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Advances in Nanoparticle synthesis techniques and their use in controlled and targeted drug delivery

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ABSTRACT

Nanotechnology involves the synthesis and characterization of particles in nanometer scale. Nanoparticle can be synthesized using different phenomenon, that involves top-down and bottom-up approach. Pharmaceutical research is now focusing on the use of nanoparticles for drug delivery. This review is based on various synthesis methods for nanoparticles, that includes chemical precipitation, sol-gel, microemulsion, and green synthesis techniques, along with their advantages and drawbacks. Owing to their distinctive properties, nanoparticles offer numerous advantages in pharmaceutical research, such as improved drug solubility, controlled and continuous release, site-specific targeting, and reduction in adverse systemic effects. In addition, the application of different nanoparticle-based delivery systems, including liposomes, dendrimers, polymeric nanoparticles, and inorganic nanoparticles, is discussed.

***Keywords**: nanoparticles, synthesis methods of nanoparticles, use of nanoparticles in drug delivery, targeted delivery.*

1. Introduction

"Nano" is a thousand millionth of a metre. The branch of nanotechnology is the name given to the science that studies structures and molecules on a nanoscale level that range from atoms to macromolecules [1] [2]. Nanotechnology works on the atomic, molecular, and sub-molecular level [3]. The properties of the nanoparticle and the bulk material shows considerable differences both physically and chemically [4] [5].

2. Synthesis of Nanoparticles

There are two fundamental methods for producing NPs: bottom-up and top-down [6].

- Top-down method: It uses the principle of breaking down larger components into smaller particles. Molecules are broken down into smaller bits before being transformed into the desired nanoparticles.[7].
- Bottom-Up Method: This works on the principle of uniting smaller particles until it attains nanoscale [8], involves synthesizing NPs by assembling them from simpler atoms, molecules, or small components [9]. There is a high probability of obtaining single-crystal NPs by the bottom-up approach.

The decrease in Gibbs free energy enables to obtain particles that attain thermodynamic equilibrium. On the other hand, the top-down method is responsible for uneven surfaces, that alters its physical and chemical properties [10].

