reduction using reducing agents that are both organic and inorganic is the most typical method for creating silver nanoparticles. Numerous reducing agents, including sodium citrate, ascorbate, sodium borohydride (NaBH4), elemental hydrogen, the polyol process, the tollens reagent, N, N-dimethylformamide (DMF), and poly (ethylene glycol)-block copolymers, are frequently used to reduce silver ions (Ag+) in aqueous or non-aqueous solutions. These reducing chemicals cause the reduction of Ag+ to metallic silver (Ag0), which then aggregates into oligomeric clusters. In the end, these clusters produce metallic colloidal silver particles. During the creation of metal nanoparticles, it's crucial to utilize stabilizing agents to keep dispersive NPs from clumping together. Additionally, NPs that can bind to or absorb onto nanoparticle surfaces should also be protected. Surfactants that have functions for interacting with particle surfaces, such as thiols, amines, acids, and alcohols, can prevent particle development from becoming sedimentary or agglomerating as well as protecting them from losing their surface qualities.[20] To stabilise NPs, polymeric substances like poly (vinyl alcohol), poly (vinylpyrrolidone), poly (ethylene glycol), poly (methacrylic acid), and polymethylmethacrylate have been reported to be useful protective agents.[21] A reduction with sodium borohydride in the presence of dodecanethiol as a stabilizing agent was performed after an Au3+ complex was phase-transferred from the aqueous to the organic phase in a two-phase liquid-liquid system. This prevented the NPs from aggregating and made them soluble in some solvents. They claimed that even minor adjustments to the synthetic variables cause significant changes in the self-assembly patterns, stability, average size, and size distribution width of nanoparticles. The polyol method and a modified precursor injection technique are used to create spherical silver NPs with a high monodispersity and adjustable size. The injection velocity and reaction temperature were crucial variables in the precursor injection approach for creating uniform-sized silver NPs with smaller sizes. At an injection rate of 2.5 ml/s and a reaction temperature of 100 °C, silver NPs with a size of 172 nm were produced. An efficient way to quickly induce nucleation and guarantee the production of silver NPs with a smaller size and narrower size distribution is to inject the precursor solution into a heated solution. To create silver colloids, use a hyperbranched polymer of (methylene bisacrylamide aminoethyl piperazine) (HPAMAM-N$(CH_3)_2$). The potent stabilising and reducing abilities of HPAMAM-N$(CH_3)_2$ are a result of the compound's hyper-branched structure, piperazine rings, tertiary amine groups, and amide moieties. The creation of monodispersed silver nanoparticles utilizing a straightforward liquid paraffin/oleylamine combination[21]. The growth, incubation, and Oatwald ripening stages could be used to categorize the production process of these NPs, Due to the higher boiling point of paraffin (300 °C), it is possible to effectively adjust the size of silver NPs by altering the heating temperature alone without changing the solvent. This provides a wider range of reaction temperatures. Additionally, the ratio of oleylamine to the silver precursor may be altered to control the size of the colloidal silver NPs in addition to altering the heating temperature and ripening time. By combining the proper metal ions with reduced polyoxometalates, which act as stabilising and reducing agents, silver NPs can be easily produced at room temperature[20]. Polyoxometalates can perform stepwise, multielectron redox reactions without causing structural change and are soluble in water. By shining a light on a polyoxometalates/S/Ag+ deaerated solution, it was shown that silver NPs were created. Additionally, it has been reported that silver nanostructures can be produced and stabilized in one step using MoV-MoVI mixed-valence polyoxometalates in water at ambient temperature.[11]

Microemulsion Techniques

Microemulsion techniques, uniform and size-controllable silver NPs can be produced. The initial spatial separation of the reactants-a reducing agent and a metal precursor into two immiscible phases is the foundation for the creation of NPs in two-phase aqueous organic systems. The interface between the two liquids and the amount of inter-phase transport between the two phases, which is mediated by a quaternary alkyl-ammonium salt, affect how quickly metal precursors interact with reducing agents. Inter-phase transporters carry stabilizer molecules from the non-polar aqueous medium that are on the surface of metal clusters generated at the interface into the organic medium, where they act as a carrier for the metal clusters.[22] The usage of extremely harmful chemical solvents is one of the main drawbacks. As a result, the finished product needs to have a lot of surfactants and the organic solvent separated from it.[23] For instance, when dodecane was used as the oily phase, there was no need to remove the prepared silver solution from the reaction mixture (it is a low-harmful and even nontoxic solvent). On the other hand, colloidal NPs made for conductive inks in non-aqueous media are well-dispersed in an organic solvent with low vapour pressure, allowing them to quickly wet the surface of polymeric substrates without agglomeration. The benefits are also present in the use of metal nanoparticles (NPs) as catalysts for the majority of organic reactions, which have been carried out in non-polar liquids. In practical applications, it is crucial to transfer metal NPs to various physicochemical conditions.[24]

