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Advantages and limitations of nanostructures for biomedical applications

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Abstract

This review examines recent progress in developing nanoscale drug delivery systems for biomedical applications. Key nanocarriers, including inorganic nanoparticles, dendrimers, protein nanoparticles, polymeric micelles, liposomes, carbon nanotubes (CNTs), quantum dots (QDs), and biopolymeric nanoparticles, were summarized. Compared with free drugs, the tunable physicochemical properties of these materials allow for the encapsulation of therapeutics and improved pharmacokinetics. However, limitations such as toxicity, poor biodegradability, lack of controlled release, and low encapsulation efficiency remain. Inorganic nanoparticles exhibit issues with accumulation and toxicity. Dendrimers require complex syntheses and demonstrations of long-term safety. Protein nanoparticles suffer from low drug loading and stability. Polymeric micelles have stability and tumor penetration limitations. Liposomes exhibit low encapsulation efficiency and rapid clearance. Carbon nanotubes demonstrate toxicity and poor aqueous solubility. Quantum dots contain heavy metals, leading to toxicity. Biopolymeric nanoparticles have low stability and control over release kinetics. Strategies such as surface engineering with polymers and ligands aim to enhance nanoparticle targeting and biocompatibility. The combination of nanostructures in hybrid systems aims to synergize benefits while mitigating individual limitations. Stimulus-responsive and multifunctional nanoparticles enable triggered release and imaging capabilities. Overall, continued research into novel bioinspired designs, smart responsiveness and hybrid approaches is critical to fully realize the clinical potential of engineered nanomedicines for advanced drug delivery applications.

Key words: drug delivery, nanoparticles, nanomedicine, targeted delivery, clinical translation

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Introduction

Modern encapsulation methods demonstrate an advantage over conventional methods of delivering biologically active substances to the target site.[1] Nanostructures are materials with at least 1 dimension in the 1–100 nm range. Their small size imparts novel optical, electronic and chemical properties compared to those of bulk materials. This has generated great interest in using nanostructures for biomedical applications such as drug delivery, bioimaging and biosensing.[2,3] However, the unique properties of nanostructures can also lead to toxicity, making it critical to consider both advantages and limitations during development.[4,5]

Nanocapsules (NCs) can target and enter select tissues at the molecular level. They provide a high absorption rate, increased cellular uptake, and precise and targeted delivery of substances to target cells without interacting with the environment.[6] In addition, nanoencapsulation of drugs results in improved absorption of poorly soluble drugs, reduces drug toxicity and minimizes or suppresses resistance resulting from physiological barriers in the body.[7]

Over the past few decades, nanostructures of various shapes and sizes have been developed for encapsulating many substances, including inorganic nanoparticles, dendrimers, protein nanoparticles, polymeric micelles, liposomes, carbon nanotubes (CNTs), quantum dots (QDs), and biopolymeric nanoparticles. Table 1 summarizes the advantages and disadvantages of these nanoparticles.[8] Figure 1 summarizes main classes of nanoparticles and their properties.

The current solution to the limitations of using each of these nanostructures individually is to use a combination of different nanostructures, resulting in a hybrid nanocapsule.[9,10] On the other hand, protein nanoparticles have attracted great interest in the field of nanotechnology due to their excellent biodegradability, low toxicity, water solubility, and high similarity to the components of the extracellular matrix.[11,12] The surface of protein nanoparticles can be chemically functionalized by adding directing ligands, such as peptides, antibodies, vitamins, hormones, or enzymes.

Table 1. Advantages and drawbacks of nanostructures[8]

