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Review

Surface Modification of Metallic Nanoparticles for Targeting Drugs

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Abstract: This review focuses on the surface modification of metallic nanoparticles for targeted drug delivery. Metallic nanoparticles, owing to their unique size, stability, and payload capacity, have emerged as promising drug carriers. However, their application necessitates surface modification to enable precise targeting. Various strategies, such as polymer coating methods, the use of functional groups, and bio-conjugation with targeting ligands, are explored. The review also discusses the selection of ligands based on target receptors, active and passive targeting approaches, and stimuli-responsive targeting. It further delves into the challenges of translating these strategies to clinical settings, including scalability, toxicity, and regulatory hurdles. The surface modification of metallic nanoparticles is a promising avenue for targeted drug delivery. Various strategies, including polymer coating, functionalization with specific groups, and bioconjugation with targeting ligands, have been explored to enhance the therapeutic potential of these nanoparticles. The challenges in clinical translation, continuous advancements in nanoparticle synthesis, and surface modification techniques offer a positive outlook for the future of targeted metallic nanoparticle systems. Despite the promising potential of metallic nanoparticles in drug delivery, there are several challenges that need to be addressed for their successful clinical translation. These include scalable fabrication and functionalization of nanoparticles, toxicity concerns, and regulatory hurdles. However, continuous advancements in nanoparticle synthesis and surface modification techniques are expected to overcome these challenges in the near future.

Keywords: nanoparticles; metallic nanoparticles; surface modification; drug delivery systems; targeted drug delivery systems

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1. Introduction

Drug delivery has been a pivotal area of research in the pharmaceutical sciences for decades, with the overarching goal of enhancing therapeutic efficacy while minimizing side effects. Nanoparticles have emerged as promising drug carriers owing to their small size, modifiability, and capacity to encapsulate therapeutic payloads [1]. Among the myriad nanoparticle formulations, metallic nanoparticles have drawn significant attention in recent years due to their high surface area to volume ratio, stability, and versatile surface chemistry [2]. However, to increase effective delivery of metallic nanoparticles as targeted drug delivery vehicles, surface modification is necessary to render them biocompatible, avoid systemic toxicity, and enable functionalization.

This review provides a comprehensive overview of various surface modification strategies for metallic nanoparticles, including bioconjugation with polymers, lipids, proteins, and targeting ligands [3]. We discuss the key considerations in designing surface coatings and highlight both passive and active targeting approaches. The current and emerging applications of surface-modified metallic nanoparticles are reviewed, spanning cancer therapeutics, vaccines, gene delivery, and beyond. Challenges such as stability, scalability, and toxicology are also examined. Finally, we present the future prospects and outlooks

for metallic nanoparticles as versatile drug delivery platforms. Overall, rational surface engineering of metallic nanoparticles holds immense promise for enabling targeted and controlled drug delivery, but continued research is needed to fully translate these cutting-edge technologies into clinical realities. With ongoing interdisciplinary collaboration and innovation in materials science, chemistry, and biomedicine, metallic nanoparticles are poised to transform disease treatment through precise and personalized drug delivery.

2. Historical Overview of Nanoparticles for Drug Delivery Systems

Nanoparticles have been classified as particles with dimensions that range between 1 and 100 nanometers. These tiny particles have surfaced as an innovative tool in the realm of drug delivery due to their unique capabilities. Their minute size enables them to cross biological barriers otherwise deemed impenetrable, thus facilitating the delivery of therapeutic agents to specific targeted sites within the body. Such an ability is paramount in treating diseases such as cancer, where traditional drug delivery methods oftentimes fail to effectively reach the tumor site.

When looking at the various classes of nanoparticles, metallic nanoparticles—primarily those composed of gold, silver, and iron oxide—have demonstrated immense potential as carriers for drugs [3]. The reason behind their success can be attributed to their unique set of properties tailored to this role. An essential property that stands out is their high surface area to volume ratio. This allows for the attachment of a large number of drug molecules, which increases the payload of the therapeutic agent that can be delivered, directly impacting the effectiveness of the treatment [4].

Notably, a subset of metallic nanoparticles, specifically magnetic metal nanoparticles, assume magnetic properties that are being harnessed for innovative medical applications. These nanoparticles serve as effective contrast agents in Magnetic Resonance Imaging (MRI), offering improved visibility of internal biological structures. Moreover, they have shown promise in cancer treatment by selectively influencing cancer cells inside the Gantry—a specialized device capable of 360-degree rotation around patients for precise positioning of radiation equipment [5]. This is achieved by heating these cells in vivo above the temperature of protein denaturation when exposed to a radiofrequency magnetic field, thus offering a targeted approach to cancer therapy.