UV Initiated Photoreduction

Silver NPs have been synthesised using a straightforward and efficient approach called UV-initiated photo reduction in the presence of citrate, polyvinylpyrrolidone, poly (acrylic acid), and collagen. Generated silver nanoparticles (NPs) by photo-reducing silver nitrate in suspensions of layered inorganic laponite clay, which acted as a stabilising agent to prevent NPs aggregation. As a function of the UV exposure period, the generated NPs' characteristics were investigated. When exposed to UV radiation for three hours, bimodal size distribution and moderately big silver NPs were produced. A relatively constant size and size distribution were obtained after further irradiation dissolved the silver NPs into smaller sizes with a single distribution method[25]. By using the poly (vinyl alcohol) and UV light photo reduction process at room temperature, silver nanoparticles (nanosphere, nanowire, and dendritic) have been created (as protecting and stabilising agent). The growth of the nanorods and dendrites was significantly influenced by the concentration of poly (vinyl alcohol) and silver nitrate.[26] The main purpose of the sonoelectrochemistry approach is to mechanically move the material. The electrolyte composition is key to the production of shapes in the pulsed sonoelectrochemical synthesis technique, which uses alternating sonic and electric pulses. According to a report, silver nanospheres could be created using sonoelectrochemical reduction with the help of the complexing agent nitrilotriacetate to prevent aggregation.[27]

ELECTROCHEMICAL SYNTHETIC METHOD

Silver NPs can be created using an electrochemical synthesis technique. By modifying the composition of the electrolytic solutions, it is possible to improve the homogeneity of silver NPs while also adjusting the electrolysis circumstances to control particle size, at the liquid/liquid interface, polyphenyl pyrrole-coated silver nanospheroids (3–20 nm in diameter) were produced electrochemically. The silver metal ion was moved from the aqueous phase to the organic phase, where it interacted with the pyrrole monomer to create this nano molecule.[28] According to the degree of silver exchange of compact zeolite film-modified electrodes, monodispersed silver nanospheroids (1–18 nm) were created by electrochemical reduction inside or outside zeolite crystals in a different study.[29] A practical electrochemical approach was also used to easily produce spherical silver NPs (10–20 nm) with narrow size distributions in an aqueous solution. The silver clusters in this study's experiment were stabilised using poly N-vinylpyrrolidone. Poly N-vinyl pyrrolidone prevents NPs from aggregating, greatly lowers the rate of silver deposition, and increases the rate of silver nucleation and particle production. The use of a revolving platinum cathode successfully addresses the technological challenge of quickly transporting metallic NPs from the cathode region to the bulk solution, prevents the formation of flocculates around the cathode, and assures monodispersity of particles. The particle size and particle size distribution of silver NPs were enhanced by adding sodium dodecyl benzene sulfonate to the electrolyte.[30]

IRRADIATION METHODS

Several irradiation techniques can be used to create silver NPs. Silver NPs with a clearly defined form and size distribution can be produced by laser irradiating an aqueous solution of silver salt and surfactant.[31] Furthermore, silver NPs were produced utilizing benzophenone and a laser in a photosensitization synthetic process. Low laser levels produced silver nanoparticles (NPs) of around 20 nm over brief periods, whereas higher laser powers produced NPs of approximately 5 nm. Silver nanoparticles can be produced using both mercury lamps and lasers as light sources.[32] Silver nanoparticle creation by illumination of Ag(NH3) + in ethanol has been done in visible light irradiation experiments as well as photosensitized growth of silver NPs utilizing thiophene (sensitizing dye).[33]

BIOLOGICAL SYNTHESIS

AgNPs are produced biologically by utilising several important living things or species. Bifidobacteria, fungi, algae, and plants are the primary sources used to create AgNPs. Living things function as reducing, stabilising, or capping agents during the production of AgNPs from biological sources. They reduce Ag+ to create Ag0. Plants or plant extracts are easily safe, available, and non-toxic concentrates that include a lot of metabolites for the production of AgNPs. The larger levels of extracellular secondary metabolites that are employed by fungi as capping and reducing agents during synthesis, as opposed to bacteria, result in higher amounts of AgNPs. The biological approach of manufacturing AgNPs is therefore seen as a potentially safer, non-toxic, and cost-effective route when taking into account the limitations of physical and chemical procedures.[34]

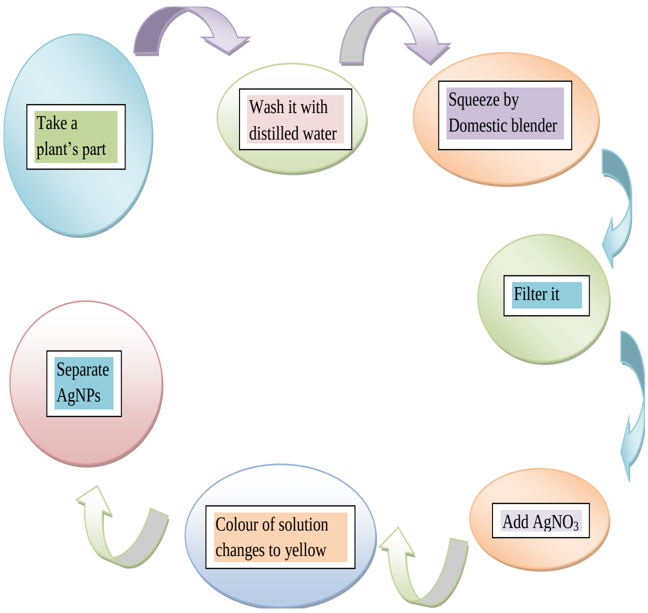

Figure 4. Biological synthesis of Ag nanoparticles.[4]

