Carbon Nanotubes for Targeted Drug Delivery: Properties, Applications, and Future Perspectives

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ABSTRACT

Carbon nanotubes (CNTs) have been recognized as promising nanomaterials for targeted drug delivery due to their physicochemical properties. Their large surface area, ability to functionalize, and high capacity for the adsorption of therapeutic agents make them versatile platforms for targeted drug delivery systems. This review provides an overview of the key properties of CNTs, including high biocompatibility, chemical stability, and tunable surface properties. Recent studies have emphasized functionalization strategies of CNTs to enhance solubility, minimize toxicity, and enhance the efficiency of targeted drug delivery. The application of CNTs in delivering chemotherapeutic agents, proteins, nucleic acids, and other biomolecules has been investigated. Despite these advantages, challenges such as potential toxicity, environmental concerns, and high production costs remain that require immediate and extensive investigation. This article analyzes the current status of CNTs in targeted drug delivery and discusses future perspectives on CNTs in advanced therapeutic systems.

Keywords: *Carbon nanotubes (CNTs), Targeted Drug Delivery Systems, Functionalization Strategies*

1. INTRODUCTION

Nanotechnology has emerged as a transformative technology widely applied in various scientific fields and has significantly improved the quality of life. Nanomaterials in drug delivery have revolutionized traditional methods and offer new solutions to old medical challenges. Suboptimal therapeutic indices and systemic toxicity often limit traditional drug delivery systems. These limitations are problematic in treating diseases, especially cancer, because precise targeting of tumor cells while sparing healthy tissues is essential for effective therapy. In this regard, targeted drug delivery systems have attracted considerable attention as a significant advancement. Targeted drug delivery systems are engineered to transport therapeutic agents directly to diseased cells while sparing healthy cells. This precision enhances drug efficacy and minimizes undesirable side effects on surrounding tissues, ultimately promoting a faster and more efficient recovery process for the patient and instilling hope for the future of medical treatment [1].

Among the nanomaterials investigated for targeted drug delivery, carbon nanotubes (CNTs) have attracted much attention due to their unique physical, chemical, and biological properties [2]. Since their discovery by Iijima in 1991, CNTs have been distinguished by their high surface-to-volume ratio, high mechanical strength, electrical conductivity, and large surface area, making them ideal candidates for novel drug delivery systems [3].

CNTs comprise rolled-up graphene sheets that form hollow, cylindrical structures with diameters in the nanometer range and lengths extending to several micrometers. Their unique architecture is defined by their chirality, determined by the chiral indices (n,m), which specify how a graphene sheet is rolled to form the cylindrical structure. The chiral vector $C_h = na_1 + ma_2$, where a_1 and a_2 are the unit vectors of the graphene lattice, dictating the type of CNT and influencing its electronic and physical properties.

Based on the values of n and m, CNTs are categorized into three distinct structures that are shown in Figure1:

- **Armchair CNTs (n = m):** These CNTs have a metallic and symmetrical structure. These two features give them high conductivity and make them suitable for applications with high electrical conductivity.
- **Zigzag CNTs (m = 0):** Depending on their structure, these CNTs can have metallic or semiconducting properties, making them suitable for various electronic applications.
- **Chiral CNTs (n ≠ m):** These CNTs have a helical structure and are typically semiconducting, which makes them valuable for optoelectronic and biomedical applications due to their tunable electronic characteristics [4].