Nanostructure	Advantages	Drawbacks
Inorganic nanoparticles	facile synthesis easy surface functionalization good stability versatility exceptional optical and electronic properties	nonbiodegradable toxicity coating required
Dendrimers	synthesis of well-defined structures high chemical and biological stability efficacy, purity and long shelf life high surface area, loading capacity and targeting biodegradable and biocompatible	complex synthetic route low yield and difficulties in obtaining higher generations
Protein nanoparticles	low toxicity biodegradability good mechanical properties versatility	chemical modifications of their surface are usually required to yield stimulus-responsive nanomedicines low drug loading efficiency
Polymeric micelles	efficient carrier system for hydrophilic drugs biodegradable and biocompatible self-assembling potential targeting functional modification low toxicity	short circulation times in blood-specific cytotoxicity need of surface modifications
Liposomes	amphiphilic structures easy surface functionalization biocompatibility	conventional liposomes: instability insufficient drug loading faster drug release shorter circulation times in blood
Carbon nanotubes	quasi-1D nanostructure easy surface functionalization exceptional surface area and cell membrane penetrability efficient loading remarkable optical and electronic properties	poor solubility in many solvents including water low biodegradability toxicity
Quantum dots	good solubility in water after surface modification strong fluorescence intensity	nonbiodegradable cytotoxicity to lung cells induction of oxidative stress
Biopolymeric nanoparticles	isolated from different natural resources (abundance) excellent geometrical dimensions high specific surface area good mechanical and barrier properties lack of toxicity biodegradable and biocompatible	hydrophobic materials poor encapsulation efficiency of medicines resistance against enzymatic degradation

These ligands accurately identify cells and tissues, promoting and improving the targeting mechanism.[13,14]

Objectives

This review summarizes the current knowledge on major nanostructure classes for biomedical applications and discusses their advantages and limitations for drug delivery, bioimaging and biosensing. We discuss key challenges related to toxicity, stability, pharmacokinetics, and accumulation that need to be addressed to enable the clinical translation of nanostructures. Our study highlights promising strategies for improving biocompatibility and innovative stimulus-responsive approaches that could optimize nanostructures for biomedicine.

Inorganic nanoparticles

Inorganic nanoparticles such as gold, iron oxide and silica nanoparticles have been widely studied for biomedical applications due to their unique properties and relative ease of synthesis.[15] Gold nanoparticles exhibit strong surface plasmon resonance, allowing for enhanced contrast in imaging modalities such as computed tomography (CT), photoacoustic imaging and multiphoton microscopy.[16] The inert nature of these materials also makes them useful for surface-enhanced Raman spectroscopy sensing.[17] Iron oxide nanoparticles demonstrate superparamagnetism, enabling their use as T2 contrast agents for magnetic resonance imaging (MRI) and magnetic particle imaging.[18] Mesoporous silica nanoparticles have high surface areas and pore volumes, permitting high payloads of imaging agents and therapeutics.[19]

However, toxicity concerns remain a significant barrier to the clinical translation of many nanomaterials.[20] Factors influencing toxicity include composition, size, shape, surface charge, and coating.[21] Inorganic nanoparticles tend to accumulate in organs such as the liver and spleen.[22] Iron oxide nanomaterials could alter iron homeostasis.[23] Silica nanoparticles have been associated with liver enzyme release.[24] Strategies, such as surface coating with proteins or polymers (e.g., polyethylene glycol (PEG); PEGylation), are being explored to improve biocompatibility.[25] The need for surface modification also complicates regulatory approval.[26] There are still open questions regarding the long-term safety, metabolism and excretion of nanoparticles.[27] Their non-biodegradable nature may lead to potential accumulation and unintended effects.[28] Overall, a thorough evaluation of nanoparticle toxicity through both in vitro and in vivo studies across multiple models is necessary to enable successful clinical translation.[29]

Dendrimers

Dendrimers are highly branched polymeric nanostructures with definable compositions and monodisperse size distributions.[30] Their stability, high loading capacity and modifiable surfaces are beneficial for drug and gene delivery.[31,32] For example, polyamidoamine (PAMAM) dendrimers have been extensively studied for use in siRNA and drug delivery due to their cationic surface charge, which allows electrostatic complexation with nucleic acids.[33] Strategies such as PEGylation or acetylation have been used to reduce cytotoxicity.[34] Drawbacks include complex syntheses, especially for higher generations, and the need to demonstrate long-term safety.[35] Toxicity has been linked to cationic charge and immunostimulation, although neutral and anionic dendrimers appear safer.[36] Additional studies focused on metabolism and excretion over months or years are still needed.[37] Overall, dendrimers are a versatile platform that shows promise for drug and gene delivery, but further studies are needed to establish clinical translatability.[38]

