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Carbon nanotubes: recent advances and future perspective in drug delivery

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KEYWORDS

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ABSTRACT:

Carbon nanotubes (CNTs) present promising prospects in drug delivery, owing to their distinctive physicochemical attributes. This review consolidates recent advancements and future trajectories in exploiting CNTs for drug conveyance applications. Functionalization methodologies of CNTs are scrutinized to augment biocompatibility, bolster drug encapsulation, and facilitate targeted delivery. Both covalent and non-covalent approaches are delineated, alongside surface modifications aimed at mitigating cytotoxicity concerns. Furthermore, the multifaceted applications of CNTs encompass delivery vectors for diverse payloads including small molecules, biologics, nucleic acids, and imaging agents. CNTs exhibit potential for precise targeting through ligand conjugation and stimuli-responsive release mechanisms, promising improved therapeutic outcomes. Despite progress, translation into clinical realms is impeded by safety apprehensions regarding CNT toxicity and regulatory exigencies. Further research is warranted to refine safety profiles and ensure regulatory compliance. Moreover, elucidating CNT pharmacokinetics and pharmacodynamics is crucial for comprehensive understanding and optimization. In synthesis, this review encapsulates strides in harnessing CNTs for drug delivery while delineating challenges and future trajectories. Through addressing these challenges and leveraging CNT properties, novel and efficacious drug delivery modalities with profound clinical ramifications can be envisioned.

Introduction

Carbon nanotubes (CNTs) have emerged as one of the most promising nanomaterials in various fields due to their exceptional physical, chemical, and mechanical properties[1]. These cylindrical nanostructures, composed of rolled-up graphene sheets, possess high aspect ratios, large surface areas, and unique electronic properties, making them highly attractive for numerous applications ranging from electronics to biomedicine[2]. In the realm of drug delivery, the utilization of CNTs offers several advantages over traditional delivery systems. The intrinsic properties of CNTs, such as their high surface area-to-volume ratio and ability to penetrate cell membranes, make them ideal candidates for encapsulating and delivering therapeutic agents to targeted sites within the body[3]. Additionally, their tunable surface chemistry allows for precise functionalization, enabling the attachment of targeting ligands and other biomolecules to enhance specificity and efficacy[4]. The motivation for harnessing CNTs in drug delivery stems from the need for more efficient and targeted therapeutic interventions. Conventional drug delivery systems often suffer from limitations such as poor bioavailability, off-target effects, and rapid clearance from the body[5]. By leveraging the

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unique properties of CNTs, researchers aim to overcome these challenges and develop novel delivery platforms capable of delivering therapeutics with improved precision, efficacy, and safety profiles[6].

This review aims to provide a comprehensive overview of recent advances and future perspectives in utilizing CNTs for drug delivery applications. We will delve into the various strategies employed for functionalizing CNTs to enhance biocompatibility, improve drug loading efficiency, and enable targeted delivery[7]. Furthermore, we will explore the diverse applications of CNT-based delivery systems in delivering a wide range of therapeutics, including small molecules, proteins, nucleic acids, and imaging agents[8]. Additionally, we will discuss the challenges and opportunities associated with translating CNT-based delivery systems from the laboratory to clinical settings. The scope of this review encompasses both experimental and theoretical studies, with a focus on highlighting the potential of CNTs as versatile platforms for drug delivery. By synthesizing the latest findings and insights from the literature, we aim to provide a comprehensive resource for researchers and practitioners interested in the burgeoning field of CNT-based drug delivery.