Furthermore, metallic nanoparticles possess customizable surface chemistry, implying that their surfaces can be modified to enhance their drug-carrying capabilities [6]. This is a notable advantage, as it permits the design of nanoparticles specifically engineered to carry and deliver a particular drug. Additionally, metallic nanoparticles, including their magnetic metal counterparts, can respond to external stimuli such as light or magnetic fields [7]. This responsiveness can be leveraged to control the drug release at the target site, thereby augmenting the precision and efficacy of the treatment [8].

3. Necessity for Surface Modification for Enhanced Targeting Capabilities

The surface of metallic nanoparticles assumes a significant role in their interaction with biological systems. Without any modification, these nanoparticles are susceptible to swift clearance by the immune system, which considerably restricts their therapeutic potential [9,10]. This happens because the immune system recognizes these alien particles and expeditiously removes them from circulation, thus barring them from reaching their intended target.

Surface modification of metallic nanoparticles can markedly enhance their stability and prevent non-specific interactions with biological molecules that could result in their premature clearance. For instance, encapsulating the nanoparticles with polymers or other biocompatible materials can offer them a protective shield from the immune system, thereby lengthening their circulation time within the body.

Additionally, surface modification can facilitate precise targeting of the nanoparticles to specific cells or tissues. This can be accomplished by fastening specific ligands, such as antibodies or peptides, to the nanoparticle surface. These ligands can bind to specific

receptors on the target cells, thereby steering the nanoparticles toward these cells. This targeted approach not only amplifies the efficacy of the drug delivery but also curtails the side effects that come with systemic drug administration [11].

4. Metallic Nanoparticles in the Domain of Drug Delivery

Metallic nanoparticles possess multiple properties, making them prime contenders for drug delivery systems. Their compact size aids them in evading the immune system's detection and infiltrating tissues deeply, an attribute particularly beneficial for the treatment of solid tumors. Moreover, their stability ensures that they retain their structure during circulation, consequently preserving their capacity to carry drugs.

The elevated surface area to volume ratio of metallic nanoparticles enables the attachment of a substantial number of drug molecules, thereby enhancing the therapeutic payload. This is especially advantageous for drugs that are potent but possess a low therapeutic index, as it permits the delivery of an adequate drug dosage without invoking systemic toxicity [12].

Metallic nanoparticles can be synthesized from an array of materials, with gold, silver, and iron oxide being predominantly used due to their biocompatibility and synthesis ease. These materials are typically well tolerated by the body and have demonstrated minimal toxicity, deeming them appropriate for utilization in drug delivery.

In comparison to other nanocarriers, such as liposomes or polymeric nanoparticles, metallic nanoparticles offer several benefits. These comprise improved stability, which ascertains that the nanoparticles retain their structure and drug-carrying capacity during circulation, and adjustable release profiles, which facilitate the controlled release of the drug at the target site [13]. Additionally, metallic nanoparticles present the opportunity to amalgamate therapy with diagnostics, a concept identified as theranostics. This strategy involves employing the nanoparticles for not only the drug delivery but also the monitoring of the treatment response, thereby offering a comprehensive approach toward disease management.

5. Therapeutic Applications of Metallic Nanoparticles

Metallic nanoparticles are being widely explored for their potential applications in cancer therapy. One promising approach involves actively targeting nanoparticles to cancer cells by functionalizing with ligands that recognize overexpressed receptors on cancer cell surfaces [14]. A prominent example includes the targeting of folate receptors, commonly overexpressed in cancers, using nanoparticles that have been conjugated with folic acid [15]. Investigations have indicated that gold nanoparticles, functionalized with folic acid and loaded with the chemotherapeutic agent methotrexate, exhibit significantly elevated cytotoxicity against cancer cells that are positive for folate receptors in comparison to normal cells or methotrexate alone [16]. The selective targeting minimizes off-target toxicity while improving anticancer efficacy.

Beyond targeting, metallic nanoparticles also offer advantages in improving the delivery and therapeutic index of chemotherapeutic drugs like doxorubicin, cisplatin, and paclitaxel [17]. By loading these drugs onto nanoparticles such as gold, higher intra-tumor accumulation can be achieved through the enhanced permeability and retention (EPR) effect. Controlled release then sustains drug exposure within the tumor while reducing systemic exposure and toxicity [18]. Additionally, payload protection by the nanoparticle carrier improves drug stability.

For gene therapy, metallic nanoparticles can be used to deliver small interfering RNA (siRNA) or microRNA (miRNA) to silence overexpressed oncogenes [19]. As an example, gold nanoparticles functionalized with tumor-targeting peptides and loaded with miR-21 inhibitors demonstrated effective silencing of the oncogene miR-21 in glioblastoma cells [20]. This suppressed cancer cell proliferation, showcasing the utility of nanoparticles for oncogene-targeted gene therapy.