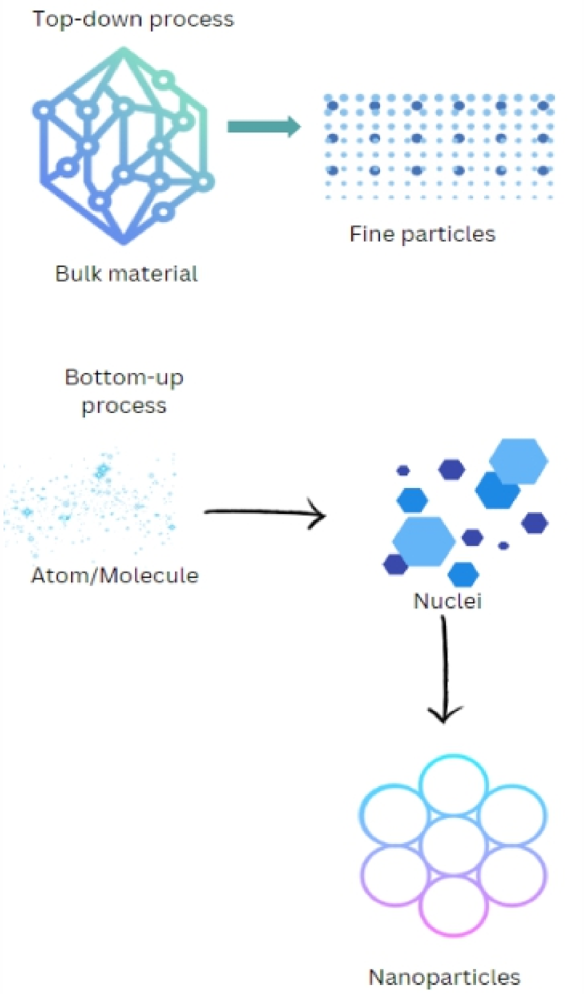

Figure 1: Nanoparticle Synthesis: Top-Down and Bottom-Up Approaches

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2.1. Top-down method

Mechanical Milling

Mechanical milling is a commonly used method [11]. It is an efficient method if the material is required on a large scale [12]. HEBM works on the principle of continuous collision between balls and the particles, causing energy transfer. This ultimately reduces the size of the particle [13]. Several factors affect the efficiency of this process, including the type of mill employed, powder loading, speed, size and distribution of the ball, milling medium (dry or wet), processing temperature, and duration of milling [14]. These factors are collectively responsible for the rate of particle size reduction and phase formation [15]. Materials like steel or tungsten carbide can be used in place of ceramic balls because of their kinetic energy [16]. Mechanical milling results in reduction of size of the particle, modifying their shape and also combining it together. Tumbler ball mills spins around their axis. Balls drop down in parallel layers. [17] [18]. The material is stirred in an agitator mill as it is being ground using an agitator that has horizontal arms called impellers and a vertical rotating shaft. Spinning of the vertical shafts causes the movement of horizontal impellers also causing the ball and powder to move [19]. The shaker mill operates by oscillating the powder and grinding media at approximately 1200 rpm. The energy imparted to the milling media depends on the mill design, and power input, of the grinding balls. The selection of ball size and distribution is also critical and must be optimized according to the milling system. The use of steel balls and containers can introduce iron impurities into the milled powder. In some refractory metal powders, prolonged milling in high-energy shaker mills may result in iron contamination exceeding 10%. [17]. In cases where contamination is particularly critical, the milling balls and container liners may be fabricated from materials with compositions similar to those of the powders being processed. [20]. The ball's "kinetic energy" as well as the characteristics of the powder and milling medium might have an impact on the milling temperature.

Advantages of milling

It enables cost-effective production of high-purity NPs with improved drug solubility and size-dependent enhanced properties [21] [22].

Disadvantages of Milling

Powder contamination is caused by steel balls, which require a long time to mill and a high level of energy. [23].

Laser ablation method

In Laser ablation, a solid target material [24] is irradiated with a high-energy laser in either a gaseous or liquid environment. Ablation refers to the removal of atoms or material from the target surface through laser- induced excitation [25] involving a single-photon or multiphoton absorption process [26] [27]. Following laser ablation, the synthesized NPs can be recovered either as a colloidal suspension or in the form of nano powder. Compared with many conventional NP synthesis techniques, laser ablation is a relatively simple, rapid, and straightforward approach. The method eliminates the need for complex multistep chemical reactions, elevated processing temperatures, and prolonged reaction times. Furthermore, it is considered an environmentally friendly and safe technique for nanomaterial production. These advantages make laser ablation an attractive and lab-compatible method for the synthesis of high-purity NP. [28]. When nanoparticles are synthesized in aqueous media, highly pure colloidal dispersions can be obtained with minimal contamination and negligible formation of reaction byproducts. Such purity makes the NP suitable for in vivo biological and biochemical applications. Moreover, the absence of insulating surface-capping agents on the synthesized NPs enhances their applicability in organic electronic devices. Surface functionalization can be readily achieved after synthesis by introducing suitable ligands into the NP suspension or by performing laser ablation directly in the presence of the desired solvent or ligand [29] and using laser ablation, high-purity nanoparticles may be created, with the majority of the particle purity being determined by the target and ambient medium purity without reactor contamination. When a focused laser beam irradiates the target immersed in a surrounding medium, rapid absorption of laser energy causes a sharp increase in temperature, leading to the vaporization of the target material [30]. The vaporized species generated during the ablation process experience rapid cooling from extremely high temperatures, leading to supersaturation and subsequent nucleation of NPs at the periphery of the plasma plume.

Advantages of Laser Ablation

It is the most commonly used method, which produces nanoparticles in the form of suspension [27]. One may modify the characteristics of nanoparticles by selecting the right type of liquid and laser parameters [31].

Disadvantages of Laser Ablation

Prolonged laser ablation causes a significant number of colloidal solution nanoparticles to form, obstructing the laser's path and absorbing laser energy into the nanoparticles in opposition to the target surface [32], this reduces the ablation rate [33].

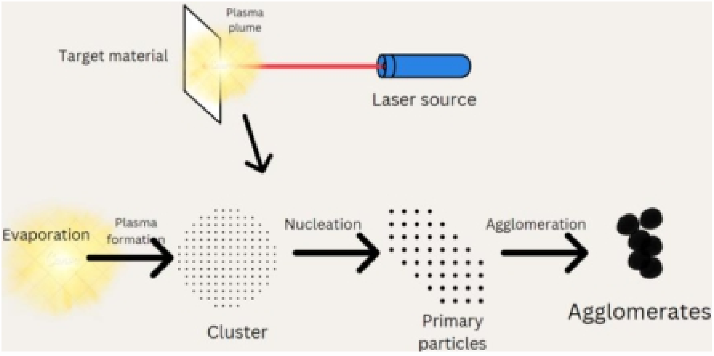

Figure 2: Laser ablation process

2.2. Bottom-up method

Chemical Vapor Deposition

In the CVD method for CNT synthesis, catalyst NPs are first deposited onto a suitable substrate and activated through thermal annealing or chemical treatment, such as ammonia etching, to promote nucleation. The prepared substrate is then placed inside a tubular reactor, where the temperature is typically maintained between 600 and 1200°C. The gases flow over the catalyst surface, where the hydrocarbon molecules decompose, releasing carbon atoms that dissolve into or diffuse across the catalyst particles. Carbon then precipitates from the catalyst, initiating the formation and growth of carbon nanotubes, typically over 15-60 minutes. Depending on the growth mode, the catalyst particle may remain at either the base or the tip of the nanotube [34].

