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Carbon Nanostructures as Promising Targeted Drug Delivery Systems of Anticancer Agents

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Figure 1. Schematic diagram illustrating CNTs and drug loading

Their needle-like shape enables them to penetrate cell membranes, effectively delivering drugs intracellularly (W. Ahmed et al., 2018).

Graphene (2D)

Graphene is a single layer of carbon atoms arranged in a two-dimensional hexagonal lattice (Inagaki et al., 2014)(Figure 2). It has a high drug-load surface area and can be easily modified with functional groups to target specific cancer cells (Sattari et al., 2021). It is renowned for its exceptional electrical conductivity, thermal conductivity, and mechanical strength. It is the basic building block for other carbon allotropes, including graphite, CNTs, and fullerenes (Mbayachi et al., 2021).

Figure 2. Schematic diagram showing drug loading on the surface of CNSs

Graphene oxide (GO), a derivative of graphene, provides additional oxygen-containing groups for drug attachment and improved dispersion in biological media (Radhapyari et al., 2020).

Other CNSs

Other CNSs include carbon nanofibers, nano-horns, and nanofoams. Due to their complex morphologies, these structures often exhibit a combination of the properties of 0D, 1D, and 2D materials (Thakur et al., 2022).

PROPERTIES OF CARBON NANOSTRUCTURES

The properties of CNSs can be attributed to the solid covalent sp^2 bonds between carbon atoms, conferring strength and stability (Z. Li et al., 2019).

Table 1. Comparison between Covalent and Non-Covalent Functionalization techniques

Covalent Functionalization (Georgakilas *et al.*, 2012)	**Non-Covalent Functionalization (Georgakilas et al., 2012; Yang *et al.*, 2012)**
Covalent bonding alters the electronic structure of CNSs, often resulting in the modification of their intrinsic properties. It provides robust attachment of functional groups but can disrupt the conjugated π-electron system, potentially affecting desirable properties such as conductivity.	Non-covalent interactions preserve the electronic structure of CNSs, maintaining their unique properties. This type of functionalization relies on weak forces, such as π-π stacking, van der Waals interactions, and hydrogen bonding.
Types of covalent functionalization	Types of non-covalent functionalization
Direct Functionalization: We are attaching functional groups directly to carbon atoms on the CNS surface, such as hydrogenation, hydroxylation, or oxidation reactions.	Supramolecular Assembly: Encapsulation of CNSs by macrocycles or other large molecules.
Cycloaddition Reactions: [2+1] or [4+2] cycloadditions that introduce new ring structures onto the carbon backbone.	Polymer Wrapping: It is encasing CNSs with polymers that interact via non-covalent forces.
Radical Reactions: Using free radicals to graft functional groups onto CNS surfaces.	Surfactant Interactions: Using surfactants to improve CNS dispersion in solvents.

Each type of CNS has unique electronic properties due to the quantum confinement and edge effects resulting from their specific dimensions and shapes (Slepicka et al., 2013).

Mechanical Properties

CNSs are among the most potent materials for tensile strength and elasticity (Arash et al., 2014). Their strength-to-weight ratios are unmatched by most other materials, making them ideal for reinforcement applications (Arash et al., 2014).

Electrical and Thermal Conductivity

CNTs and graphene exhibit high electrical and thermal conductivity (D. K. Lee et al., 2022). These properties are being exploited in various applications, from electronic devices to heat-dissipation materials (D. K. Lee et al., 2022).

Chemical and Physical Stability

CNSs are chemically inert and thermally stable, which makes them suitable for harsh environments (W. Liu & G. Speranza, 2019). This stability also means they can be functionalized with various chemical groups to tailor their properties for specific applications (W. Liu & G. Speranza, 2019).

Functionalization of Carbon Nanostructures

Functionalization is key to enhancing the biocompatibility and targeting capability of CNSs (Z. Li et al., 2019). This can be achieved through covalent or non-covalent modifications, attaching targeting ligands, therapeutic agents, which can impart solubility in various solvents, introduce reactive sites, or confer specificity for applications such as drug delivery or sensing or imaging probes to the nanostructures (Dubey et al., 2021; B. Singh et al., 2016). Such modifications enhance selectivity and compatibility with matrices, improve solubility, reduce toxicity, and mitigate some inherent limitations, such as poor dispersion in solvents or polymeric matrices, providing a personalized approach to cancer therapy (Najafi rad et al., 2022).

METHODS OF FUNCTIONALIZATION

Functionalization of CNSs can be broadly classified into covalent and non-covalent methods (Guo et al., 2021)

Characterization of Functionalized CNSs

The characterization of functionalized CNSs is essential to understanding the changes in their properties (Sarode et al., 2023):

- Spectroscopic Techniques: Raman spectroscopy, FTIR, and NMR provide insight into the types of functional groups attached and the extent of functionalization (Eid, 2022).
- Thermal Analysis: TGA can measure functional groups' stability and weight percentage (Basu, 2018).
- Microscopic Techniques: TEM, SEM, and AFM help visualize the morphology and distribution of functional groups (Venkateshaiah et al., 2020).