Photothermal tumor ablation using gold nanoparticles is another innovative cancer treatment strategy [21]. These nanoparticles strongly absorb near-infrared light and convert it into heat, which can be used to induce localized tumor cell death. Targeting ligands can further enhance selective accumulation in tumor tissues. Overall, metallic nanoparticles enable diverse treatment modalities against cancer.

6. Biochemical Sensing Applications in Drug Targeting

While metallic nanoparticles have been extensively studied for their roles in targeted drug delivery, they also show promise in the realm of biochemical sensing within therapeutic applications. One intriguing example involves fluorescently labeled DNA oligonucleotides adsorbed onto iron oxide nanoparticles via the backbone phosphate, leading to fluorescence quenching. Interestingly, arsenate ions can exchange with the adsorbed DNA, resulting in an increase in fluorescence. This innovative mechanism allows for the sensitive detection of arsenate ions down to concentrations as low as 300 nM [22].

Such sensing capabilities are not just academic exercises; they have practical implications in therapies involving arsenate or other ion-based drugs. Real-time monitoring of arsenate levels within the tumor microenvironment could provide immediate feedback on the drug delivery efficacy, allowing for dynamic adjustments to be made to treatment protocols [22]. This real-time monitoring could be particularly crucial in adaptive therapies where drug concentrations need to be precisely controlled to optimize treatment outcomes and minimize side effects.

In essence, the potential for metallic nanoparticles to serve both as drug delivery vehicles and as biochemical sensors offers a dual functionality that could revolutionize the field. The ability to not only deliver but also monitor therapeutic agents in real-time represents a significant advancement in targeted drug delivery systems.

7. Antimicrobial Therapy

Metallic nanoparticles show promising utility in combating drug-resistant bacterial infections [23]. For instance, conjugating silver nanoparticles with antibiotics like vancomycin enhances antimicrobial potency, even against vancomycin-resistant Staphylococcus aureus [24]. The nanoparticles disrupt the bacterial cell wall, increasing permeability for enhanced antibiotic delivery at much lower doses than vancomycin alone [25].

Metallic nanoparticles also provide a platform for the improved delivery of antimicrobial peptides [26]. pH-responsive gold nanoparticles loaded with the frog-derived antimicrobial peptide esculentin-1a demonstrated a triggered release of the peptide payload within the acidic endosomes of bacteria [27]. This resulted in reduced systemic exposure and enhanced antibacterial activity.

Additionally, laser-activated photothermal heating of gold nanoparticles bound to bacteria enables rapid contact-free killing [28]. As an example, immunoglobin-conjugated gold nanoparticles bound to Pseudomonas aeruginosa were killed with near-infrared light via localized photothermal effects [28]. Overall, metallic nanoparticles have versatile utilities in combating bacterial drug resistance.

8. Cardiovascular Disease

Metallic nanoparticles are being investigated for the targeted delivery of therapeutics against cardiovascular diseases like atherosclerosis [29]. Strategies include targeting cardiovascular drugs to disease sites and delivering small interfering RNA/micro RNA (siRNA/miRNA) to modulate underlying disease pathways [30]. For instance, atorvastatin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles grafted with peptides targeting vascular smooth muscle cells showed enhanced anti-inflammatory effects in atherosclerotic plaque sites [31].

siRNA delivery with metallic nanoparticles also holds promise for treating dyslipidemia by silencing genes involved in cholesterol regulation [32]. As an example, PLGA nanoparticles mimicking low-density lipoprotein and loaded with anti-PCSK9 siRNA si-

lenced the target gene in liver cells following intravenous injection [33]. This durably lowered blood cholesterol in vivo, showcasing the utility of nanoparticles for targeted gene therapy.

Additionally, nanoparticles can be used to detect atherosclerotic plaques when conjugated with targeting ligands and imaged via MRI or fluorescence techniques [34]. Overall, metallic nanoparticles enable targeted drug delivery and gene therapy for addressing cardiovascular diseases.

9. Neurological Disorders

A major challenge in treating neurological conditions is overcoming the blood–brain barrier to deliver therapeutics to the brain [35]. Metallic nanoparticles present opportunities to enhance central nervous system (CNS) drug delivery through strategies like functionalization with transcytosis ligands [10]. For example, intranasally administered fentanyl loaded in transferrin-conjugated nanoparticles exhibited rapid transport into the brain, providing prolonged pain relief in preclinical models [36]. The transferrin ligand enabled brain permeability by binding transferrin receptors onto nasal epithelial cells.