During CVD, CNTs generally grow through two distinct mechanisms: base (root) growth and tip growth [35]. In the base-growth mechanism, the catalyst particle remains firmly anchored to the substrate throughout the nanotube formation [35]. Environment, carbon supply, catalyst, and temperature are the three main factors that affect the development of CVD in CNTS [36]. Transition metals (Fe, Co, Ni) from nitrates, organometallocenes, and other sources are widely used as catalysts for the growth of carbon nanotubes [37]. The technology may be applied to grow carbon nanotubes (CNTS) in a variety of forms, including entangled or aligned, straight or coiled [38], or arranged in a specific pattern on a substrate with patterns [39].

Advantages of CVD

Chemical vapour deposition is a good coating technology with high film persistence. It produces controlled surface morphology nanoparticles [40]. Scaling up is easy [41].

Disadvantages of CVD

Potential for chemical hazards resulting from explosive, caustic, and toxic precursor gases. Multicomponent material deposition is difficult.

Sol-Gel Process

This approach offers excellent control over the surface properties, morphology, and textural characteristics of the resulting materials [42]. The formation of metal oxide NPs requires an oxygen source, which may be supplied either by water in aqueous systems or by organic solvents in nonaqueous systems. Based on the reaction medium, the reaction can be classified into aqueous or non-aqueous. Acidic or basic catalyst hydrolyzes the reaction that enhance the conversion process. The structure of the resulting gel depends on the amount of water as well [43]. Increased water content promotes the formation of bridging oxygen bonds during condensation, leading to a more highly polymerized, cross-linked, and branched network structure. [44]. Polycondensation involves the condensation of adjacent hydrolysed molecules with the elimination of water or alcohol, resulting in the formation of metal-oxygen-metal linkages and a colloidal polymeric network. This process occurs through two mechanisms, olation and oxolation [45], with oxolation leading to the formation of oxo-bridged M–O–M bonds that strengthen the metal oxide network. Condensation, also known as polycondensation, raises the solvent's viscosity and produces a porous structure that preserves the liquid phase [43], or gel. The alkoxide precursor and fluid pH are the primary determinants of colloidal particle size and cross-linking [46]. Removal of organic components may disrupt the structure of the gel. It may also prevent drying. Drying of the gel is crucial for the gel network. Heat treatment eliminates any pores and densifies the material, producing a xerogel that has reduced pore volume, less surface area, and shows significant shrinkage [47]. Supercritical drying maintains the gel structure, which helps to obtain aerogels having large surface area and pore volume [48]. On the other hand, freeze-drying removes the solvent, producing cryogels that show less shrinkage as compared to xerogels [49]. Calcination removes water and residual impurities, while temperature significantly influences pore size and density [43].

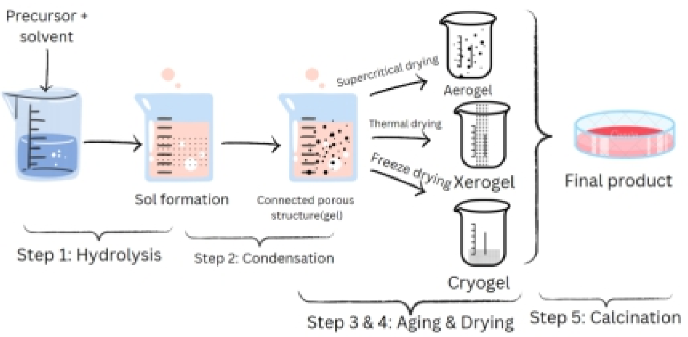

Figure 3: Schematic representation of sol-gel method

Advantages of Sol-Gel

Precise regulation of reaction parameters enables controlled tuning of particle size and morphology [50].

Laser Pyrolysis

It uses laser energy to form NPs. In CO_2 laser pyrolysis, rapid nucleation is followed by particle growth through coagulation and coalescence, producing spherical particles at high temperatures and aggregated, non-spherical particles at lower temperatures [51]. High supersaturation leads to the formation of spherical NPs, generating many nuclei, followed by rapid cooling to prevent any further growth. Laser irradiation of gas or vapor phase leads to the formation of condensed NPs. Laser energy is absorbed either by precursor or by photosensitizers such as ethylene, sulfur hexafluoride, or ammonia, promoting precursor decomposition and NP formation [52]. When molecules absorb sufficient energy to exceed their dissociation threshold, they decompose into volatile or condensable species that subsequently undergo chemical reactions. Laser pyrolysis enables rapid and localized heating of small volumes, resulting in fast nucleation and particle growth followed by rapid quenching within milliseconds [53].

Advantages of Laser Pyrolysis

Laser pyrolysis is a clean method that produces NPs with controlled size distribution. Particle size can be regulated by adjusting the precursor flow rate [54], making the technique suitable for large-scale nanomaterial production. [30].