MECHANISMS OF ACTION OF SILVER NANOPARTICLES

Antimicrobial Action of AgNPs

The AgNPs have shown a broad-spectrum antibacterial action on both Gram-positive and Gram-negative organisms, as well as many medication-resistant species. The most typical ways of action can be free silver ions uptake that interrupts ATP molecules and prevents DNA replication, generation of reactive oxygen species by AgNPs, or direct destruction of the cell membrane by Silver ions (Ag+). It is understood that AgNPs cause enhanced permeability and cell death by forming pits in the cell walls of gram-negative organisms. Generally speaking, AgNPs promote denaturation and oxidation of the cell wall, which results in organelle rupture and cell lysis. Additionally, AgNPs alter the phosphotyrosine profile of peptides, which disrupts the organism's signal transduction and inhibits its ability to multiply. The release of Ag+ ions is the primary cause of AgNPs' antibacterial effect. Compared to bigger AgNPs, the release of Ag+ is greater when fine AgNPs (less than 10 nm particle size) are utilised for antibacterial action.

Antiviral Action of AgNPs

AgNPs may attach to the exterior proteins of viruses, preventing their binding and multiplication, according to certain theories. Although the antiviral mechanism of AgNPs is not yet fully understood, there is still room for further investigation.

Antifungal Action of AgNPs

44 isolates of distinct fungus species were exposed as being susceptible to antifungal activity by AgNPs. AgNPs' ability to limit cell development against Candida albicans may include destroying the integrity of the cell membrane. So, one of the treatments to stop fungal infections of oral structures could be AgNPs. AgNPs included in resins at a concentration of 1 g/ml demonstrated strong antifungal action without cytotoxicity.[8]

CHARACTERIZATION OF SILVER NANOPARTICLES

Particle-particle interactions at the nanoscale are dominated by weak Vander Waals forces, stronger polar and electrostatic interactions, or covalent interactions. The characterization of nanoparticles is required to determine phase purity, shape, size, morphology, electronic transition plasmonic character, atomic environment, surface charge, and so on. AFM, electron energy loss spectroscopy, surface-enhanced Raman scattering, scanning electron microscopy, transmission electron microscopy, and their corresponding energy-dispersive X-ray spectroscopy (EDX), as well as selected area electron diffraction, are examples of advanced analytical techniques (SAED for crystallinity).[35] Electron microscopy techniques are used to analyse elements to determine properties like surface morphology, size, and overall shape. Fourier transform infrared (FTIR) spectroscopy, fluorescence correlation spectroscopy (FCS), X-ray diffraction (XRD for phase purity with crystal parameters and particle size), diffuse light scattering (DLS can probe the size distribution of small particles), UV-Vis spectroscopy (band gap, particle size electronic interaction), and X-ray photoelectron spectroscopy are examples of optical analysis techniques. The characteristics of nanomaterials, such as size distribution, dispersibility, and average particle diameter, can be assessed using this analysis. The charge also has an impact on the distribution of the nanoparticles in vivo and their physical stability.[21]

X-ray Diffraction Spectroscopy (XRD)

The popular analytical method known as X-ray diffraction (XRD) has been used for a variety of purposes, including the analysis of crystal and molecular structures, the qualitative identification of different compounds, the quantitative resolution of chemical species, the determination of crystallinity, isomorphous substitutions, particle sizes, and others. When X-ray light reflects on any crystal, it causes the formation of numerous diffraction patterns, which reflect the physicochemical properties of the crystal structures. Diffracted beams typically originate from a powder specimen and reflect the physicochemical and structural properties of the sample. The structural characteristics of a variety of materials, such as inorganic catalysts, superconductors, biomolecules, glasses, polymers, and more, can thus be analysed using XRD. Diffraction patterns are crucial for the analysis of these materials. By comparing the diffracted beams with the reference database in the Joint Committee on Powder Diffraction Standards (JCPDS) library, it is possible to define and identify each material because each material has a distinct diffraction beam. The diffracted patterns also reveal the purity or impurity of the sample materials. Thus, forensic samples, industrial materials, and geochemical sample materials have all been defined and identified using XRD for a very long time.[36]

The primary method for determining the crystalline nature at the atomic level is XRD. X-ray powder diffraction is a non-destructive technique with great potential for characterizing both organic and inorganic crystalline materials. This technique has been applied to samples from a variety of scientific fields, including geological, polymer, environmental, pharmaceutical, and forensic sciences, to quantify phase identification, conduct quantitative analysis, and identify structural imperfections. In recent times, the applications have grown to include characterizing different nanomaterials and their characteristics. Bragg's law is the guiding principle of X-ray diffraction. Wide-angle elastic scattering of X-rays serves as the foundation for most XRD techniques. XRD has a lot of benefits, but it also has some limitations, such as the inability to obtain results for more than one conformation or binding state and the difficulty in growing crystals. Another drawback of XRD is the lower intensity of diffracted X-rays compared to electron diffractions.[37]