Metallic nanoparticles also facilitate the delivery of drugs and genes that target pathological accumulations in the brain, such as amyloid beta plaques in Alzheimer's disease [37]. For instance, curcumin-loaded PLGA nanoparticles modified with glucose and wheat germ agglutinin lectin crossed the blood–brain barrier and bound to amyloid beta aggregates after intravenous injection [38]. The multifunctional nanoparticles enabled delivery, targeting, and potential disruption of neurotoxic plaques.

Moreover, nanoparticles can ferry neuroprotective proteins like the glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor into the brain following systemic administration [39]. As an example, GDNF loaded into polysorbate 80-coated polybutylcyanoacrylate nanoparticles elicited neuroprotective effects in the brain against neurotoxin-induced damage when intravenously injected [40]. Overall, metallic nanoparticles present diverse opportunities to overcome the blood–brain barrier and enable targeted CNS therapy.

10. Metallic Nanoparticles for Treating Diabetes

Metallic nanoparticles are enabling the oral delivery of peptides and proteins like insulin, which normally undergo degradation when administered via the oral route [41]. Overcoming the barriers to effective oral protein delivery could transform diabetes management. The approaches being explored with metallic nanoparticles include protective encapsulation, permeation enhancement, and the glucose-responsive release of insulin.

Encapsulation of insulin in nanoparticle carriers protects the protein from the harsh conditions in the gastrointestinal tract including acidity and enzymes, thereby improving stability [42]. Nanoparticles composed of mucoadhesive polymers like chitosan have demonstrated enhanced oral insulin delivery through mucus permeation and paracellular transport [43]. The positive surface charge in chitosan nanoparticles favors interaction with the negatively charged mucosal surface, enabling adhesion and permeation. Co-formulation with penetration enhancers like sodium caprate further improves the insulin absorption [44].

Surface modification is another key strategy to impart permeability enhancement and stability. For instance, coating insulin-loaded PLGA nanoparticles with thiolated chitosan or cell-penetrating peptides has been shown to enhance oral bioavailability through improved mucoadhesion and permeation [45,46]. Similarly, gold nanoparticles coated with thiolated polyethylene glycol (PEG) and the permeation enhancer sodium cholate facilitated oral insulin delivery across intestinal enterocytes [47]. The PEG coating provided stability, while sodium cholate loosened tight junctions to enable transport.

Covalent conjugation of insulin to the nanoparticle surface is another emerging approach to protect against enzymatic degradation [33]. For example, gold nanoparticles modified with glutaraldehyde allow the covalent attachment of insulin through amine

crosslinking [48]. This improved stability and prolonged blood glucose reduction compared to simple encapsulation.

In addition to stability and permeation enhancement, the glucose-responsive release of insulin can potentially improve therapeutic outcomes [44]. Conformational switching of phenylboronic acid ligands on nanoparticles in response to glucose has been leveraged for this purpose [49]. Competitive binding of glucose displaces insulin from phenylborate-functionalized chitosan nanoparticles, enabling self-regulated insulin release proportional to blood glucose levels [50].

Overall, metallic nanoparticles enable multifaceted strategies to address the challenges of oral protein delivery using rational design approaches. While still early in translation, the field holds promise for developing oral insulin nanoparticle systems that leverage mucus permeation, permeation enhancement, protease inhibition, and glucose-responsive release. Metallic nanoparticles with tailored coatings and bioconjugation could open up oral delivery as a needle-free, patient-friendly route for insulin and other protein therapeutics against diabetes. Realizing this potential will require continued interdisciplinary research spanning nanotechnology, polymer chemistry, pharmaceutical science, and medicine.

11. Surface Modification Strategies

The surface modification of metallic nanoparticles is a critical step in enhancing their stability, reducing non-specific interactions and improving their precision in drug delivery. Various strategies have been employed to achieve this, including polymer coating and functional group attachment. A study by Santos et al. (2019) provides a comprehensive overview of these strategies [51].

Polymer coating, such as PEGylation or chitosan coating, is a common approach used to improve the stability of nanoparticles. PEGylation involves the attachment of polyethylene glycol (PEG) chains to the nanoparticle surface, which can prevent protein adsorption and reduce clearance by the immune system. Chitosan coating, on the other hand, can enhance the biocompatibility and mucoadhesive properties of nanoparticles, making them suitable for oral or nasal drug delivery [52].

While polymer coatings and functional groups offer well-established routes for surface modification, emerging approaches involving nucleic acids have shown promising results in enhancing nanoparticle stability and functionality. As such, the interaction between single-stranded DNA and citrate-capped gold nanoparticles has been shown to increase the stability of the nanoparticles, which has potential applications in various fields. For example, the programmable nature of DNA has been passed to gold nanoparticles (AuNPs), making it possible to synthesize AuNP oligomers, random aggregates, periodic structures, and crystalline superlattices. Additionally, DNA adsorption has been used to control the growth of AuNPs, tune catalytic activities of AuNPs, and improve the specificity of polymerase chain reactions.