Biological Method

This method, also known as "green synthesis," uses safe, non-toxic, and environmentally friendly agents. Growing attention has been directed toward green synthesis approaches, particularly those based on biological systems, which offer environmentally friendly, safe, and efficient alternatives for producing well-controlled nanostructures [55]. The successful synthesis of stable and well-characterized NPs depends on selecting suitable microorganisms and optimizing growth and reaction conditions. Key factors include nutrient availability, inoculum size, pH, temperature, light, mixing speed, and buffer strength [56]. Careful control of these parameters enhances NP yield, stability, and the formation of desired sizes and shapes in microbial systems such as fungi and bacteria [57]. Lead and cadmium can be produced by yeasts; gold, silver, and cadmium can be produced by fungi; gold can be produced by algae; and gold, silver, cadmium, zinc, magnetite, and iron can be produced by bacteria [58].

Nps can be produced both inside and outside the cell. In the case of intracellular synthesis, metal ions bind to the microbial cell walls that are negatively charged. This leads to reduction with the help of enzymes that ultimately lead to NP synthesis. [59]. There is various green synthesis methods listed below.

Green Synthesis Using Plants

Plant extracts offer a cost-effective and eco-friendly method for synthesizing metal NPs. Biomolecules such as proteins, enzymes, amino acids, vitamins, polysaccharides, and organic acids act as reducing and capping agents, facilitating NP formation and stabilization [60]. Synthesis of NP using plants involves 3 stages: activation (reduction of metal ion and nucleation), growth and termination or stabilization [61]. Research has shown that terpenoids frequently interact with nanoparticles, and that terpenoids in extracts from geranium leaves aid in the conversion of silver ions into nanoparticles[62]. The functional groups of flavonoids enable NP formation, and during enol-keto tautomerism, reactive hydrogen is released that helps in reducing metal ions[63]. Flavonoids can also assist in reducing Au^{3+} ions through internal chemical transformations such as conversion of ketone groups to carboxylic acids. Their π-electron systems and carbonyl groups enable strong binding with metal ions[64]. These processes may be responsible for the ability of flavonoids to adsorb onto a nascent nanoparticle surface. [65]. Sugar in plant extracts can act as reducing agents for metal NP synthesis. Monosaccharides like glucose, due to their aldehyde group, are effective in reducing metal ions and producing NPs of various shapes. Fructose can also aid in forming monodisperse gold and silver NPs, but glucose is generally a stronger reducing agent because fructose's antioxidant ability is limited by tautomeric changes *[66].* FTIR analysis indicated that plant-synthesized NPs are stabilized by proteins. Metal ions bind to amino acids via amino, carboxyl, carbonyl, and imidazole groups, while residues like tyrosine, glutamine, and asparagine help reduce Ag^+ ions [67].

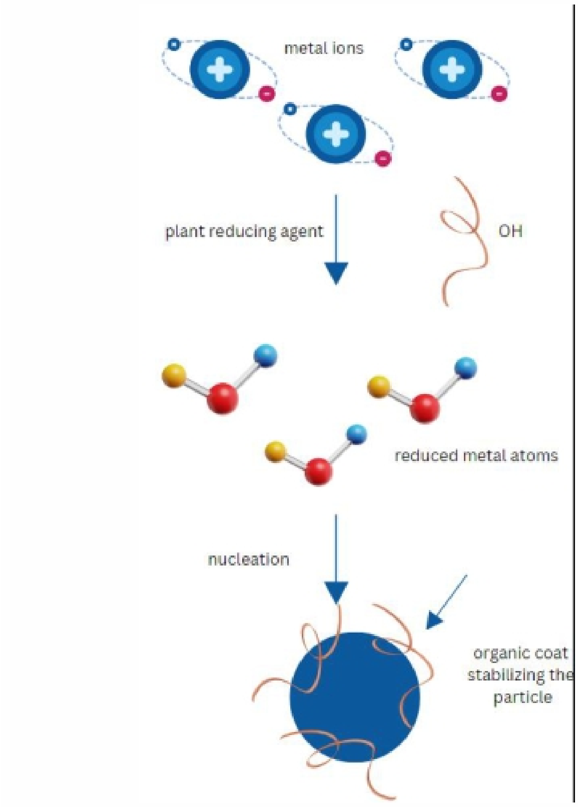

Figure 4: NP formation with the help of metal ions [68].

Distilled water is used to wash and boil plant material for NP synthesis. After filtration and addition of required solutions, a visible color change indicates NP formation, allowing their separation [69]. Several NPs, including iron, zinc oxide, silver, and gold, have been successfully synthesized using green methods [70]. Plant leaves are washed, sterilized with double-distilled water, and air-dried before being crushed and weighed. The material is then extracted in Milli-Q water at a suitable concentration under heating and continuous stirring, followed by filtration through Whatman filter paper to obtain a clear plant extract for NP synthesis [71].