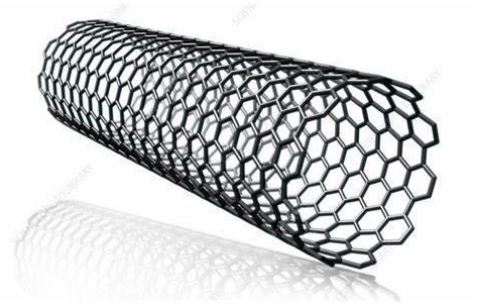

Figure 1: Carbon nanotube molecular model

Functionalization of Carbon Nanotubes for Drug Delivery

Carbon nanotubes (CNTs) possess inherently unique properties that make them attractive candidates for drug delivery applications[9]. However, to fully exploit their potential, it is often necessary to modify their surfaces through functionalization. Functionalization strategies can broadly be classified into covalent and non-covalent methods, each offering distinct advantages and challenges[10]. Additionally, surface modification techniques play a crucial role in enhancing biocompatibility, reducing toxicity, and improving drug loading capacity, thereby optimizing the performance of CNT-based drug delivery systems[11].

Covalent Functionalization

Covalent functionalization involves the chemical modification of CNT surfaces by forming strong, stable bonds between functional groups and the carbon atoms of the nanotube structure. This approach offers precise control over the type and density of functional groups attached to the CNTs, thereby enabling tailored surface properties and enhanced compatibility with biological systems[12,5]. One common method of covalent functionalization is the introduction of carboxyl or hydroxyl groups onto the CNT surface through oxidation processes such as acid treatment or electrochemical oxidation. These functional groups not only enhance water dispersibility but also serve as anchoring sites for further conjugation with targeting ligands or therapeutic molecules[13]. For example, carboxylated CNTs have been conjugated with antibodies or peptides for targeted drug delivery to specific cell types or tissues. Another covalent functionalization strategy involves the attachment of polymer chains onto the CNT surface[14]. Polymers such as polyethylene glycol (PEG) or polyethyleneimine (PEI) can be covalently grafted onto CNTs to improve

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biocompatibility, prolong circulation time, and reduce immunogenicity. Additionally, polymers can serve as carriers for hydrophobic drugs, enabling efficient encapsulation and controlled release[2,6]. Despite the advantages of covalent functionalization, this approach may also introduce defects or structural modifications to the CNTs, potentially altering their intrinsic properties. Moreover, the synthesis of covalently functionalized CNTs often requires harsh reaction conditions, which can lead to structural damage or aggregation[15].

Non-covalent Functionalization

Non-covalent functionalization methods rely on weak, reversible interactions such as π-π stacking, hydrophobic interactions, or electrostatic forces to attach functional molecules to the CNT surface[16]. Unlike covalent functionalization, non-covalent approaches typically preserve the integrity of the CNT structure and require milder reaction conditions, making them more suitable for preserving the intrinsic properties of CNTs[17]. One of the most used non-covalent functionalization strategies involves the adsorption or wrapping of surfactant molecules onto the CNT surface. Surfactants such as sodium dodecyl sulfate (SDS) or Triton X-100 can interact with the hydrophobic surface of CNTs through hydrophobic interactions, resulting in improved dispersion in aqueous solvents[5,7]. Additionally, surfactants can facilitate the loading and release of hydrophobic drugs by forming stable complexes with the CNTs. Another non-covalent approach is the use of biomolecules such as proteins, peptides, or nucleic acids to functionalize CNTs[18]. These biomolecules can selectively bind to specific sites on the CNT surface through complementary interactions, enabling targeted drug delivery or bio-sensing applications. For example, DNA-functionalized CNTs have been employed for the delivery of therapeutic nucleic acids or as biosensors for detecting biomolecular interactions[2]. Non-covalent functionalization offers several advantages, including simplicity, versatility, and reversibility. However, the stability of non-covalently functionalized CNTs may be compromised under physiological conditions, leading to premature drug release or aggregation. Additionally, the choice of surfactants or biomolecules must be carefully optimized to ensure compatibility with biological systems and minimize potential immunogenicity or cytotoxicity[10].