Scanning Electron Microscopy (SEM)

The development of various high-resolution microscopy techniques to study objects on a very fine scale with a beam of highly energetic electrons has been influenced by the fields of nanoscience and nanotechnology. SEM is a surface imaging method that can resolve various particle sizes, size distributions, the shapes of nanomaterials, and the surface morphology of synthesised particles at the micro and nanoscale. By manually measuring and counting the particles or by using specialized software, we can use SEM to examine the morphology of the particles and derive a histogram from the images. SEM and energy-dispersive X-ray spectroscopy (EDX) can be used to examine the morphology of silver powder and analyse its chemical makeup. SEM has the drawback of not being able to resolve internal structure, but it can still be very useful in determining the purity and level of particle aggregation.

Modern high-resolution SEMs can determine the morphology of nanoparticles smaller than 10 nm.[35]

Transmission Electron Microscope (TEM)

An incident beam of electrons is transmitted through an ultra-thin sample in TEM analysis, where it interacts with the sample and transforms into unscattered electrons, elastically scattered electrons, or inelastically scattered electrons. According to the density of unscattered electrons, a series of electromagnetic lenses concentrate the scattered or unscattered electrons, which are then projected on a screen to produce electron diffraction, amplitude-contrast images, phase-contrast images, or shadow images of varying darkness. Transmission electron microscopy is a type of microscopy that uses electrons to Silver Nanoparticles: Synthesis, Characterization, and Applications techniques can provide direct imaging, diffraction and spectroscopic information, the chemical composition of the specimen with an atomic or sub-nanometer spatial resolution, either simultaneously or serially. When combined with other techniques like nano diffraction, scanning tunneling microscopy (STM), atomic resolution electron energy-loss spectroscopy, and nanometer resolution X-ray energy dispersive spectroscopy, high-resolution TEM imaging is essential for conducting important fundamental research for the fields of nanoscience and nanotechnology[38]. Various synthesis methods can produce surfaces with various structures. The aforementioned electron microscopic techniques are used to examine the surface morphology of the silver nano-structural features. In comparison to SEM, TEM has two advantages: it can offer better spatial resolution and the ability for more analytical measurements. The drawbacks of TEM include a high vacuum requirement, a thin sample section, and the necessity of lengthy sample preparation. Therefore, to produce the best images possible, sample preparation is crucial.[39]

Scanning Tunneling Microscopy (STM)

STM produces atomic-scale electron density images of biomolecules attached to conductive substrates and conductive/semiconductive surfaces using quantum tunneling current.[40] Basic STM instrumentation parts include a sharp scanning tip, a piezo scanner that controls the tip's lateral and vertical movement, a coarse control unit that places the tip close to the sample within the tunneling range, a vibration isolation stage, and feedback regulation electronics. It operates on the general premise of bringing a vulnerable probe very near the surface of an object being measured to observe how the probe responds.[41]

Atomic Force Microscopy (AFM)

The size, shape, structure, sorption, dispersion, and aggregation of nanomaterials can all be examined using the AFM. It provides extremely high resolution in particle size measurement (>100 times better than optical diffraction) and is based on a physical scanning of samples at the sub-micron level using a probe tip of atomic scale. This nondestructive technique's ability to image non-conducting samples without any special pretreatment or significant surface damage is one of its main benefits.[42] The main disadvantages of this method include (i) the cantilever tip's size, which is typically larger than the dimensions of the nanomaterials to be examined, which caused an unfavourable overestimation of the lateral dimensions of the samples, and (ii) AFM's inability to detect or locate specific molecules. Recent advancements in single-molecule force spectroscopy, which employs an AFM cantilever tip carrying ligands, have, however, eliminated this drawback.[43]

Electron Energy-Loss Spectroscopy (EELS)

To have a better understanding of the atomic processes in solids, there is an increasing need for high-resolution imaging, diffraction, and spectroscopy techniques. The increased human interest in nanomaterials has increased this demand. While transmission electron microscopy (TEM) can provide structural information with an excellent spatial resolution (down to atomic dimensions) through high-resolution TEM imaging and electron diffraction technique, electron energy-loss spectroscopy offers special opportunities for the analysis of nanoscale thin materials (plasmonic).[44] Because the high energy electrons interact with the specimen atoms in a variety of inelastic ways, from phonon interactions to ionisation processes, EELS and their combination with TEM offer the capability to map the elemental composition of a specimen for studying the physical and chemical properties of a wide variety of biological and non-biological materials. Additionally, for universal dispersions of surface plasmons in flat nanostructures, the 3D distribution of the surface plasmons around metal nanoparticles, and the energy distribution of all inelastically scattered electrons provide details about the immediate surroundings of the atomic electrons in exotic nanostructures.[45]