Advantages

Plant-based synthesis is safer than fungal or bacterial methods and typically yields more uniform NPs.

Disadvantages

Higher temperatures used during heating increase the overall cost of NP production.

Green Synthesis Using Bacteria

Green synthesis using bacteria has a low energy requirement and thus is suitable [72]. Bacteria can synthesize metal NPs both intracellularly and extracellularly [73]. Ion channels, active transport, endocytosis, and diffusion allow the metal ions to enter within the bacteria [74]. Intracellular NP synthesis involves three main steps: trapping of metal ions, bioreduction, and capping of the formed NPs [75]. Extracellular synthesis involves bioreduction, particle capping, and enzyme secretion [76]. NP growth and stability are influenced by bacterial protein functional groups such as $–NH_2$, –OH, –SH, and –COOH, which act as binding sites for metal ions. These groups help in metal ion fixation and reduction, often located in the cell wall or periplasmic space [77]. Peptides and amino acids play an important role in microbial synthesis of AgNPs. When added to silver ion solutions, they interact with metal nuclei and help stabilize growing nanoclusters by limiting surrounding ion access [78]. AgNPs can be synthesized using peptides containing amino acids such as cysteine, methionine, arginine, and lysine, which bind to the surface of the NP nucleus and aid in stabilization [79]. Tyrosine can act as a reducing agent in alkaline conditions because its phenolic group can be oxidized to a quinone form [80]. Tyrosine-containing oligopeptides at the N-terminus help stabilize nanoparticles and facilitate metal recovery [81]. Tryptophan can act as a reducing agent in NP synthesis due to its ability to transfer electrons. During this process, it is oxidized to a tryptophol radical [82].

Advantages

It is easily accessible and resilient under challenging conditions [83].

Green synthesis using fungi

Myconanotechnology is an emerging field that uses fungi to synthesize nanomaterials with controlled size and shape [84]. “Myco NPs” are NPs synthesized using fungi. Different fungal species require specific growth conditions and media. Typically, fungal hyphae are first grown in a liquid medium and then washed with distilled water to remove residual nutrients.

They are incubated in distilled water for 1-2 days under shaking conditions, after which the mycelium is separated, and the supernatant is mixed with metal ion solutions to initiate NP formation, which is monitored over 2-3 days. In an alternative method, fungal hyphae are directly exposed to metal ion solutions, eliminating the need for filtrate preparation; common metal sources include silver nitrate for AgNPs, chloroauric acid for AuNPs, and cadmium sulfide for cadmium-based NPs [85]

Myconanoparticles can be synthesized both intracellularly and extracellularly. In intracellular synthesis, fungal biomass is exposed to metal salt solutions and incubated, where bioreduction occurs inside the cells. In extracellular synthesis, fungal filtrate reacts with metal ions on the cell wall surface, accelerating NP formation. Metal ions are initially trapped through electrostatic interactions with the fungal cell wall, followed by enzymatic reduction leading to NP formation and precipitation. Overall, this process typically yields small-sized NPs [87]. NP biosynthesis depends on factors like temperature, pH, incubation time, metal ion concentration, and fungal biomass, which influence size, shape, and yield. High metal ion levels may inhibit formation, while pH changes alter morphology, producing different shapes across acidic to alkaline conditions. Temperature also affects fungal activity and the rate of NP synthesis [89].

Advantages of using fungi

Mycelial fungi enable easy scale-up of NP production and simplify downstream processing due to their large surface area and flexibility. Compared to bacteria, fungi secrete higher amounts of protein, leading to improved productivity [91].

Disadvantages of using fungi

There are safety concerns, and the resulting NPs often show variability in size [92].

3. Nanoparticles as drug delivery agent

The use of nanoparticles in particular, and nanotechnologies in general, has significantly altered how medications are delivered. [93]. NPs are promising drug carriers due to their high surface reactivity and ability to cross biological barriers. Various nanocarriers, such as liposomes, lipid NPs, dendrimers, polymers, silica/carbon systems, and magnetic NPs, are used in drug delivery [94]. NPs are effective drug carriers because they can target specific tissues, reach deep molecular sites, and enable controlled drug release [95]. Effective targeted therapy requires proper drug conjugation and targeting strategies. Drugs can be loaded into nanocarriers through adsorption, covalent bonding, or encapsulation. Covalent bonding makes it possible to precisely regulate how many drug molecules are bonded to the nanocarrier, improving the efficiency of medicinal chemical delivery. Nanocarriers can target specific cells via active or passive mechanisms. Active targeting involves using recognition ligands such as antibodies, folic acid, or peptides to direct drug-loaded carriers to diseased sites. The active approach entails adjusting physical indicators like pH, magnetism, and temperature. When tumor tissues show enhanced vascular permeability and retention (EPR), passive targeting takes place [96]. For the best possible therapeutic agent delivery or encapsulation, nanoparticles, nanospheres, and nanocapsules can all have different qualities and release characteristics. Drugs are frequently embedded, dispersed, adsorbed, bonded, or encapsulated inside nano-matrix structures [97]. Targeting ligands are engineered onto nanocarriers, along with long-circulating systems that have optimized surface properties, to control receptor binding, stability, aggregation, and downstream biological interactions. This is essential for effective NP design [98]. Fullerene soluble derivatives are being explored for anticancer, antioxidant, and anti-apoptotic applications, including potential therapeutic roles in neurodegenerative diseases [99]. Nanoshells are an advanced drug delivery system that can transport chemotherapeutic agents directly to tumours, making them a promising approach in cancer therapy. After being administered into the body, nanoshells coated in polymers holding drugs gather close to tumour cells [100].