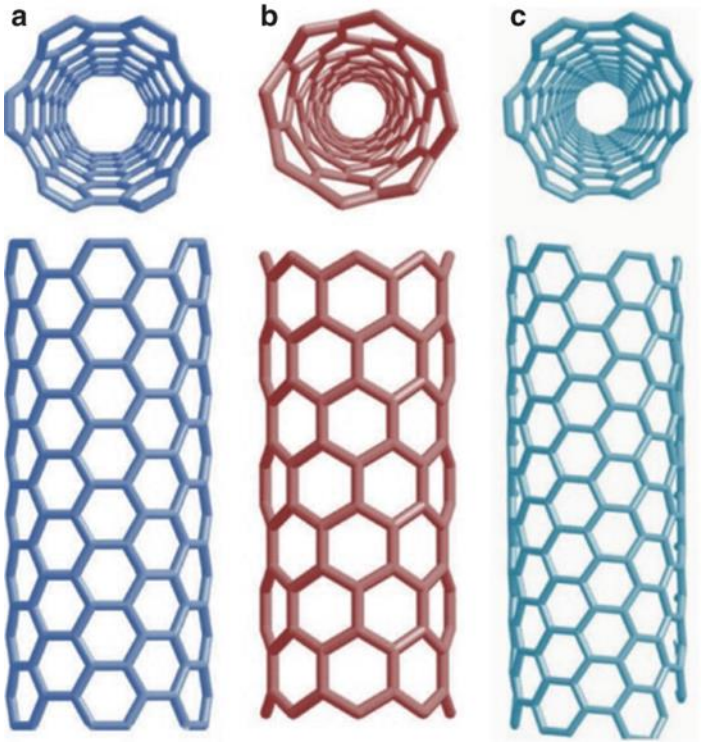

Fig. 1. a) armichair CNT, b) zigzag CNT, c) chiral CNT [5]

CNTs are generally categorized into three main types: single-walled (SWCNTs), double-walled (DWCNTs), and multi-walled (MWCNTs), as shown in Figure 2. Single-walled nanotubes are made of a single layer of graphene and have unique electrical and mechanical properties that have attracted much attention due to these characteristics. Double-walled nanotubes consist of two intertwined layers of graphene, which have some of the properties of single-walled nanotubes and some of the properties of multi-walled nanotubes. Finally, multi-walled nanotubes are made of several layers of graphene, making them very strong, stable, and suitable for various applications that require high strength [6, 7]. Due to their unique characteristics, these three types of nanotubes have found extensive applications in fields such as drug delivery [8, 9].

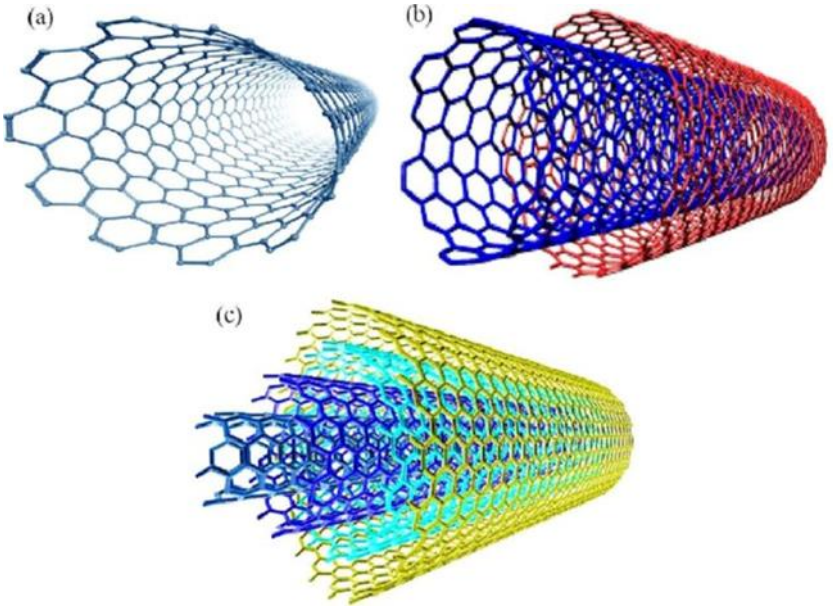

Fig. 2. a) single-walled (SWCNTs) b) double-walled (DWCNTs) c) multi-walled (MWCNTs) [10]

CNTs have many unique properties, including tunable chemical reactivity, high surface area, and exceptional mechanical strength, which have enabled them to be used in various scientific fields, including drug delivery, electronics, and energy storage .The high electrical conductivity and structural rigidity of CNTs in transistors, sensors, and conductive films enable increased efficiency in electronics. Their high surface-to-volume ratio and exceptional electron mobility increase the capacity and efficiency of batteries and supercapacitors for energy storage applications. In addition, the tunable surface chemistry of CNTs and their ability to functionalize and cross-cell membranes in drug delivery systems enable precise delivery of therapeutic agents, reduce adverse effects, and improve drug efficacy [11].