Surface Modification for Enhanced Biocompatibility and Drug Loading Capacity

In addition to functionalization strategies, surface modification techniques play a crucial role in optimizing the biocompatibility and drug loading capacity of CNT-based drug delivery systems. Surface modifications can be tailored to address specific challenges such as minimizing protein adsorption, reducing opsonization, or enhancing cellular uptake[19]. One common approach to enhancing biocompatibility involves the coating of CNTs with biocompatible polymers or biomolecules. For example, PEGylation, the attachment of PEG chains onto the CNT surface, has been widely used to improve the stealth properties of CNTs and reduce nonspecific interactions with biological components[2,20]. Similarly, the functionalization of CNTs with cell-penetrating peptides or other cell-targeting ligands can enhance cellular uptake and improve the efficacy of drug delivery. Moreover, surface modification techniques can be employed to increase the drug loading capacity of CNTs. Functional groups such as amine or thiol moieties can be introduced onto the CNT surface to enable covalent conjugation with therapeutic molecules[12]. Alternatively, mesoporous CNTs with high surface area and pore volume can be synthesized to encapsulate drugs within their internal cavities, allowing for controlled release and prolonged drug retention[21].

Targeted Delivery Using Carbon Nanotubes

Carbon nanotubes (CNTs) have garnered considerable interest in the field of drug delivery due to their potential for targeted delivery of therapeutic agents to diseased tissues. Targeted delivery offers several advantages over conventional drug delivery systems, including enhanced efficacy, reduced side effects, and improved patient compliance[22].

Ligand Conjugation for Specific Targeting

Ligand conjugation involves attaching targeting moieties, such as antibodies, peptides, or small molecules, onto the surface of CNTs to facilitate specific binding to receptors overexpressed on the surface of diseased cells or

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tissues[23]. This approach allows for precise localization of therapeutic agents, thereby minimizing off-target effects and maximizing therapeutic efficacy. For example, CNTs functionalized with targeting ligands that recognize cancer-specific biomarkers can selectively deliver anticancer drugs to tumor cells while sparing healthy tissues[24]. Similarly, targeted delivery to inflamed or diseased tissues can be achieved by conjugating CNTs with ligands that recognize endothelial cell adhesion molecules or inflammatory markers[25]. The choice of targeting ligands depends on the specific disease or condition being targeted. Antibodies or antibody fragments are commonly used for cancer targeting due to their high affinity and specificity for tumor-associated antigens. Peptides or small molecules may be preferred for targeting other diseases such as inflammatory disorders or infectious diseases[26].

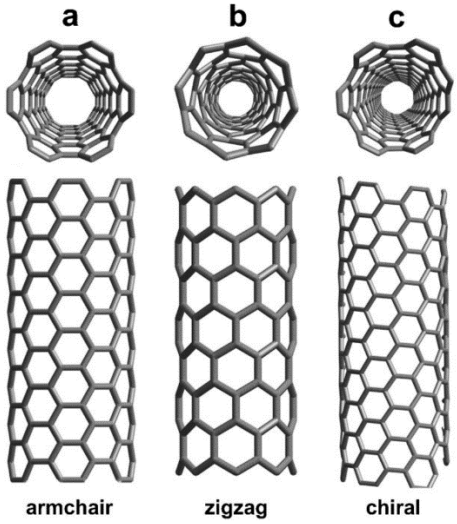

Figure 2: Types of carbon nanonubes

Stimuli-Responsive Drug Release from Carbon Nanotubes

Stimuli-responsive drug delivery systems enable controlled release of therapeutic agents in response to external stimuli such as pH, temperature, light, or magnetic fields[27]. By incorporating stimuli-responsive components into CNT-based delivery systems, researchers can achieve spatiotemporal control over drug release, further enhancing targeting efficacy and minimizing off-target effects[28]. For example, pH-responsive polymers or supramolecular assemblies can be conjugated onto the surface of CNTs, enabling selective release of encapsulated drugs in acidic tumor microenvironments. Similarly, light-responsive molecules such as azobenzene derivatives can be incorporated into CNT-based nanocarriers, allowing for on-demand drug release triggered by external light irradiation[29]. Moreover, magnetic nanoparticles or nanocrystals can be encapsulated within CNTs to enable magnetically guided drug delivery to specific anatomical sites or tissues. By applying an external magnetic field, CNT-based nanocarriers can be directed to the target site, where drug release is triggered by the application of a secondary stimulus[31,2].