3.1 How are nanoparticles effective?

Optimized physicochemical and biological properties of nanocarriers facilitate greater absorption by cells, rendering them efficient vehicles for the transport of bioactive chemicals [101]. Nanoparticles may carry massive payloads, shield therapeutic agents from physiological barriers, and increase the bioavailability of drugs that are insoluble in water. NP formulations enhance drug delivery by improving bioavailability, enabling controlled release, and allowing precise intracellular targeting [102]. Polymeric NPs are increasingly popular due to their stability and ease of surface modification [103]. The tunable properties and surface chemistry of polymers enable controlled drug release and targeted localization to specific disease sites [104]. The tunable properties and surface chemistry of polymers enable controlled drug release and targeted localization to specific disease sites [105]. Consequently, the two main essential properties of nanoparticles that account for their advantages in medicine administration are their small size and the use of biodegradable materials. Nanoparticles can infiltrate tumors, extravasate through inflammatory regions' endothelium, and enter microcapillaries due to their small size [106].

3.2 Characteristics of nanoparticles for drug delivery

For medical use, nanocarriers must be biocompatible and non-toxic to avoid an immune response. NPs with a hydrodynamic size of about 10-100 nm generally show better in vivo pharmacokinetics. Smaller particles may undergo renal clearance or tissue leakage, while larger ones are more readily removed from circulation by the reticuloendothelial system [107].

Size

NPs are mainly defined by their small size and dispersion, which influence drug loading, stability, and release behaviour. Numerous studies show that they provide significant advantages over microparticles in drug delivery applications [108]. Due to their small size and higher mobility, NPs achieve better tissue penetration and cellular uptake than microparticles. Their distribution, toxicity, and targeting ability are strongly influenced by size and shape, which also affect how they are recognized by biological systems [109] [110]. As particle size decreases, the surface area-to-volume ratio increases, allowing more drug to be present at or near the surface.

This leads to a faster release rate compared to larger particles, where the drug is more deeply embedded [111]. The lymphatic system is stimulated by particles 200 nm or larger, which causes quicker removal from circulation [112]. During storage, transportation, and dispersion, smaller particles are more likely to clump together. Smaller NPs allow easier diffusion of PLGA degradation products, whereas larger particles release them more slowly, which can lead to autocatalytic degradation effects [113]. Larger particles have been reported to influence drug release and polymer degradation rates, although the exact mechanisms remain unclear and require further investigation. In contrast, very small particles (1-20 nm) with longer circulation times can pass from blood vessels into interstitial spaces and are transported through lymphatic channels to lymph nodes [114]. Differences in tissue vascularization and blood flow should be considered in NP drug design, as they influence leakage into lymph nodes through porous endothelium. Particle migration to lymph nodes can also be used to enhance diagnostic imaging signals. Additionally, hyperosmotic mannitol can disrupt endothelial tight junctions, temporarily increasing blood-brain barrier permeability to improve drug delivery for conditions such as brain tumours [115].

Surface properties

Optimal targeting ligands, surface curvature, and reactivity are essential for optimising nanoparticle drug delivery to prevent aggregation, ensure stability, promote receptor binding, and achieve pharmacological effects [116]. It is necessary to first address nanosystem clearance. The lymphatic system may identify nanoparticles, which trigger the body's immune response to foreign substances [117]. Coating NPs with polymers or surfactants such as PEG, polyethylene oxide, poloxamers, poloxamines, and polysorbate reduces protein adsorption and opsonization. This helps avoid macrophage recognition and decreases liver and spleen accumulation [118]. PEG is a hydrophilic, inert polymer that reduces adsorption of plasma proteins on NP surfaces, thereby minimizing drug loss. By decreasing opsonization and macrophage uptake, PEGylated NPs enable more controlled and sustained drug delivery [119]. The particle size should be just large enough to keep fluid from seeping into blood capillaries, but not so large that macrophages can readily remove it [120]. When drugs are delivered using conventional carriers, they are often taken up by the MPS, particularly in the liver, spleen, lungs, and bone marrow. After intravenous administration, NPs can be recognized by the immune system and cleared from circulation by phagocytic cells [121].