Protein nanoparticles

Nanoparticles fabricated from proteins such as albumin have good biocompatibility and biodegradability.[39] As natural materials, they are generally nontoxic and do not elicit unwanted immunological responses.[40] Albumin is particularly attractive due to the presence of numerous functional groups, which enable modifications as well as high thermal and aqueous solution stability.[41] Albumin nanoparticles can transport drugs via both encapsulation in the core and absorption on the surface.[42] They have been applied for the delivery of anticancer compounds, including paclitaxel, doxorubicin and methotrexate.[43–45]

However, under physiological conditions, albumin undergoes relatively rapid enzymatic degradation and breakdown, which can limit controlled drug release.[46] Therefore, it is important to modify the surface of these carriers to impart desired stimuli-responsive release properties.[47] For example, researchers have developed a new drug delivery system based on amine-functionalized mesoporous silica (SBA-15) loaded with bovine serum albumin (BSA), which was subsequently coated with a thin layer of poly(acrylic acid) (PAA). It was found that BSA is released from such a system at a higher pH of 7.4 rather than at a lower pH of 1.2. This finding suggested that this approach may be useful for the release of protein or drugs in environments with higher pH values, such as the small intestine or colon.[48] The proposed drug carrier utilizes electrostatic interactions between the protein and the silica nanoparticles and regulates drug release through changes in the pH of the environment. Therefore, these findings highlight the prospect of targeted delivery of protein drugs to specific organs of the gastrointestinal tract. Another strategy of targeted delivery is crosslinking albumin using aldehydes, which enhances its stability and allows for the conjugation of ligands recognized by cancer cells.[49]

For some hydrophobic drugs, a low loading efficiency of less than 10% into albumin nanoparticles has been