Intriguingly, temperature also plays a vital role in the adsorption process. Freezing conditions have been demonstrated to accelerate the adsorption of thiolated DNA strands onto AuNPs. This rapid adsorption under low temperatures opens new avenues for the controlled assembly of nanoparticle structures and the optimization of their biochemical properties. The quick adsorption process can be particularly advantageous in applications requiring rapid and robust functionalization, such as point-of-care diagnostics or in situ environmental sensing.

Thus, applications related to drug delivery can also be envisioned. By modifying the surface of AuNPs with single-stranded or thiolated DNA, the nanoparticles can be tailored to have enhanced stability and functionality, which can be useful in a wide range of applications.

Functional groups, like thiols and amines, can be used to attach drug molecules or targeting ligands to the nanoparticle surface. This process, known as bioconjugation, can significantly enhance the targeting abilities of nanoparticles. For instance, Santos et al. demonstrated that the attachment of trimethyl chitosan (TMC) to the surface of mag-

netite nanoparticles improved their adsorption capacity for sulfamethoxazole, a common antibiotic [53].

Bioconjugation with targeting ligands can direct the nanoparticles to specific cells or tissues, thereby improving the precision of drug delivery. This is particularly important in cancer therapy, where targeted drug delivery can enhance the therapeutic efficacy and reduce side effects. Santos et al. showed that TMC-coated magnetite nanoparticles could be reused in multiple adsorption/desorption cycles, although their adsorption capacity gradually decreased over time [54].

12. Targeting Ligands

Targeting ligands are molecules that can selectively bind to receptors or antigens that are overexpressed on the surface of target cells, thereby directing nanoparticles to specific tissues or cells [55]. The selection of targeting ligand depends on the target receptor and desired pharmacokinetic properties. Ligands can be broadly classified as antibodies/antibody fragments, aptamers, peptides, carbohydrates, and small molecules [56].

Monoclonal antibodies that recognize tumor-associated antigens are perhaps the most extensively explored ligands for targeted drug delivery [57]. The exquisite specificity of antibodies makes them well suited for directing nanoparticles to cancer cells that are overexpressing cognate receptors [58]. However, the large size of antibodies may hinder deep tumor penetration. Hence, smaller antibody fragments such as Fabs, scFvs, and nanobodies are increasingly being evaluated [59].

Aptamers composed of single-stranded oligonucleotides can also recognize cell surface receptors with high affinity and are emerging as targeting ligands [60]. Compared to antibodies, aptamers offer advantages such as smaller size, a lack of immunogenicity, ease of modification, and stability [61]. However, their nucleic acid nature requires chemical modification and conjugation strategies to be effectively incorporated onto nanoparticles [62].

13. Advanced Nucleic Acid Strategies in Targeting

Another exciting development in the realm of targeting ligands is the emergence of Spherical Nucleic Acids (SNAs). SNAs are three-dimensional nanostructures consisting of nucleic acids that are densely functionalized and spherically oriented around a nanoparticle core. Unlike traditional nucleic acid ligands, SNAs exhibit unique cellular uptake behavior. They enter cells more rapidly and in higher quantities without requiring transfection agents, engaging scavenger receptors that facilitate caveolin-mediated endocytosis. This has led to their use in miRNA profiling, mRNA detection in living cells via SNA-based NanoFlare constructs, and even in immunomodulation by engaging Toll-like receptors (TLRs). The unique properties of SNAs offer a new frontier in the design of targeting ligands, expanding the possibilities for more effective and versatile drug delivery systems.

Peptides are also widely used as targeting ligands given their high receptor affinity, low immunogenicity, ease of synthesis, and small size [37]. Targeting peptides can be identified through phage display screening or rational design based on interacting motifs [63]. Finally, small molecules, carbohydrates, vitamins (e.g., folic acid), and other receptor-binding moieties are also utilized as ligands [64].

Overall, combining the strengths of different targeting ligands on multifunctional nanoparticles can potentially improve delivery selectivity and efficacy. Further innovation in ligand design and bioconjugation strategies will continue expanding the repertoire of active targeting options for enhanced drug delivery [65].

14. Active vs. Passive Targeting Approaches

In nanoparticle-based drug delivery, two main targeting strategies are commonly employed: passive targeting and active targeting. Passive targeting relies on the EPR effect, whereby nanoparticles extravasate through leaky tumor vasculature and accumulate in the tumor interstitium [66]. The aberrant architecture of the tumor neovasculature results in increased vascular permeability compared to normal tissues, enabling nanoparticle

accumulation. However, the EPR effect is heterogeneous in tumors and alone provides limited specificity [67,68].