UV-Visible Spectroscopy Analysis

UV-vis spectroscopy is a very useful and reliable technique for the primary characterization of synthesised nanoparticles, as well as for monitoring the synthesis and stability of AgNPs. AgNPs have distinct optical properties that cause them to interact strongly with specific wavelengths of light. Furthermore, UV-vis spectroscopy is quick, easy, simple, sensitive, selective for different types of NPs, requires only a short measurement time, and no calibration is required for particle characterization of colloidal suspensions. The conduction band and valence band in AgNPs are very close to each other, allowing electrons to move freely. Due to the collective oscillation of the silver nanoparticles' free electrons in resonance with the light wave, a surface plasmon resonance (SPR) absorption band is created. Depending on the particle size, the dielectric medium, and the chemical environment, AgNPs absorb differently. It has been well documented that this peak, which has been linked to a surface plasmon, can be seen for a variety of metal nanoparticles ranging in size from 2 to 100 nm. AgNPs produced using biological techniques were tracked for more than a year and an SPR peak at the same wavelength was discovered using UV-vis spectroscopy.[46]

Surface-Enhanced Raman Scattering Spectroscopy (SERS)

SERS is a sensitive and specific method that can be used to identify molecules. When exposed to visible light, nano-noble metals exhibit localized surface plasmon resonance (LSPR), which produces powerful electromagnetic fields.[47] If the Raman scattered is placed close to these amplified nano-noble metal electromagnetic fields, the induced dipole grows, increasing the intensity of the inelastic scattering. The extinction and scattering cross-sections of the nanoparticle can have similar relationships.[48] The spectroscopic signature of activating the LSPR is represented by the nanoparticles' maximum extinction and scattering cross-sections at resonant wavelengths. An SER spectrum also provides more accurate information about molecular structure and the local environment in condensed phases than any other electronic spectroscopy technique. A typical example of surface-enhanced Raman scattering (SERS) in which the coupling effect still dominates the SERS and the flower-like silver nanoparticle dimer image with large hot areas is 10 to 100 times larger than the individual nanoparticles.[49]

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR can provide accuracy, reproducibility, and a good signal-to-noise ratio. FTIR spectroscopy allows for the detection of small absorbance changes on the order of 10^{-3}, enabling different spectroscopy to separate the large background absorption of the entire protein from the small absorption bands of functionally active residues. FTIR spectroscopy is frequently used in academic and industrial research to determine whether biomolecules are involved in the synthesis of nanoparticles. Additionally, FTIR has been used to investigate nanoscale materials, including the verification of functional molecules covalently grafted onto gold, silver, carbon nanotubes, graphene, and silver nanoparticles, as well as interactions between enzyme and substrate during the catalytic process. It is also a non-invasive technique.[35] Finally, FTIR spectrometers have a faster data collection rate, a stronger signal, a higher signal-to-noise ratio, and less sample heat-up. Recently, advancements in an FTIR method known as attenuated total reflection (ATR)-FTIR spectroscopy have been made. When compared to traditional FTIR, ATR-FTIR makes sample preparation simple, allowing us to determine the chemical characteristics of the polymer surface. To determine the part that biological molecules play in the conversion of silver nitrate to silver, FTIR is a suitable, useful, non-invasive, economical, and straightforward technique.[50]

Dynamic Light Scattering

For the analysis of biological activities using radiation scattering techniques, the physicochemical characterization of prepared nanomaterials is crucial. DLS can examine the size distribution of small particles in suspension or solution on a scale ranging from submicron to one nanometer. A technique that relies on light and particle interaction is dynamic light scattering. This technique can be used to measure narrow particle size distributions, particularly in the 2-500 nm range. DLS is the technique used the most frequently to characterise nanoparticles. DLS primarily relies on Rayleigh scattering from the suspended nanoparticles to measure the light scattered from a laser that passes through a colloid[17]. The analysis of the modulation of the intensity of the scattered light as a function of time is then used to calculate the hydrodynamic size of the particle. Any nanomaterials characterization in solution is necessary to assess its toxic potential. As a result, DLS is primarily used to assess particle size and size distributions in physiological or aqueous solutions. Typically, DLS yields larger sizes than TEM, which may be explained by Brownian motion. The average diameter of nanoparticles dispersed in liquids can be determined using the nondestructive technique known as DLS. It has the unique benefit of simultaneously probing a large number of particles, but it has several sample-specific restrictions.[51]

APPLICATIONS OF AgNPs

Antimicrobial Activity

Several accredited organizations, including the USFDA, USEPA, the testing agency in Korea, and the SIAA of the Japan Institute of Research have approved the use of products made with silver nanoparticles. AgNPs containing silver sulfadiazine are added to medications and applied to burns to prevent infections due to their antimicrobial and antimicrobial potential. AgNPs are used in many consumer products today, such as deodorizing sprays and creams for acne vulgaris. They are also involved in expanding the field of nanotechnology. The size, environmental factors (size, Ph, tonic strength), capping agent, and environmental conditions all affect how antimicrobial silver nanoparticles are. When silver nanoparticles are combined with ampicillin, amoxicillin, and chloramphenicol, antimicrobial activity improves synergistically; however, reports of antagonistic interactions between silver nanoparticles and amoxicillin or oxacillin antibiotics combined with silver nanoparticles have suggested improved therapeutic activity.[52]