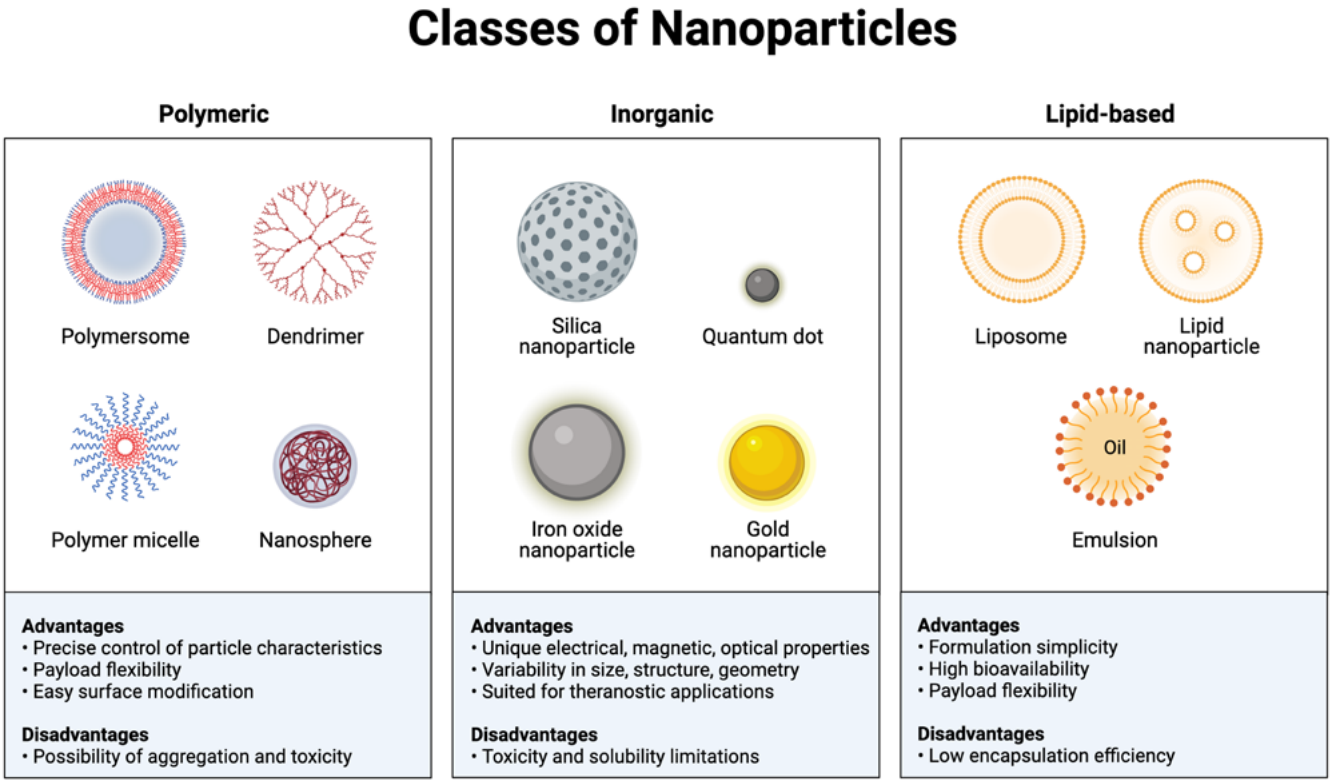

Fig. 1. Main classes of nanoparticles and their properties. The sizes given are the most common diameter ranges of these nanoparticles. However, these are approximate values because the dimensions of actual nanoparticles depend on many factors, such as the method of their synthesis or the materials used

demonstrated.[50] This may require surface modification with amphiphilic substances or solvent saturation techniques.[51] Other limitations include a potentially overly slow release of active compounds, as well as difficulties with scalability and standardization of manufacturing processes.[52]

The main methods for preparing albumin nanoparticles include desolvation, self-assembly, thermal gelation, spray-drying, emulsification, double emulsification, nanoparticle albumin-bound (Nab)-technology, and pH coacervation.[51] The resulting carriers differ in size, morphology and surface properties depending on the production conditions. For example, high temperature and pH lead to the aggregation and formation of larger particles.[50] In addition to albumin, other proteins, such as gelatin, are used. Gelatin can ionize and form complexes with nucleic acids.[52] However, the surface properties of these materials are inferior to those of albumin and their stability is lower.

Despite certain challenges, protein nanoparticles constitute a promising therapeutic platform, and further research into improving their pharmacokinetic and pharmacodynamic properties is warranted.[53] For instance, the modification of albumin with PEG can increase the plasma circulation time and tumor accumulation via the enhanced permeability and retention (EPR) effect.[54] Conjugation with targeting ligands enables active targeting of cancer cells.[45] Novel approaches also include using albumin in hybrid nanostructures together with lipids, polymers, or CNTs.[55] These systems combine the advantages of different materials and may enhance therapeutic performance.

In summary, protein nanoparticles, especially albumin-based nanoparticles, demonstrate several promising properties as anticancer drug carriers. One successful example of protein nanoparticles already used in clinical practice is albumin-bound paclitaxel nanoparticles, which are sold under the name Abraxane®. This drug was obtained through high-pressure homogenization of a drug and bovine albumin solution, resulting in nanoparticles approx. 130 nm in size that are easy to administer intravenously. The production of Abraxane could be easily scaled up to an industrial level without loss of stability or therapeutic activity. Therefore, methods such as simple pressure homogenization used in Abraxane constitute a promising strategy for the development of other albumin-based formulations. Nevertheless, there is still a need to optimize advanced protein nanostructures in terms of pharmacokinetic properties and drug release profiles.

Polymeric micelles

Polymeric micelles formed through the self-assembly of amphiphilic block copolymers have emerged as promising carriers for delivering hydrophobic drugs such as anticancer agents.[56] The core-shell nanostructure comprises an inner hydrophobic domain stabilized by a hydrophilic

outer layer, allowing encapsulation of water-insoluble drugs within the core. Polymeric micelles can enhance the solubility, bioavailability and tumor-targeting potential of hydrophobic therapeutics.[57] Common polymers investigated include PEG, poly(epsilon-caprolactone) (PCL) and poly(lactic acid) (PLA) due to their biocompatibility and biodegradability. Polyethylene glycol results in an outer brush-like "stealth" layer that inhibits protein adsorption and opsonization, thereby increasing circulation time.[58]

A key advantage of polymeric micelles is their ability to accumulate in tumors through the EPR effect from leaky tumor vasculature and poor lymphatic drainage.[56] Passive targeting of tumors has been demonstrated with various micelle formulations.[59] Active targeting can also be achieved by attaching targeting ligands to recognize receptors overexpressed on cancer cells.[6] However, limitations exist, such as a lack of adequate tumor penetration into poorly permeable tumors and toxicity concerns.[60]