In contrast, active targeting involves decorating nanoparticles with affinity ligands to molecularly recognize and engage overexpressed receptors on target cells [44]. Ligands such as antibodies, aptamers, peptides, carbohydrates, and small molecules can be utilized to impart selectivity [69]. While passive targeting leverages a generic tumor physiology phenomenon, active targeting confers molecular recognition, achieving precision drug delivery [70]. However, designing and implementing active targeting poses challenges, including identifying suitable ligand–receptor pairs, optimizing ligand density, and potential immunogenicity [71].

Despite these challenges, active targeting continues to demonstrate improved therapeutic efficacy over passive EPR-based targeting in preclinical studies [71,72]. Recent advances include targeting nanoparticle drug delivery to tumor cells using ligands against overexpressed receptors such as transferrin, folate, epidermal growth factor, and prostate-specific membrane antigen [73–76]. In addition to targeting tumor cells, active ligands can be directed against overexpressed receptors on tumor vasculature [77].

An emerging approach involves combining EPR-based passive accumulation with active molecular targeting to achieve enhanced permeability and retention along with selectivity [78]. Dual passive and active targeting represents a promising strategy to improve nanoparticle delivery and efficacy. Overall, advances in material science, bioconjugation, and molecular targeting promise continued innovation in actively targeted nanoparticle systems for drug delivery [79].

15. Stimuli-Responsive Targeting

Stimuli-responsive targeting is a promising approach that involves the release of the drug in response to specific internal or external stimuli. External triggers include heat, light, and ultrasound, while internal stimuli include pH, enzymes, and redox conditions. This approach can provide spatial and temporal control over drug release, thereby enhancing therapeutic efficacy and reducing side effects [80].

For instance, Santos et al. demonstrated that TMC-coated magnetite nanoparticles could adsorb sulfamethoxazole in response to changes in pH. This suggests that these nanoparticles could potentially be used for pH-responsive drug delivery, which could be particularly useful for targeting acidic tumor microenvironments [81].

In conclusion, surface modification strategies, targeting ligands, and targeting approaches play crucial roles in enhancing the performance of metallic nanoparticles for drug delivery. Further research is needed to optimize these strategies and to overcome the challenges associated with nanoparticle-based drug delivery [82].

The fabrication and functionalization of nanoparticles are critical steps in their development for clinical applications. However, these processes can be complex and challenging to scale up. For instance, the synthesis of nanoparticles often requires precise control over the reaction conditions to ensure uniform size and shape [83]. This uniformity is crucial as it directly impacts the nanoparticles' behavior in biological systems, including their circulation time, biodistribution, and cellular uptake. Achieving such precision on a large scale, while maintaining cost-effectiveness, remains a significant challenge in the field [84].

Furthermore, the functionalization of nanoparticles with targeting ligands or drug molecules requires careful control over the surface chemistry [85]. This process, known as bioconjugation, involves attaching specific molecules to the nanoparticle surface, which can enhance their stability, prevent non-specific interactions, and enable precise targeting. However, bioconjugation can be a complex process, requiring specialized knowledge and techniques. Moreover, the bioconjugated nanoparticles must retain their functionality after the modification, which adds another layer of complexity to the process [86].

Another major concern for the clinical translation of metallic nanoparticles is their potential toxicity. Nanoparticles can interact with biological systems in unintended ways, leading to potential adverse effects such as oxidative stress, inflammation, and cytotox-

icity [87–89]. These interactions can be influenced by various factors, including the size, shape, surface charge, and coating of the nanoparticles. Therefore, extensive in vitro and in vivo safety testing is required to assess the potential risks associated with nanoparticle-based therapies.

Regulatory hurdles also pose significant challenges for the clinical translation of metallic nanoparticles. Nanoparticle-based systems are often considered novel therapies and are therefore subject to additional scrutiny by regulatory agencies such as the FDA and EMA. These agencies require extensive data on the safety, efficacy, and quality of nanoparticle-based therapies before they can be approved for clinical use. This can involve conducting rigorous preclinical and clinical trials, which can be time-consuming and costly.

Lastly, the heterogeneity of diseases, such as cancer, complicates the design of universally effective nanoparticle systems. Different types of cancer cells can express different levels of target receptors, which can affect the efficacy of targeted drug delivery [90]. Moreover, the tumor microenvironment, which can vary greatly among patients and even within the same tumor, can influence the delivery and efficacy of nanoparticles. Therefore, personalized approaches may be needed to fully harness the potential of nanoparticle-based therapies for cancer treatment.