Overcoming Biological Barriers for Enhanced Targeting Efficacy

Effective targeted delivery using CNTs requires overcoming various biological barriers encountered during the delivery process, including systemic circulation, extravasation, cellular internalization, and intracellular trafficking[32]. Strategies to enhance targeting efficacy

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involve optimizing the physicochemical properties of CNT-based delivery systems to improve circulation time, tissue penetration, and cellular uptake. Surface modification with stealth coatings such as polyethylene glycol (PEG) can prolong circulation time by reducing recognition and clearance by the reticuloendothelial system (RES)[21]. Additionally, optimizing the size, shape, and surface charge of CNTs can facilitate passive targeting through enhanced permeability and retention (EPR) effects, particularly in tumors with leaky vasculature[23].

Furthermore, functionalization with cell-penetrating peptides or other cell-targeting ligands can enhance cellular uptake and intracellular delivery of therapeutic agents[15]. By exploiting receptor-mediated endocytosis or membrane fusion mechanisms, CNT-based nanocarriers can overcome cellular barriers and deliver payloads directly to the cytoplasm or organelles of target cells[24]. Overall, targeted delivery using CNTs holds immense promise for improving the efficacy and safety of drug delivery systems. By combining ligand conjugation, stimuli-responsive drug release, and strategies to overcome biological barriers, researchers can develop highly selective and efficient CNT-based nanocarriers for a wide range of therapeutic applications[33].

Applications of Carbon Nanotubes in Drug Delivery

Carbon nanotubes (CNTs) have demonstrated versatile applications in drug delivery, offering unique advantages such as high drug loading capacity, tunable surface chemistry, and the ability to penetrate cellular membranes.

Delivery of Small Molecule Drugs

CNTs serve as efficient carriers for small molecule drugs, offering protection from degradation, enhanced solubility, and controlled release profiles[34]. Hydrophobic drugs can be encapsulated within the internal cavities of CNTs or adsorbed onto the surface through non-covalent interactions, while hydrophilic drugs can be conjugated via covalent bonding or encapsulated within polymer-coated CNTs[15,6]. The high surface area and aspect ratio of CNTs allow for high drug loading capacities, making them ideal candidates for delivering potent chemotherapeutic agents such as doxorubicin, paclitaxel, or camptothecin. Moreover, the tunable surface chemistry of CNTs enables selective targeting of diseased tissues or cells, further enhancing the therapeutic efficacy of small molecule drugs[21].

Protein and Peptide Delivery

CNTs offer a biocompatible platform for the delivery of proteins, peptides, and biologics, preserving their structural integrity and bioactivity. Proteins can be adsorbed onto the surface of CNTs or encapsulated within polymer-coated CNTs to protect them from enzymatic degradation and enhance their stability in biological environments[34]. One potential application of CNTs in protein delivery is in the treatment of neurological disorders, where therapeutic proteins such as growth factors or neurotrophic factors can be delivered directly to the central nervous system. Additionally, CNT-based delivery systems offer opportunities for targeted delivery to specific cell types or tissues, minimizing off-target effects and improving therapeutic outcomes[17,1,7].