This study analyzes the use of CNTs in targeted drug delivery systems and examines their potential to improve traditional drug delivery methods. In this study, the unique physicochemical properties of CNTs that make them suitable for targeted drug delivery are studied, including their large surface area, tunable chemical reactivity, and ability to penetrate cell membranes. The review then discusses various functionalization methods to enhance the biocompatibility and ability of CNTs to deliver therapeutic agents. Finally, drug loading and release mechanisms into the target cell are reviewed. In addition, the paper addresses the challenges, limitations, and prospects of CNTs in drug delivery systems.

2. PROPERTIES OF CNTS IN TARGETED DRUG DELIVERY

CNTs have attracted much attention as targeted drug delivery systems due to their unique structural, physicochemical, and biological properties [12]. Below are the key characteristics of CNTs that make them excellent candidates for targeted drug delivery applications.

2.1 High Drug-Loading Capacity

CNTs can remarkably carry drugs thanks to their unique hollow and tubular shape. This design allows them to hold therapeutic agents inside their inner cavity while attracting them to their large outer surface. Because of this combination, CNTs can deliver drugs much more effectively than traditional carriers [13].

Carbon nanotubes' large external surface area facilitates the non-covalent binding of hydrophobic drugs via π-π stacking interactions between the aromatic rings of the CNTs and the drug molecules. This technique maintains the stability and the activity of drugs, ensuring their efficacy. For example, doxorubicin, an anticancer drug, is hydrophobic and has been successfully loaded onto pristine CNTs using π-π stacking interactions, allowing its transport and diffusion into the target cell [14].

In addition to physical adsorption, CNTs can be functionalized with reactive groups, such as carboxyl or amine groups, to enable covalent attachment of hydrophilic drugs. This approach increases therapeutic agents'

solubility and stability in aqueous environments, enabling targeted delivery and precise drug release. For example, methotrexate is hydrophilic and was covalently attached to functionalized CNTs and successfully delivered and released into the target cell [15].

2.2 Cell Membrane Penetration

CNTs can effectively penetrate cell membranes without causing significant cellular damage [16]. This ability is due to the needle-like shape of CNTs and their nanoscale dimensions, which not only do not damage the cell membrane but also facilitate entry into the cell [17]. CNTs can traverse cellular barriers via passive diffusion, bypassing conventional endocytotic pathways [18].

This endocytosis-independent uptake minimizes drug degradation in lysosomes, thereby enhancing the therapeutic efficacy of delivered agents. For example, CNT-mediated delivery of small interfering RNA (siRNA) has demonstrated superior cellular uptake and enhanced gene silencing efficiency compared to traditional delivery systems [19].

Furthermore, the functionalization of CNTs with biocompatible molecules reduces cytotoxicity during cellular penetration. Unlike other nanocarriers, functionalized CNTs show minimal membrane disruption and lower cytotoxic effects, making them safer for in vivo applications. Combining efficient membrane penetration and reduced cellular damage makes CNTs a powerful platform for targeted intracellular drug delivery [20].

2.3 Surface Functionalization and Tunability

The carbon atoms in CNTs have sp^2 hybridization, which allows for significant surface functionalization and tunability. This capability provides many advantages for carbon nanotubes, such as increasing solubility, reducing toxicity, and enabling selective targeting. Functionalization with hydrophilic groups, such as polyethylene glycol (PEG), improves the dispersion of CNTs in aqueous solutions and overcomes their inherent hydrophobicity. For example, PEGylated CNTs have effectively delivered paclitaxel, a widely used chemotherapy drug, to target cells [21].

CNTs can be conjugated with biomolecules such as antibodies, peptides, or aptamers to achieve targeted drug delivery. For example, in one study, CNTs were functionalized with folic acid. This targeted approach enables precise delivery of therapeutic agents directly to cancer cells, reducing unwanted effects on healthy tissues [22].

Furthermore, advanced functionalization strategies enable CNTs to release their cargo in response to specific stimuli, such as changes in pH or temperature. For instance, CNTs functionalized with pH-sensitive linkers are designed for controlled drug release in acidic tumor microenvironments, ensuring that therapeutic agents are predominantly released near tumor cells. This targeted release enhances treatment efficacy while reducing systemic side effects [23, 24].

3. FUNCTIONALIZATION STRATEGIES FOR CNTS IN DRUG DELIVERY

Functionalization is a pivotal strategy for enhancing carbon nanotubes' biocompatibility, solubility, and specificity (CNTs) for drug delivery applications. These modifications can be broadly classified into two main categories: non-covalent and covalent functionalization, each offering distinct advantages depending on the application [25].