Stability is a major issue affecting polymeric micelle drug carriers. Upon dilution, micelles can dissociate below the critical micelle concentration, interact with cells/proteins or undergo changes in temperature, pH or ionic strength.[59] This can lead to premature drug release during circulation. Strategies to improve stability include core crosslinking, increasing polymer hydrophobicity, introducing hydrogen bonding, and shell crosslinking.[61] Shell crosslinking with disulfide bonds can provide redox-responsive release intracellularly.[62]

Controlling the rate of drug release remains a key challenge. Drug release from polymeric micelles relies on diffusion and polymer erosion mechanisms. Diffusion-controlled release can be too slow, while erosion-dominated release decreases control.[62] Tuning polymer properties, such as molecular weight and copolymer block ratios, modulates degradation.[61] The introduction of stimuli-responsive components triggers release in response to changes in pH, temperature or enzymatic activity.[63]

Another major limitation is the systemic toxicity of polymers and degradation products. Polymers need to be safely eliminated from the body. Polymer cytotoxicity has been associated with effects on membranes, protein binding, mitochondria, and the induction of apoptosis. Strategies to reduce toxicity include utilizing biodegradable and biocompatible polymers, limiting molecular weights, and optimizing micelle stability to prevent premature release.[64] Extensive in vitro and in vivo testing is critical.[65,66]

While polymeric micelles offer versatility in design and tunable properties for cancer therapy, key challenges in stability, drug release kinetics, tumor penetration, and toxicity must still be overcome for clinical translation.[67,68] Further optimization of polymeric micelle systems through novel bioinspired designs and stimulus-responsive approaches continues to be an active area of pharmaceutical research.[69,70]

Liposomes

Liposomes are biocompatible vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs.[71] The tunable surface chemistry and composition of these materials make them versatile drug carriers.[72,73] Conventional liposomes constructed from phospholipids such as phosphatidylcholine have been extensively investigated for the delivery of anticancer agents, antibiotics, peptides, proteins, and nucleic acids.[74,75] Hydrophobic drugs can be incorporated into the lipid bilayer, while hydrophilic drugs can be entrapped in the aqueous core.[76]

However, conventional liposomes have significant limitations, including poor stability, short circulation half-lives and low encapsulation efficiency. Liposomes are prone to aggregation, fusion, lipid oxidation, and enzymatic degradation.[77] Upon intravenous administration, liposomes are rapidly cleared by the mononuclear phagocyte system, limiting bioavailability.[78] Strategies to overcome these issues include the use of a cholesterol formulation to strengthen membranes, PEGylation to provide a steric barrier against opsonization, and charge modulation to increase stability.[79]

Another key challenge is the low encapsulation efficiency of conventional formulations for hydrophilic drugs. Remote loading approaches have been developed to actively load preformed liposomes using an ionic or pH gradient. Active loading provides high-efficiency encapsulation but requires an optimized lipid composition and consideration of drug ionization. Alternative methods using new drug encapsulation methodologies, such as the use of genetically engineered elastin-like recombinamers and supercritical fluid techniques, could lead to more precise drug delivery systems.[80]

Controlling the release rate of encapsulated drugs also remains an issue. Conventional liposomes exhibit burst release and limited ability to provide sustained, localized delivery. Stimulus-responsive liposomes engineered to be thermosensitive, pH sensitive or degrade enzymatically allow for triggered release.[78] Localized delivery can also be achieved using liposomes embedded within hydrogel matrices.[81]

Overall, liposomal drug carriers have progressed significantly with innovations in formulation, stimulus responsiveness and surface functionality. However, the stability, encapsulation efficiency, sustained release, and therapeutic efficacy of these materials must continue to be enhanced for clinical translation.[82] Further advances in liposome technology through multicomponent systems and synergistic delivery with external triggers show promise for cancer therapy.[83]

Carbon nanotubes

Carbon nanotubes have emerged as promising nanocarriers for drug delivery due to their high aspect ratio, ultrahigh surface area and ability to penetrate cells. Both

single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs) have been explored for biomedical applications. The needle-like shape of these cells allows for the piercing of cell membranes, enabling penetration of the cytoplasm and nucleus.[84] This approach facilitates the delivery of therapeutics such as small molecule chemotherapeutics, proteins, peptides, and nucleic acids into hard-to-access cells. Carbon nanotubes also have a very high drug-loading capacity due to their extensive surface area. Drugs can be loaded inside CNTs, in the interstitial spaces between nanotubes in bundles or attached to the external surface.[85]