Antiviral Activity

Silver nanoparticles have been shown to have antiviral action against HIV-1 at non-cytotoxic concentrations; however the mechanism behind this activity is still not completely understood. The study found that giving mice intranasal silver nanoparticles enhanced survival, reduced lung virus titers, and caused only modest pathologic lesions in lung, and remarkable survival benefits after infection with the H3N2 influenza virus, suggesting that AgNPs had a significant role in mice survival. Biologically prepared silver nanoparticles inhibited the viability in herpes simplex virus (HSV) types 1 and 2 and human para influenza virus type 3 based on size and zeta potential. The replication of the paste des petits ruminants virus was significantly inhibited by the treatment of Vero cells with non-cytotoxic concentrations of silver nanoparticles (PPRV). The viral replication processes are brought on by the contact of silver nanoparticles with the virion core. Through direct interaction, blocked virus attachment, penetration, and further spread, tannic acid-mediated synthesis of different sizes of silver nanoparticles was able to decrease HSV-2 infectivity both in vitro and in vivo.[53]

Antibacterial Activity

One of the non-materials with the greatest commercial potential is silver nanoparticles. Silver nanoparticles were used as antibacterial agents for a variety of purposes, including water treatment, disinfecting household and medical equipment, and home appliances. AgNPs are being used in a wide range of fields, including textiles, medical devices, food storage, and healthcare products. The main factor contributing to AgNPs' broad-spectrum antibacterial potential is the slower rate of release of free silver ions combined with their higher surface area, which creates an unfavourable environment.[54]

AgNPs in Cancer Control

AgNPs have a strong anticancer potential because it inhibits the mitochondrial respiratory chain, boost the production of reactive oxygen species (ROS), and ultimately cause DNA damage and cancer cell death. The treatment with camptothecin and silver nanoparticles significantly raises the levels of cancer cells.[55] In comparison to a single treatment, it increases oxidative stress markers and decreases anti-oxidative stress markers. These findings collectively suggested that camptothecin and silver nanoparticles cause cell death by altering the permeability of the mitochondrial membrane and activating caspase. Increased ROS formation and antioxidant depletion appear to be related to the synergistic cytotoxicity and apoptosis effect. Contrary to immunotherapy, a combination of CPT and silver nanoparticles has a favourable effect in the treatment of cervical cancer.[56]

Anti Diabetic Activity of AgNPs

Silver nanoparticle synthesis via Tephrosia tinctoria stem extracts was assessed for blood sugar level control. AgNPs scavenged free radicals decreased the levels of the enzymes responsible for the hydrolysis of complex carbohydrates, and as a result, increased glucose consumption. The silver nanoparticles from *Ananascomosus* (L.) have demonstrated some encouraging anti-diabetic activity, in a manner dependent on dose. The stomach's alpha-glucosidase enzyme is inhibited by AC-AgNPs, Which is beneficial for diabetic patients not taking insulin. Additionally, the silver nanoparticles made with *Argyreia nervosa* leaf extract demonstrated strong anti-diabetic properties. They primarily block the enzymes responsible for lowering blood sugar levels and breaking down carbohydrates into monosaccharides.[57]

Antifungal Activity of AgNPs

AgNPs are effective antifungal agents for a variety of fungi-related diseases. When combined with fluconazole, biologically produced AgNPs exhibit enhanced antifungal activity against the *Candida albicans* species *phomaglomerata*. When compared to traditional antifungal agents, AgNPs stabilised by sodium dodecyl sulphate demonstrated greater antifungal activity against *Candida albicans*. At a concentration of 8 g/ml, the AgNPs produced by bacillus species exhibit potent antifungal activity against the plant pathogenic fungus *fusariumoxysporum*. With a MIC of 0.5ug/ml, AgNPs have demonstrated promising antifungal activity against T. asahii by destroying the cell wall and its constituent parts. Due to their small size, nanoparticles can easily enter cells. Where it binds to various cell components and prevents certain cell processes. When combined with antimicrobials like ketoconazole, they have demonstrated excellent antifungal activity with MICs of less than 0.5 mg/ml against Malassezia, where they have a synergistic effect and help the antifungal agent form pores in the cell.[58]

Anti-Angiogenic Activity of AgNPs

In the model of retinal endothelial cells, the antiangiogenic potential of green synthesised AgNPs is primarily produced by the inhibition, proliferation, and migration of BRECs at 500 nm concentration. The silver nanoparticles in the CAM model (chorioallantoic membrane of the chicken embryo) can reduce angiogenesis by up to 73%. compared to other antiangiogenic compounds. They exert a dose-dependent cytotoxic action on blood vessel endothelial cells to prevent the growth of new blood vessels in the tumour region. Additionally, the silver nanoparticle produced by *Rubina tinctorum* demonstrated antigiogenic activity using the same model, i.e. the CAM assay. Blood vessel inhibition by Ru-AgNP has been observed. Ru-AgNPs' antiangiogenic effect causes the length of the embryo in the CAM model to decrease.[59]