Nucleic Acid Delivery for Gene Therapy and RNA Interference

CNTs hold promise for delivering nucleic acid-based therapeutics, including plasmid DNA, siRNA, and mRNA, for gene therapy and RNA interference applications[12]. The large surface area and unique physical properties of CNTs enable efficient encapsulation and protection of nucleic acids from nuclease degradation, facilitating their intracellular delivery and gene regulation[7]. In gene therapy, CNTs can serve as vectors for delivering therapeutic genes to target cells, offering potential treatments for genetic disorders, cancer, and other diseases. Similarly, CNT-based nanocarriers can deliver siRNA molecules to silence specific genes or mRNA sequences, offering a potent tool for modulating gene expression and treating diseases at the molecular level[35].

Imaging Agent Delivery for Diagnostic Applications

In addition to therapeutic applications, CNTs have been utilized for delivering imaging agents such as contrast agents or fluorescent probes for diagnostic purposes. By conjugating imaging agents onto the surface of CNTs or encapsulating them within polymer-coated CNTs, researchers can develop multimodal imaging platforms

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capable of visualizing diseased tissues or monitoring therapeutic responses in real-time[36]. For example, CNT-based nanocarriers loaded with contrast agents such as gadolinium or iron oxide nanoparticles can enhance the contrast of magnetic resonance imaging (MRI) or magnetic particle imaging (MPI), enabling precise localization and characterization of tumors or other pathological lesions. Similarly, CNTs functionalized with fluorescent probes or quantum dots can be used for fluorescence imaging or optical imaging applications, offering high sensitivity and spatial resolution for detecting molecular targets in biological samples[37].

Table1 : Different Medical Applications of Carbon Nanotubes (CNTs)

Name of CNTs	Application	Description	References
Multi-walled CNTs	Drug Delivery	Multi-walled carbon nanotubes (MWCNTs) have been utilized as carriers for various therapeutics, offering high drug loading capacities and controlled release profiles.	[38]
Single-walled CNTs	Biomedical Imaging	Single-walled carbon nanotubes (SWCNTs) have demonstrated potential as contrast agents for various imaging modalities, including MRI, CT, and fluorescence imaging.	[39]
Functionalized CNTs	Gene Delivery	Functionalized carbon nanotubes have been employed for delivering nucleic acids such as siRNA, mRNA, and plasmid DNA for gene therapy applications.	[40]
Polymer-coated CNTs	Tissue Engineering	Polymer-coated carbon nanotubes have been integrated into scaffolds for tissue engineering, promoting cell adhesion, proliferation, and differentiation.	[41]
CNT-based Biosensors	Disease Diagnostics	Carbon nanotube-based biosensors have been developed for detecting biomolecular interactions and diagnosing diseases such as cancer, infections, and diabetes.	[42]
SWCNTs	Neural Prosthetics	Single-walled carbon nanotubes have been explored for developing neural prosthetics, interfacing with neurons to restore sensory or motor functions in neurological disorders.	[43]
MWCNTs	Photothermal Therapy	Multi-walled carbon nanotubes have been used as photothermal agents for cancer therapy, selectively heating tumor tissues upon exposure to near-infrared light.	[44]
Peptide-functionalized CNTs	Targeted Drug Delivery	Peptide-functionalized carbon nanotubes have been engineered for targeted drug delivery to specific cell types or tissues, enhancing therapeutic efficacy and minimizing off-target effects.	[45]
SWCNT-based Electrodes	Bioelectronic Devices	Single-walled carbon nanotubes have been incorporated into electrodes for bioelectronic devices, enabling high	[46]

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		sensitivity and stability for applications such as biosensing and neural recording.	
Carbon Nanotube-based Composites	Orthopedic Implants	Carbon nanotube-based composites have been used in orthopedic implants to enhance mechanical properties, reduce wear, and promote osseointegration for improved longevity and performance.	[47]

Challenges and Future Perspectives

The promising applications of carbon nanotubes (CNTs) in drug delivery are accompanied by several challenges that must be addressed to realize their full potential in clinical settings.