3.1 Non-Covalent Functionalization

Non-covalent functionalization of CNTs involves the attachment of molecules through weak interactions, such as π-π stacking, van der Waals forces, or hydrophobic interactions, preserving the intrinsic properties of CNTs like electrical conductivity and mechanical strength. In applications where the strength and structural integrity of materials are of great importance, this method of non-covalent functionalization of CNTs can be very useful [26].

One common approach is surfactant-assisted functionalization, where surfactants such as sodium dodecyl sulfate (SDS) or Pluronic F127 wrap around CNTs, forming stable dispersions in aqueous media. This enhances the solubility of CNTs and provides a platform for further drug loading. For instance, SDS-functionalized CNTs have been shown to improve the delivery of hydrophobic anticancer drugs like paclitaxel [27].

Another strategy involves polymer wrapping, where polymers like polyethylene glycol (PEG) or polystyrene sulfonate (PSS) adsorb onto CNT surfaces, increasing their solubility and biocompatibility. PEGylated CNTs are commonly employed for delivering drugs such as doxorubicin due to prolonged

circulation time and reduced immunogenicity. Studies have demonstrated that PEG-functionalized CNTs can effectively deliver doxorubicin to cancer cells, enhancing therapeutic efficacy while minimizing side effects [28].

Additionally, biomolecule adsorption entails the attachment of biomolecules, including DNA, RNA, and proteins, onto CNTs via π-π stacking or electrostatic interactions, which is particularly useful for gene therapy applications. For example, DNA-functionalized CNTs successfully delivered therapeutic genes to cancer cells. This method facilitates the translocation of genetic material across cell membranes, offering a promising avenue for targeted gene therapy [26].

3.2. Covalent Functionalization

Covalent functionalization of CNTs involves forming strong chemical bonds between functional groups and the CNT surface, providing robust and stable modifications. While this approach may slightly alter the CNT structure, it offers enhanced stability and functionality, making it valuable for various biomedical applications [29].

One common method is oxidation and carboxylation, where carboxyl (-COOH) groups are introduced onto the CNT surface using strong acids like a mixture of nitric and sulfuric acids. These carboxyl groups serve as anchor points for further conjugation with drugs or targeting ligands. For instance, carboxyl-functionalized CNTs have been utilized to attach folic acid, facilitating targeted delivery to cancer cells that overexpress folate receptors [30].

Another approach is amidation and esterification. Amidation involves reacting carboxyl groups on CNTs with amines to form amide bonds, while esterification connects hydroxyl (-OH) groups to alcohols or acids. These methods are widely employed to attach chemotherapeutic drugs or imaging agents to CNTs. For example, amidation has been used to link CNTs with the anticancer drug methotrexate, enhancing its stability and targeted delivery [31].

Click chemistry offers a modular and efficient approach for functionalizing CNTs. Reactions such as azide-alkyne cycloaddition have attached various bioactive molecules to CNTs. This strategy has proven effective in designing multifunctional CNTs for simultaneous drug delivery and imaging applications [32].

3.3. Dual and Multifunctional Functionalization

Dual and multifunctional functionalization of CNTs has significantly advanced their application in targeted drug delivery and imaging. CNTs can achieve precise targeting, effective imaging, and controlled drug release by integrating various functional groups.

Functionalizing CNTs with both targeting ligands and imaging agents enables simultaneous tumor targeting and imaging. For instance, CNTs conjugated with folic acid and quantum dots have demonstrated effective tumor targeting and imaging capabilities [33].

Incorporating stimuli-responsive polymers onto CNTs facilitates controlled drug release in specific environments, such as the acidic tumor microenvironment. Recent studies have shown that CNTs functionalized with pH-sensitive polymers can selectively release therapeutic agents like doxorubicin in cancerous tissues, thereby minimizing harm to healthy cells [34].

These multifunctional strategies significantly enhance the therapeutic efficacy of CNT-based systems by ensuring targeted delivery and controlled release of therapeutic agents.

4. APPLICATIONS OF CNTS IN DRUG DELIVERY

Due to their unique structural and chemical properties, CNTs have garnered significant attention in drug delivery. Their applications span various therapeutic areas, including:

4.1 Anticancer Drugs Delivery

CNTs have been extensively investigated as carriers of anticancer agents. CNTs are well-suited for targeted cancer therapy due to their ability to penetrate intracellular membranes and accumulate in tumor tissues. Functionalization of CNTs with specific ligands, in addition to minimizing systemic toxicity, makes them ideal for treating cancer cells [35].