Diagnostic, Biosensor and Gene Therapy Applications of AgNPs

Nanoparticles have an advantage over current therapies because they can be engineered to have specific properties or to behave in a specific way. They're useful for cellular imaging. Because of its stronger and sharper Plasmon resonance, silver is important in imaging systems. Currently, a silver biosensor is being used as a powerful tool to detect cytochrome P53 in squamous cell cancer of the head and neck. Because of their colourimetric sensing ability, silver nanoparticles can detect heavy metal ions such as nickel, cobalt, and mercury, as well as sulphide traces. All varieties of silver nanoparticles, but particularly those with a triangular shape have increased anisotropy and the lightning rod effect, which makes them popular for use in the production of Plasmon sensors or Plasmon detectors, which are used to find mercurial ions in solutions. The electrochemical sensor used to detect the ubiquitous herbicide atrazine was also developed using silver nanoparticles. On the other hand, the speedy collection and detection of malachite's green residue are owing to the in situ growth and development of silver nanoparticles on polydopamine-traced filter paper.[60]

Anti-Inflammatory Activity of AgNPs

The anti-inflammatory response of AgNPs is still in its infancy, despite its antibacterial reputation. Nanocrystalline silver (NP32101) treatment in rats reduced colonic inflammation by a significant amount whether given intra-colonically or orally at doses of 4 mg/kg or 40 mg/kg. In a dose-dependent manner, AgNPs demonstrated quick healing and improved cosmetic appearance. The extraction of silver using petroleum ether and a tiny amount of ethyl acetate results in nanoparticles with strong cyclooxygenase-2 inhibitory properties. This means that the anti-inflammatory activity of the silver Nanoparticles produced when extracting silver with petroleum ether is boosted when one adds a natural extract having an anti-inflammatory activity to them. Recently, some researchers extracted silver nanoparticles from naphtha sp., a soft coral species that already had anti-inflammatory properties. These silver nanoparticles of naphtha sp. had extremely potent anti-inflammatory properties, which were determined by analysis and molecular docking techniques.[61]

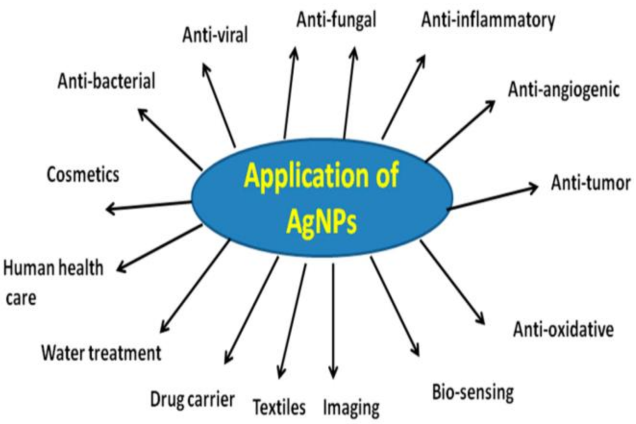

Figure 5. Application of AgNPs.[51]

Therapeutic Nanoparticles and Their Targeted Delivery

Drug delivery methods based on nanotechnology are the best for the clinical management and treatment of a variety of diseases. The main benefit of these systems has been demonstrated to be an increase in circulation and retention times, which enhances the half-life and bioavailability of drugs and ultimately results in a higher level of efficacy.[62]

The nanoparticles can be made into intelligent systems that contain therapeutic and imaging agents as well as having properties by manipulating their size, surface properties, and material composition. Furthermore, these systems can provide controlled release therapy and drug delivery to specific tissues. Recent biomedical scientific investigations successfully improved the design of therapeutic agents used in the treatment of disease. The delivery of therapeutic agents to the target area, however, poses a significant barrier to the effectiveness of treatment for a variety of diseases. Utilizing traditional therapeutic agents has drawbacks like non-selectivity, unfavorable side effects, low efficiency, and poor biodistribution.[63]

As a result of this targeted approach, the therapeutic agent is more concentrated in cells and tissues, allowing for the use of low doses, especially when there is a conflict between the therapeutic activity and the agent's toxic effects. By enhancing their efficacy and/or increasing their tolerability in biological systems, therapeutic agents with higher concentrations in the target area also have a higher therapeutic index. It is also possible to combine nanoparticles with therapeutic agents that are not water soluble to increase their bioavailability and shield them from physiological barriers. Therefore, the goal of current research is to develop multifaceted, well-controlled delivery systems. A promising strategy for delivering a variety of molecules to specific parts of the body involves combining therapeutic agents with nanoparticles that have distinctive physicochemical and biological properties and designing their pathways for effective targeting.[64]