Safety Concerns and Toxicity Issues

One of the primary concerns surrounding the use of CNTs in drug delivery is their potential toxicity to biological systems[48]. CNTs have been shown to induce inflammation, oxidative stress, and cellular damage in vitro and in vivo, raising concerns about their long-term biocompatibility and safety. Moreover, the physicochemical properties of CNTs, such as length, diameter, surface chemistry, and aggregation state, can influence their biological interactions and toxicity profiles[49,50]. To address these concerns, researchers have focused on modifying the surface properties of CNTs to enhance biocompatibility and reduce toxicity[51]. Surface functionalization with biocompatible polymers or coatings can mitigate adverse effects and improve the pharmacokinetics of CNT-based delivery systems[52,53]. Additionally, thorough biocompatibility assessments and toxicity studies are essential to evaluate the safety profiles of CNTs and guide their rational design for biomedical applications[54-57].

Regulatory Challenges in Clinical Translation

The clinical translation of CNT-based drug delivery systems is hindered by regulatory challenges related to safety, efficacy, and quality control. Regulatory agencies such as the U.S[58]. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require rigorous preclinical evaluations and comprehensive toxicological assessments to ensure the safety of nanomaterial-based therapeutics before entering clinical trials[59,60]. Moreover, the complex nature of CNT-based delivery systems, including variability in synthesis methods, surface functionalization, and batch-to-batch consistency, poses challenges for standardization and quality control[61,62]. Robust manufacturing processes and characterization techniques are needed to ensure the reproducibility and reliability of CNT-based formulations for clinical use[63]. Furthermore, regulatory frameworks for nanomedicines may need to be adapted to accommodate the unique properties and challenges associated with CNTs[64]. Clear guidelines and standards for the characterization, testing, and clinical evaluation of CNT-based drug delivery systems are essential to facilitate their regulatory approval and commercialization[65,66].

Opportunities for Further Research and Development

Despite the challenges, CNTs hold immense promise for revolutionizing drug delivery and improving therapeutic outcomes[67]. Future research efforts should focus on addressing the safety concerns and regulatory hurdles associated with CNT-based delivery systems while exploring new avenues for optimizing their efficacy and targeting capabilities[68,69]. One area of research is the development of advanced nanomaterials and nanocomposites with enhanced biocompatibility and reduced toxicity[70]. By engineering CNT-based delivery systems with tailored physicochemical properties, researchers can minimize adverse effects and maximize therapeutic efficacy in vivo[71]. Additionally, there is a need for innovative strategies to improve the specificity and targeting efficiency of CNT-based drug delivery systems. Advances in nanotechnology, bioconjugation chemistry, and molecular targeting approaches hold promise for developing next-generation CNT-based nanocarriers capable of precise and selective delivery to diseased tissues or cells[72,73]. Moreover,

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interdisciplinary collaborations between researchers, clinicians, and regulatory agencies are essential for advancing the field of CNT-based drug delivery[74]. By fostering collaboration and knowledge exchange, researchers can accelerate the translation of CNT-based therapeutics from bench to bedside and address the unmet medical needs in various disease areas[75].

Conclusion

Carbon nanotubes (CNTs) have emerged as versatile platforms for drug delivery, offering unique advantages such as high drug loading capacity, tunable surface chemistry, and the ability to penetrate biological barriers. Despite challenges related to safety, toxicity, and regulatory hurdles, significant progress has been made in harnessing the potential of CNTs for clinical applications. Through surface functionalization, targeted delivery strategies, and advancements in nanotechnology, researchers have developed innovative CNT-based drug delivery systems with enhanced biocompatibility, specificity, and therapeutic efficacy. Moreover, interdisciplinary collaborations and ongoing research efforts hold promise for addressing safety concerns, navigating regulatory pathways, and optimizing the performance of CNT-based therapeutics. As the field continues to evolve, CNTs are poised to play a pivotal role in revolutionizing drug delivery and advancing personalized medicine, offering novel solutions to address unmet medical needs and improve patient outcomes in diverse disease settings.

Conflict of interest

None

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