4.2 Gene Delivery

The potential of CNTs as carriers for gene therapy has been studied due to their capacity to deliver genetic agents to the cells under study. Functionalized CNTs can deliver DNA or RNA molecules in gene therapy and

facilitate the modulation of gene expression. One study highlighted the use of functionalized CNTs for the delivery of small interfering RNA (siRNA) to silence specific genes in cancer cells, demonstrating an effective reduction of cancer gene function with minimal cytotoxicity [36].

4.3 Protein and Peptide Delivery

CNTs have been used to deliver therapeutic proteins and peptides to diseased cells, protect them from degradation, and increase their stability in the body. Functionalization methods can cause proteins to be adsorbed onto CNTs, facilitating protein transport across cell membranes. Studies show that peptide-functionalized CNTs can effectively target therapeutic proteins in cells [37].

4.4 Stimuli-Responsive Drug Delivery

CNTs can be designed to release their cargo, which includes therapeutic agents, in response to specific environmental stimuli such as pH changes, temperature changes, or light exposure in the target cell. This property of CNTs is widely used in treating many cancer cells, especially in targeting the acidic environment of tumors. For example, one study demonstrates the development of pH-responsive CNTs for the controlled release of anticancer drugs, increasing drug accumulation in tumor tissues while reducing systemic toxicity [38].

4.5 Imaging and Diagnostics

Functionalized CNTs serve as contrast agents in imaging modalities to aid in detecting pathogenic cells. CNTs have intrinsic optical properties, and their ability to be surface-modified enables their use in imaging techniques such as near-infrared fluorescence and magnetic resonance imaging (MRI). For example, CNTs conjugated with imaging agents accelerate and facilitate tumor imaging and greatly aid in diagnosing and monitoring cancer progression [39].

4.6 Antibacterial and Antiviral Therapies

CNTs have antimicrobial properties that can be used to deliver antimicrobial agents, especially antibacterial and antiviral agents. Functionalized CNTs can target specific cells and enhance the efficacy of antimicrobial therapies. Recent research has investigated the use of targeted carbon nanotube therapeutic systems for the delivery of antiviral drugs, indicating the potential of CNTs in treating viral infections [40].

4.7 Tissue Engineering

CNTs act as scaffolds for delivering growth factors or other therapeutic agents to regenerate damaged tissue in tissue engineering. Their mechanical strength and ability to enhance cell growth make them suitable candidates for developing biomimetic scaffolds. Studies have shown that CNT-based bone tissue engineering scaffold enhances osteogenic differentiation and bone formation [41].

5. CHALLENGES AND LIMITATIONS

Although CNTs have shown great promise as targeted drug delivery systems, challenges prevent their widespread clinical application.

5.1 Toxicity and Biocompatibility

Pristine CNTs can cause oxidative stress, inflammation, and cellular damage due to their hydrophobic nature and interaction with biological membranes. Accumulation in organs like the liver and lungs raises concerns about chronic toxicity. Functionalization with hydrophilic molecules, such as polyethylene glycol (PEG), has reduced toxicity and improved biocompatibility. For instance, PEGylated CNTs have demonstrated reduced inflammatory responses and better systemic tolerance [42].

5.2 Solubility and Aggregation

CNTs have hydrophobic surfaces, which make them poorly soluble in biological fluids and cause aggregation. This reduces their efficacy and prevents drug biodistribution. To overcome this weakness, CNTs can be functionalized with polar groups or surfactants, which increase solubility. For example, CNTs functionalized with amine groups increase dispersion in aqueous media and drug loading potential [43].

5.3 Immunogenicity

CNTs may cause inflammation or allergic reactions by stimulating immune responses. Unwanted stimulation of immune cells can have unintended consequences that lead to damage. To prevent this, biocompatible coatings, such as dextran, can minimize irritation of the ecchymosis cells. For example, studies have shown that CNTs coated with dextran reduce immune cell activation and allergic reactions [44].

5.4 Scalability and Cost

Production of CNTs on a large scale is costly and challenging. Impurities present in the carbon nanotube production line can negatively impact their safety and efficacy. To address this challenge, chemical vapor deposition methods have been developed that have shown promising results for scalability and lower costs [45].