However, concerns about CNT toxicity have hindered its clinical translation. Toxicity is influenced by structural factors such as length, diameter, surface chemistry, and degree of aggregation. Longer CNTs appear more toxic due to frustrating phagocytosis, where immune cells cannot fully engulf lengthy nanotubes.[86] Chemical functionalization of CNT surfaces with -COOH groups reduces toxicity compared to that of pristine nanotubes.[87] PEGylation is another strategy for decreasing immunogenicity and increasing biocompatibility. Carbon nanotubes have also demonstrated dose-dependent toxicity to vital organs such as the lungs, liver and kidneys after intravenous administration.[88]

Another major limitation of CNTs is their non-biodegradable nature, which can lead to long-term accumulation in the body.[89] To date, attempts have been made to develop biodegradable CNTs using techniques such as oxidation cutting, polymer coating and nucleic acid hybridization, but with only partial degradation.[90] Carbon nanotube aggregation and poor solubility in aqueous solutions also pose challenges.[91] Ultrasonication and the use of surfactants such as sodium dodecyl sulfate improve dispersibility but may inadvertently increase toxicity.[89] An alternative method for dispersing CNTs is their noncovalent functionalization with amphiphilic polymers or DNA; however, maintaining the stability of CNTs in a biological environment remains a challenge.[92]

A promising strategy to improve the biocompatibility and solubility of CNTs while decreasing their systemic toxicity is encapsulation of CNTs in micelles, liposomes or hydrogel particles.[93] Although CNTs have great potential as nanocarriers for drugs, overcoming key limitations related to their toxicity, degradability and solubility is necessary. Possible solutions include engineering new hybrid structures that combine CNTs with organic and polymeric materials. This approach allows the unique properties of CNTs to be exploited for drug delivery and release.[94]

Quantum dots

Quantum dots are semiconductor nanocrystals that possess unique optical properties derived from quantum confinement effects.[95] By tuning the QD size and composition, the fluorescence emission can be precisely controlled from the visible to near-infrared range.[96] This has enabled widespread exploration of QDs for biomedical imaging both in vitro and in vivo.[97] Compared with organic dyes and fluorescent proteins, QDs have greater brightness, greater stability against photobleaching, and narrower emission spectra. These advantages have led to QD applications in immunofluorescence assays, targeted cancer cell imaging, lymph node mapping, and multifunctional nanoparticles.[98]

However, the toxicity of QDs remains a major concern hindering clinical translation. Most QDs contain heavy metal components such as cadmium that are known to be cytotoxic.[99] Metal release through QD oxidation or degradation is a primary toxicity mechanism.[100] Quantum dots can also induce reactive oxygen species (ROS) formation, leading to oxidative stress and inflammation.[101] Coating strategies using inert shells and polymers aim to prevent direct QD exposure, but stability and potential leaching issues persist. The coating thickness and charge affect cellular interactions and toxicity profiles. Furthermore, there are remaining questions regarding the long-term accumulation, metabolism and excretion of QDs in vivo.[102]

A key limitation of QDs is their non-biodegradable nature. Attempts have been made to develop biodegradable QDs using less toxic elements such as indium, zinc and silicon.[103] Combining QDs with organic polymers and biomolecules is another approach to impart biodegradability.[104] However, maintaining the optical properties of QDs after biodegradation remains challenging. Engineering smaller QDs less than 5 nm in diameter may enable renal clearance and prevent bioaccumulation.[105] However, ultrasmall QDs sacrifice brightness and tend to be less stable.

The solubility and dispersion of QDs in biological environments also require optimization. Quantum dot surface modification with hydrophilic ligands, polymers, silica shells, and amphiphilic coatings enhances water solubility.[106] Conjugation to proteins, peptides and DNA improves colloidal stability and biocompatibility.[107] Incorporating QDs into larger nanocarriers such as liposomes may help overcome limitations related to their toxicity and solubility.[108] However, maintenance of fluorescence and prevention of leaching needs to be demonstrated.