3.3 Mechanism of action

Oral intake, inhalation, and injection are the three main ways that nanoparticles can enter the body. Before being distributed to various organs, particles first interact with proteins when they enter the bloodstream [122]. Once the particles have been absorbed from the blood capillaries, the lymphatic system may distribute and eliminate them. An efficient nanoparticle drug delivery system targets specific diseased tissues while minimizing or eliminating damage to healthy tissues. The most widely used strategy is coating NPs with specific targeting ligands. The stability, controllability over conjugation chemistry, and ease of synthesis of small organic molecules make them popular targets. Targeting ligands may lack ideal specificity, but biotin, due to its strong binding to streptavidin, is widely used for NP conjugation [123]. Folic acid (vitamin B9) binds strongly to folate receptors, making it useful for targeting cancers that overexpress these receptors [124]. Liposomes are an important tool for targeted drug delivery. They can be engineered from lipid monomers that mimic cell membranes and tailored in terms of size, charge, and surface ligands to improve targeting and performance [125]. There are two ways to carry out targeted delivery: actively and passively. Combining a tissue- or cell-specific ligand with the therapeutic drug or carrier system is known as active targeting. [126]. Through the EPR effect, drugs bound to macromolecules or enclosed in nanoparticles can passively target tumors. As an alternative, catheters might be used to administer nanoparticles to certain tissues or organs. Administering drug-containing nanoparticles locally to vascular restenosis sites can offer a prolonged release of drugs at specific regions of the arterial wall [127]. The body's natural clearance mechanisms provide a basis for designing effective nanoparticle-based drug delivery systems [128]. The vascular and lymphatic systems carry nutrients, waste products, and drugs to the body after systemic delivery. Complement proteins and blood opsonic factors that are deposited on the surface of intravenously administered particles help Kupffer cells and macrophages remove the particles from the bloodstream. Clearance and opsonization depend on particle size and surface properties. Compared to very small particles, NPs around 200 nm tend to show increased complement activation and faster clearance from the body[129].

Drug loading and release

There are two methods for achieving drug loading. In the integration method, the drug is incorporated during NP formation, resulting in reduced burst release and sustained drug release over time [130]. Adsorption/absorption methods involve loading drugs onto pre-formed NPs by incubating the nanocarriers with concentrated drug solutions. The solubility of the drug in its solid state inside the matrix material or polymer determines the effectiveness of drug loading and trapping[131]. Macromolecules load most efficiently at their isoelectric point, where reduced solubility enhances adsorption [132]. Key factors in designing nanoparticulate drug delivery systems include drug release and polymer degradation [133]. The interaction between medication and auxiliary substances produces a less water-soluble molecule, which leads to steadier release that is steadier and less impact in bursts. [134]. Drug release can be enhanced by adding auxiliary agents such as ethylene oxide–propylene oxide block copolymer (PEO–PPO) to chitosan systems. These agents reduce drug–matrix interactions through competitive electrostatic interactions with chitosan, thereby promoting faster release [135]. Depending on the kind of nanoparticle used, drug release varies. Depending on their composition, polymeric nanoparticles can be categorized as either nanospheres or nanocapsules. Polymer chains are organized into nanospheres in a homogeneous environment, resembling a phase isolated from the main solution, where surfactants form micelles [136]. Nanospheres are matrix-type systems where the drug is uniformly dispersed and released mainly through matrix degradation. Release can occur initially in a burst due to weak surface binding, followed by a sustained release over time [137].

The initial burst release occurs due to weakly bound or surface-adsorbed drug on the large nanoparticle surface area. Nanospheres can enhance immune responses through advances in encapsulation technology. In nanocapsules, drug release is mainly controlled by diffusion through the polymeric layer, making polymer permeability a key factor. Drug release from nanoparticles is commonly studied using methods such as diffusion cells (with artificial or biological membranes), dialysis bag techniques, reverse dialysis, ultracentrifugation/centrifugation, and ultrafiltration under controlled agitation [138].

4. Different types of nanoparticles for drug delivery

Liposomes

Liposomes are colloidal nanocarriers typically ranging from 80–300 nm in size. Drugs are commonly loaded into liposomes using encapsulation techniques. Their prolonged circulation can enhance therapeutic activity but may reduce available drug concentration over time. Enhanced lipid–lipid interactions with the liposomal membrane also allow lipophilic drugs, such as paclitaxel, to integrate into the lipid bilayer and be efficiently delivered into target cells [139]. To achieve organ-specific drug delivery, multifunctional liposomes can be engineered with proteins, antigens, or other biological components as targeting elements. This approach improves therapeutic precision and effectiveness.