5.5 Regulatory and Ethical Concerns

The lack of clear guidelines for clinical approval and long-term studies poses challenges. Comprehensive preclinical studies and standardized protocols are being developed to assess CNTs' safety, paving the way for regulatory acceptance [46].

5.6 Environmental Concerns

The persistence of CNTs in the environment poses risks to ecosystems. CNT waste can be toxic to aquatic and terrestrial organisms. Biodegradable CNTs and waste management protocols can reduce environmental risks. Recent research highlights the development of eco-friendly CNTs for biomedical use [47].

5.7 Uncontrolled Drug Release

CNTs often lack mechanisms for precise and targeted release into the pathogen cell. This deficiency causes unwanted side effects and reduces the effectiveness of the treatment. Recent studies have used stimuli-responsive drug delivery systems to overcome this challenge and deliver drugs precisely [48].

6. EMERGING TRENDS AND FUTURE PERSPECTIVES

CNTs have been developed as useful tools in targeted drug delivery systems. Studies in this field minimize existing challenges using advanced innovations, increase therapeutic efficacy, and open new drug delivery and medicine horizons.

6.1 Smart and Stimuli-Responsive CNTs

Targeted drug delivery systems using stimuli-responsive CNTs are being developed. These carbon nanotubes can precisely release drugs in response to environmental stimuli such as temperature, pH, and light changes. For example, pH-sensitive CNTs enable selective drug release in acidic tumor microenvironments [49].

6.2 Hybrid Nanocarriers

Hybrid systems that combine CNTs with other nanomaterials, such as gold nanoparticles, liposomes, or polymers, are emerging to enhance multifunctionality. For instance, in preclinical studies, CNT-liposome hybrids have shown improved drug encapsulation, reduced toxicity, and better biodistribution .Future efforts will focus on designing hybrids for combined therapeutic and diagnostic (theranostic) applications, enabling real-time monitoring of drug delivery [50].

6.3 Personalized Nanomedicine

By identifying and categorizing biomolecules such as peptides and antibodies in each patient, functionalized CNTs can be used to target unique molecular markers, creating so-called personalized drug delivery systems. Functionalized CNTs can be conjugated to patient-specific biomolecules, such as antibodies or peptides, to target unique molecular markers. Future studies using artificial intelligence and machine learning tools could create personalized CNTs for specific diseases and patients [51].

6.4 Biodegradable CNTs

Recent studies indicate that biodegradable nanotubes are being developed that could reduce safety and environmental concerns and enable CNTs to degrade after drug release. Future studies to scale up the

production of biodegradable CNTs represent a promising avenue for the use of CNTs in clinical-scale drug delivery systems [52].

6.5 Theranostics

CNT-based theranostic platforms combine therapeutic and diagnostic capabilities, enabling simultaneous drug delivery and imaging. For example, CNTs can be used with imaging agents such as magnetic nanoparticles for early detection and targeted treatment of cancer cells. Prospects and studies in CNTs are aimed at developing CNTs with high imaging resolution [53].

6.6 Clinical Translation

Regulatory guidelines and standardization protocols must be established to utilize the results and achievements of studies on CNTs on a clinical scale. For this purpose, some regulatory bodies, including universities, industry, and regulatory agencies, are trying to provide frameworks for evaluating the safety and efficacy of CNTs in the transport and release of drugs in targeted drug delivery systems [48].

7. Conclusion

Carbon nanotubes (CNTs) have been welcomed as promising systems in nanomedicine, especially for targeted drug delivery. Their unique structural, chemical, and physical properties, such as high surface area and ability to penetrate cell membranes, increase therapeutic efficacy and reduce side effects. CNTs also have several inherent weaknesses, such as toxicity and low solubility, which can be overcome by functionalization and increase their potential for drug delivery to target cells. CNTs show diverse and abundant applications in medicine. For example, they can show potential in transporting anticancer drugs, proteins, and genetic materials. New approaches and perspectives, such as drug release in response to stimuli and hybrid nanocarriers, are being developed; innovations in biodegradable CNTs make CNTs safer and more effective for clinical use. Despite these advances, several challenges remain, including concerns about long-term biocompatibility, which recent studies are trying to solve by addressing the widespread application of CNTs in clinical therapy.

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