Overall, despite their advantageous optical properties, QDs still have significant unresolved issues associated with the toxicity of heavy metals they contain, lack of biodegradability, oxidative effects, and colloidal stability. Before fully harnessing their potential in biomedicine, advanced engineering approaches are necessary to address these key challenges.[99,109]

Biopolymeric nanoparticles

Nanoparticles fabricated from natural biopolymers have attracted increasing interest as drug delivery systems due to their biocompatibility, biodegradability and abundance in nature. Chitosan, alginate, gelatin, and albumin are

among the most extensively explored materials.[110] Chitosan is derived from chitin found in crustacean shells and has mucoadhesive properties useful for mucosal delivery.[111] The alginate obtained from seaweed contains carboxyl groups that enable crosslinking for hydrogel particle formation.[112] Gelatin is derived from collagen and has excellent cell adhesion potential and low antigenicity. The serum albumin concentration is known to be derived from serum and has versatile drug-binding abilities.[113] These biopolymers are generally regarded as safe and have low toxicity.

However, biopolymeric nanoparticles, especially those containing hydrophobic drugs, have limitations, including poor encapsulation efficiency.[110] The porous structures of these materials allow rapid diffusion and burst release of payloads. Chemical or ionic crosslinking is often required to reinforce structures, control swelling and enable sustained release.[114] However, excessive crosslinking can improperly retard drug release. Biopolymers also tend to have low stability against enzymatic degradation, limiting their circulation time. Shell hardening techniques such as polyelectrolyte coating provide some protection.[115]

Another challenge is scaling up biopolymeric nanoparticle production while maintaining consistent physicochemical properties between batches. Variables such as polymer source, purification methods and crosslinking affect reproducibility.[110] The storage stability over the shelf life also needs to be demonstrated. Sterilization methods can impact drug release characteristics and particle integrity.[116]

Furthermore, compared with synthetic polymers, most biopolymers lack functional groups for facile surface modification and ligand conjugation. This restricts opportunities for active targeting. The intrinsic immunogenicity of some biopolymers, such as chitosan, may also cause concerns.[117]

In summary, biopolymeric nanoparticles offer the advantages of biocompatibility, sustainability and tunable properties that provide versatility in drug delivery design. However, continued research to improve the encapsulation efficiency, colloidal and enzymatic stability, scale-up processes, and reproducible manufacturing is needed to fully harness the potential of these materials.

Limitations

While this review provides a broad overview of nanostructures for biomedical applications, it has certain limitations that should be acknowledged. First, the focus was on summarizing key nanostructure classes without comprehensive coverage of all existing and emerging nanostructures. However, certain novel systems, such as protein-polymer hybrids, DNA origami and lipid-polymer assemblies, have not been discussed in depth. Second, the review was limited to nanostructures for drug delivery, bioimaging and biosensing, while excluding other biomedical areas such as tissue engineering, biomarkers and nanostructured surfaces. Furthermore, only selected key references were cited for each nanostructure type and application due to space constraints. The examples highlighted specific advantages and challenges but did not capture all ongoing research or clinical developments related to nanostructures.

Conclusions

Nanotechnology has enabled the engineering of nanoparticles with tremendous potential for targeted drug delivery and controlled release. Key advancements have been made in the field of inorganic nanoparticles, dendrimers, protein nanoparticles, polymeric micelles, liposomes, CNTs, QDs, and biopolymeric nanoparticles. Each platform offers unique advantages but also limitations that must be mitigated. Surface modification strategies, including PEGylation and ligand bioconjugation, can enhance nanoparticle biocompatibility, stability and active targeting abilities. Stimulus-responsive engineered nanoparticles enable triggered release in response to tumor microenvironment cues. The combination of nanostructures in multifunctional hybrid systems aims to synergize benefits while compensating for individual drawbacks. However, issues related to scale-up manufacturing, storage stability, pharmacokinetics, tumor penetration, and clinical toxicity remain barriers to translation. Overall, continued interdisciplinary research across chemistry, materials science, biology, and medicine focused on bioinspired designs, multifunctionality and novel responsiveness mechanisms is critical to fully realize the clinical potential of engineered nanoparticles for advanced drug delivery.

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