Types of Therapeutic Nanoparticles

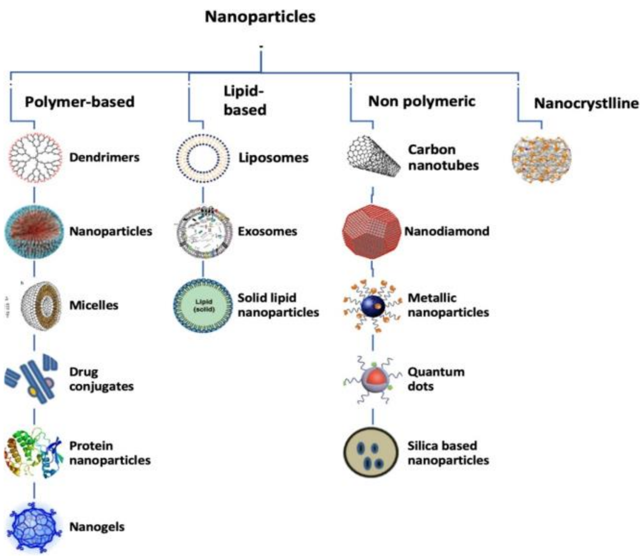

Figure 6. Types of therapeutic nanoparticles.[63]

Silver Nanoparticles for Drug Delivery

The pharmacokinetics and pharmacodynamics of drugs are just as significant in medicine as their inherent therapeutic effects. Nanoparticles received a lot of attention in the design and development of new and improved drug-delivery systems because the specific and selective delivery and action of therapeutic agents became one of the most researched topics for improving current human healthcare practice. AgNPs-based nano system in particular were considered to be effective delivery systems for several therapeutic molecules, including anti-inflammatory, antioxidant, antimicrobial, and anticancer substances. Targeting inflammatory, infectious, and cancerous diseases, innovative and performance-enhanced drug delivery systems that react to thermal, optical, or pH modulations were successfully developed using hybrid molecular units built of AgNPs.[65] AgNPs were given special consideration for this field because of their inherent anticancer properties, and they were successfully tested as efficient anti-tumor drug delivery systems, acting either as passive or active nanocarriers for anticancer drugs. Different methods, including radiolysis, micro-emulsion, organic-water two-phase synthesis, and reduction in aqueous solution, were employed to create biocompatible AgNPs. The creation of AgNPs-based drug-delivery platforms has recently received a lot of attention, scientific understanding, and financial support due to the inherent properties of nano silver, such as its capacity to bind a wide variety of organic molecules, its tunable and strong absorption properties, and its low toxicity.[66] AgNPs may be used as vaccine and drug carriers for precise and selective cell or tissue targeting, according to recent studies. Nanostructure systems based on silver are highly recommended as specific, selective, and adaptable candidates for drug-delivery applications due to their excellent optical properties, which are also governed by localized surface Plasmon resonance and specific surface Plasmon resonance, respectively.[67]

Nanotechnology in Disease Diagnostic Techniques

The development of better diagnostic methods to screen for complex diseases is currently the focus of bioengineering and medical technology's most significant research efforts. For diseases like cancer, cardiovascular, or neurodegenerative diseases, screening is necessary to determine the cause of illnesses and to track any improvement or progression of those conditions. It has been demonstrated that nanotechnology has the potential to increase sensitivity and selectivity and reduce the cost of a diagnosis. Nanotechnology allows for the manipulation of materials at the nanoscale. The harmful bimolecular can be located using the red-shifted absorbance of gold nanoparticles, a change in the conductance of a nanowire or nanotube, as well as the deflection of a micro- or nano-cantilever.[68] Several different nanomaterials, including metals, metal-oxides, and quantum dots, have demonstrated significant advantages over conventional diagnosis, intracellular labelling, and visualization of target cells/tissues. The use of point-of-care devices to enhance the visualization of tissues, cells, DNA, and proteins has now been made possible thanks to several new avenues that nanotechnology has opened up. An easy-to-use nano-fluidic device for quicker disease diagnosis could be built around protein or gene chips made with nanomaterials.[69]

CONCLUSION

Nano-delivery systems are of the highest concern for precisely targeting the desired area in the treatment of many diseases, and they have received a great deal of attention in the last ten years due to the extensive study of the development of nanoparticle-based therapeutic agents. At the moment, lipids or polymers are the majority of the nanoparticles used in the targeting delivery strategy. Despite having many benefits for treating diseases, polymeric nanoparticles also have drawbacks, including scaling issues, the need for organic solvents during the manufacturing process, biocompatibility issues, cytotoxicity issues, and immunogenicity. Therapeutic nanoparticles are currently primarily created for the treatment or prevention of a single disease. Due to their size-related desirable physicochemical properties and biological functionality, including their potent antimicrobial effectiveness and non-toxic makeup, AgNPs are actively being investigated as nanostructures for novel and improved biomedical applications. Applications for drug delivery, dressing for wounds, tissue scaffolding, and protective coatings can all benefit from AgNPs-based nanosystems and nanomaterials. AgNPs offer additional mechanical, optical, chemical, and biological peculiarities that make them ideal for the development of performance-enhanced biomaterials and medical devices, as well as for their production, testing, and clinical evaluation. However, as researchers began combining different drug molecules and different kinds of nanoparticles, the development of multi-therapeutic nanoparticles, which has a variety of medical applications, is the direction that therapeutic nanoparticles are headed in the future. We still know very little about the metabolism, clearance, and toxicity of nanoparticles, although they significantly improve efficiency, reduce side effects and improve bioavailability in targeted therapy.

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