In conclusion, while the clinical translation of metallic nanoparticles for targeted drug delivery holds great promise, it is important to address these challenges to ensure the safe and effective use of these therapies in patients.

16. Challenges and Barriers in Clinical Translation

Accumulation in Scavenger Cells

One of the most formidable barriers to the clinical application of metallic nanoparticles is their unintended accumulation in the reticuloendothelial system (RES), particularly in the liver and spleen cells [91]. This not only diverts nanoparticles away from the target pathological site but also raises concerns about systemic toxicity and immunogenicity. Scavenger receptors like SR-A1, SR-B1, LOX-1, and MARCO play a pivotal role in this context, recognizing nanoparticles through various molecular patterns [91].

Various strategies have been proposed to address this issue. For instance, the transient saturation of RES cells through the use of commercial liposomes has been demonstrated to be effective, along with preconditioning strategies like in situ stealth coating of liver scavenger wall cells using a two-armed PEG [92]. These RES blockading strategies have shown reduced RES uptake of nanoparticles. To minimize macrophagic scavenger cell recognition, nanoparticles can be coated with hydrophilic polymers like PEG, zwitterionic ligands, or CD47 "do not eat me" signals. CD47 interacts with SIRPα on macrophages, offering a self-recognition cue that prevents phagocytosis—note that SIRPα is not a scavenger receptor [93]. Glycan modifications like sialic acid or glycosaminoglycans can also assist nanoparticles in evading scavengers. In addition to coatings, particle shape and deformability influence macrophage uptake. Filamentous, worm-like micelles show longer circulation times compared to spherical nanoparticles. Soft hydrogel particles can maneuver through biological barriers, thus evading filtration organs [94].

17. Endosomal Entrapment

Endosomal entrapment presents another significant barrier, especially for nanoparticles intended for gene delivery applications, such as those coated with small interfering RNA (siRNA). Upon cellular internalization, these nanoparticles often find themselves trapped within endosomes, limiting their therapeutic efficacy. To tackle this, hydroxychloroquine, a well-known endosomal escape-enhancing agent, can be conjugated onto the surface of siRNA-coated gold nanoparticles [95,96]. This specialized surface modification not only ensures more effective endosomal escape but also enhances the cytosolic delivery of the therapeutic genes. Traditional methods for enhancing endosomal escape include the use of pH-sensitive polymers, pore-forming peptides, and fusogenic lipids. These substances interact with the endosomal membrane in the acidic intracellular environment,

inducing membrane destabilization and thereby facilitating the release of the nanoparticle payload into the cytoplasm [97]. In addition to chemical strategies, physical methods such as photothermal disruption of endosomes upon laser irradiation have been explored. Collectively, these approaches signify that a multifaceted strategy, combining both chemical modifications and physical methods, is essential for overcoming the dual challenges of RES accumulation and endosomal entrapment.

18. Low Delivery Efficiency and Poor Clinical Translation

One of the main challenges is the low delivery efficiency to solid tumors and poor clinical translation. This can be attributed to various factors, including the characteristics of the nanocarriers and macromolecules, vascular and physiological barriers, the heterogeneity of tumor blood supply, and the transport and penetration depth of nanoparticles in the tumor matrix [98]. To overcome these challenges, it is necessary to address the barriers that affect the efficiency of the enhanced permeability and retention (EPR) effect for nanoparticle delivery systems [93].

19. Limited Tumor-Targeting Efficiency

Another challenge is the limited tumor-targeting efficiency of nanoparticles. The number of biological receptors on the tumor cell surface is intrinsically limited, resulting in saturated nanoparticle binding [94]. Additionally, tumor heterogeneity can lead to the expression of different types and amounts of targetable receptors, necessitating the consideration of alternative active targeting strategies.

20. Protein Corona Formation

Protein corona formation on the surface of nanocarriers is another barrier to clinical translation. Protein corona can affect targeting yields and direct unfavorable biodistribution, hindering the specific delivery of drugs [99].

Biocompatibility and In Vivo Model Selection

Furthermore, the evaluation of surface-modified nanoparticle biocompatibility and in vivo model selection is an area that requires improvement. While fabrication and assessment techniques for nanoparticles have advanced, the evaluation of their interaction with the immune system has lagged behind. Standardized pathways for evaluating biocompatibility and selecting appropriate in vivo models can facilitate clinical translation [100].