Nanoparticles based on solid lipids

Solid lipid matrices, consisting of lipids that remain solid at body temperature, form the basis of three main carrier systems: solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and lipid drug conjugates (LDC) [140] [141]. SLN is composed of solid lipid particles such as complex glyceride mixtures, very pure triglycerides, or waxes stabilized by various surfactants [140] [142]. Drawbacks include high water content in dispersions, drug ejection during crystallization, and poor loading capacity because of drug solubility and lipid matrix structure [143]. Limitations of conventional SLNs have been overcome by modified lipid-based systems such as NLCs and LDCs. NLCs are formed by mixing solid and liquid lipids, creating a less ordered structure that improves drug loading and reduces drug expulsion. They are classified into three types: multiple types (drug protected by solid lipid), amorphous types (prevent crystallization and drug leakage), and imperfect types (matrix imperfections create space for higher drug incorporation) [144]. NLC is mainly used for dermal applications [145]. Lipid drug conjugates (LDCs) were developed to improve delivery of lipophilic drugs using lipid-based carriers.[146].

Polymeric nanoparticles

Polymeric nanoparticles (PNPS) have a diameter of 10–100 nm [147]. Non-ionic surfactants are commonly used to coat polymeric nanoparticles (PNPs) to reduce immunological interactions such as opsonization and CD8 T-cell recognition, as well as intermolecular forces like van der Waals interactions, hydrophobic interactions, and hydrogen bonding [148]. During polymerization, drugs can be either encapsulated within or adsorbed onto the surface of polymeric nanoparticles (PNPs) [149]. Using biodegradable nanosystems for nanomedicine is a highly effective approach. Biodegradable polymeric nanocarriers degrade in the body via hydrolysis into monomers such as lactic acid and glycolic acid [150]. Kumari et al. reported that PLGA-based systems generally show low systemic toxicity in biomaterial and drug delivery applications [151]. These nanoparticles are compatible with both cells and tissue [152].

Carbon nanomaterials

CNTs are graphite layers with a high thermal conductivity and a large surface area that are either single-walled or multi-walled [153]. Large interior volumes, the ability to act on both internal and exterior surfaces, and a variety of construction techniques are all features of nanotubes [154]. Single-walled carbon nanotubes (SWCNTs), due to their high mechanical strength, are used to improve the performance of polymeric and non-polymeric composite carriers[155].

5. Shortcomings of nanoparticles as drug carrier

Many drugs have not demonstrated improved efficacy with current nanoparticle systems. According to the authors, several factors are responsible for these limitations and failures: the weight proportion of the drug transported relative to carrier material is called drug loading, and it is usually less than 5%. Insufficient drug loading or excessive carrier material can lead to toxicity and unwanted side effects [156]. The rapid “burst release” may occur when drug molecules are adsorbed on the nanocarrier surface. Because of this, a significant amount of the drug is released into the body before it reaches its intended target, which causes a drop in activity and an increase in negative effects [93]. Nanomaterials around 100 nm in size can induce toxicity through multiple mechanisms. When inhaled, they may cause lung inflammation and oxidative stress [157]. Because of their small size, nanoparticles have a greater relative surface area in [158] the atmosphere, which can cause harmful processes such as redox cycling, hydrophobic interactions, and the production of free radicals. A 20 nm particle can be significantly more biologically reactive than a 2 mm particle at the same mass dose due to its much higher surface area. Carbon nanotubes used in drug delivery may also exhibit toxicity depending on their shape and structural properties [159]. The high aspect ratio of carbon nanotubes and the inherent properties of graphite can contribute to their potential toxicity. Additionally, impurities such as residual metals and excess carbon can increase reactive oxygen species (ROS) production, leading to oxidative stress in cells [160]. It has been shown that in macrophage cell lines [161], carbon nanotubes cause necrosis or apoptosis in addition to changes in cell structure [162]. High doses of SWCNTs have been shown to induce oxidative stress in bronchial epithelial cells and keratinocytes, leading to increased ROS production, lipid peroxidation, and mitochondrial dysfunction [163].

Conclusion

Metal nanoparticles are increasingly used across multiple fields, and their synthesis is a complex and dynamic process with several established methods for controlling particle shape. Each technique has its own advantages and limitations. Green synthesis is considered cost-effective, environmentally friendly, and free from toxic chemical residues. However, despite many existing methods, improved approaches are still needed to overcome current limitations and enable large-scale commercial applications.

Nanocarrier-based drug delivery systems aim to enhance the pharmacological and therapeutic performance of conventional drugs. Due to their small size, nanocarriers can cross biological barriers such as the blood–brain barrier and act at the cellular level. Although many nanoparticle-based therapeutics are under development and preclinical evaluation, only a few are currently available in the market, mainly due to existing technical and biological limitations. Therefore, further focused and systematic research is required to achieve significant therapeutic advancements.

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