21. Potential and Conclusion

Despite these challenges and barriers, surface modification of metallic nanoparticles for targeting drugs holds promise for clinical translation. For example, magnetic iron oxide nanoparticles have shown potential as multifunctional nanoparticles for clinical translation due to their superparamagnetic properties and ability to be easily tailored with targeting moieties, fluorescence dyes, or therapeutic agents [101,102]. In conclusion, overcoming these challenges will require addressing the barriers associated with the enhanced permeability and retention effect, developing alternative targeting strategies, optimizing surface modifications, and improving the evaluation of nanoparticle biocompatibility.

21.1. Regulatory Approvals for Metallic Nanoparticles

Hensify®/NBTXR3, developed by Nanobiotix, are crystalline hafnium oxide nanoparticles, 20–50 nm in size, that are designed to enhance radiotherapy. The nanoparticles absorb energy from ionizing radiation and amplify localized energy transfer to tumor tissues, leading to increased tumor cell death. Hensify received FDA approval in 2019 through the accelerated pathway for treating locally advanced head and neck squamous cell carcinoma. It is currently undergoing trials for other cancer types.

NanoTherm®, by MagForce AG, contains 15 nm aminosilane-coated iron oxide nanoparticles that generate heat through magnetic hyperthermia. It was approved by the EMA in

2010 for therapy of recurrent glioblastoma multiforme and is also being investigated for pancreatic and prostate cancers. NanoTherm is delivered directly into tumors by injection, then activated by an alternating magnetic field generator.

Feridex®/Endorem® are iron oxide nanoparticles, 80–150 nm in size, coated with dextran. They were developed by AMAG Pharmaceuticals and approved by the FDA in 1996 as MRI contrast agents for imaging the liver, spleen, and lymph nodes. Feridex was commonly used for detecting liver lesions until it was discontinued from markets in 2008.

21.1.1. Ferumoxtran-10/Combidex®/Sinerem®

Approved by the FDA in 2005, Ferumoxtran-10, commercially known as Combidex® or Sinerem®, are ultrasmall superparamagnetic iron oxide nanoparticles designed specifically for imaging lymph node metastases. Their ultrasmall size allows for rapid extravasation from the vascular compartment, thereby enhancing their specificity for lymphatic tissues. This makes them particularly valuable for assessing the spread of cancers like melanoma or breast cancer to lymph nodes.

21.1.2. GastroMARK™/Umirem®/Ferumoxsil

GastroMARK™, also known as Umirem® or Ferumoxsil, received FDA approval as an MRI contrast agent with a specialized focus on delineating the bowel from other organs and tissues. This is particularly useful in diagnosing conditions like Crohn's disease, intestinal obstructions, or tumors in the gastrointestinal tract. The iron oxide nanoparticles in this agent improve the contrast between the bowel and surrounding tissues, making it easier for clinicians to identify abnormalities.

21.1.3. Resovist®/Cliavist®/Ferucarbotran

Approved by the European Medicines Agency (EMA) in 2011, Resovist®, also known as Cliavist® or Ferucarbotran, is another iron oxide nanoparticle contrast agent, but its primary application is for visualizing liver lesions. The nanoparticles are uptaken by the liver's Kupffer cells, enhancing the contrast in MRI scans. This makes it particularly useful for detecting liver metastases or assessing the severity of liver diseases like cirrhosis or hepatitis.

In summary, regulatory agencies have approved various metallic nanoparticles like hafnium oxide and iron oxide for diverse applications in cancer therapy, medical imaging, and bowel delineation, showing progress in the clinical translation of nanotechnology.

22. Conclusions

In summary, this manuscript offers an in-depth exploration of the role of metallic nanoparticles in drug delivery systems, emphasizing the critical importance of surface modification for enhanced therapeutic outcomes. From historical perspectives to current applications in treating conditions like cardiovascular diseases and diabetes, metallic nanoparticles have demonstrated exceptional versatility. The text further highlights various surface modification strategies that have been employed, such as polymer coating, DNA adsorption, and the use of targeting ligands for both active and passive targeting [103,104].

Despite these advancements, the work acknowledges the challenges that impede clinical translation. Accumulation in the reticuloendothelial system, endosomal entrapment, and the complex landscape of tumor heterogeneity remain hurdles to effective drug delivery. Various strategies to overcome these challenges, such as PEGylation and alternative targeting strategies, are discussed, drawing attention to the need for ongoing research.

Additionally, the manuscript underscores the significance of regulatory considerations by citing FDA/EMA-approved metallic nanoparticles. This serves as an impetus for more robust clinical studies and regulatory discussions.

In closing, while the field of metallic nanoparticles for drug delivery is laden with challenges, it also presents numerous avenues for groundbreaking advancements. Through continued interdisciplinary efforts in surface modification, targeting strategies, and reg-

ulatory compliance, metallic nanoparticles hold the promise to revolutionize the future landscape of drug delivery systems.

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