- Applications of Functionalized CNSs (Abdalla et al., 2015; Palaniappan et al., 2023; Slepicka et al., 2013)
- Functionalized CNSs have found applications across diverse fields:
- Vb Polymer Composites: Improved dispersion and interaction with polymer matrices enhance the mechanical properties of composites (C. Li et al., 2022).
- Drug Delivery: Functional groups can target CNSs to specific biological sites or facilitate drug loading and release (Yu et al., 2010).
- Sensors: Functional groups can provide specificity and sensitivity in detecting various analytes (Khazaei et al., 2023).
- Energy Storage: Functionalization can improve the electrochemical properties of CNSs in batteries and supercapacitors (Sun et al., 2017).

Challenges in Functionalization (Bagheri et al., 2022)

While functionalization has expanded the utility of CNSs, several challenges remain:

- Control over Functionalization: Achieving precise control over the density and orientation of functional groups (Geißler et al., 2021).
- Scalability: Developing methods for functionalized CNSs production (L. Zheng et al., 2018).
- Preservation of Inherent Properties: Minimizing the impact of functionalization on desirable CNS properties (Mohd Nurazzi et al., 2021).

CNSs in Anticancer Drug Delivery

Carbon nanostructures have emerged as a significant player in anticancer drug delivery, offering numerous advantages due to their unique properties (Ravi Kiran et al., 2020). Carbon nanostructures are utilized in anticancer drug delivery, including carbon nanotubes, graphene, fullerenes, and carbon nano-horns (Bagheri et al., 2022). Each has distinct physical and chemical properties that make them suitable for different applications (M. M. Ahmed, 2019; M. Elsayed, 2021; M. M. Elsayed et al., 2022). One of the key benefits of carbon nanostructures is their ability to deliver drugs directly to cancer cells (Madani et al., 2011). They can be functionalized by targeting moieties that recognize and bind to specific markers on the surface of cancer cells (Madani et al., 2011). CNSs can be tailored to respond to specific environmental conditions at disease sites, like the acidic environment of a tumor, triggering targeted drug release and minimizing side effects, thereby improving the efficiency of drug delivery and reducing side effects on healthy cells (J. Singh et al., 2023). Carbon nanostructures (CNSs) possess unique properties that are ideal for drug loading and controlled release in medical applications, particularly in delivering therapeutics (Jha et al., 2020). CNSs like carbon nanotubes, graphene, and fullerenes have a high surface area-to-volume ratio, enabling substantial drug molecule loading (Gergeroglu et al., 2020). Their surfaces can be chemically modified for drug attachment through covalent or non-covalent interactions, with the latter being gentler for sensitive drugs (Debnath & Srivastava, 2021; S. Zheng et al., 2022). Controlled drug release from CNSs is achievable via stimuli-responsive mechanisms, such as pH, temperature, and light sensitivity. For instance, a pH-sensitive drug delivery system can modulate the release rate of a drug depending on the pH of the local environment (J. H. Lee & Yeo, 2015). This is particularly advantageous in cancer therapy, as tumor tissues often exhibit a lower pH than normal tissues, enabling targeted drug release (Jagusiak et al., 2020; Zhao et al., 2023). The encapsulation of drugs within CNSs addresses another critical challenge in drug delivery (Kumari et al., 2014). Some drugs are inherently unstable or possess low solubility in biological fluids, which can limit their therapeutic efficacy (Adepu & Ramakrishna, 2021). Encapsulation within CNSs provides a protective shield against degradation and enhances solubility, thereby improving the bioavailability of these drugs (Naqvi et al., 2019; Zare-Zardini et al., 2022). Specific carbon nanostructures can absorb near-infrared light and convert it into heat, making them useful for photothermal therapy (Y. Chen et al., 2022). This can be combined with drug delivery for a synergistic effect in killing cancer cells (Sundaram & Abrahamse, 2020).

Additionally, they can generate reactive oxygen species under light irradiation for

photodynamic therapy (Lagos et al., 2022). CNSs are explored in gene therapy and immunotherapy (Bates & Kostarelos, 2013; Mostafavi & Zare, 2022). Their versatility stems from the ability to be functionalized with various molecules.

There is a growing interest in developing multifunctional CNS-based systems that simultaneously carry multiple drugs, diagnostic agents, and targeting moieties (Sajja et al., 2009). This approach could lead to more effective combination therapies and enable theragnostic applications (combined therapy and diagnostics) (Masoudi Asil et al., 2023; Y. Zhang et al., 2018). The difficulty of addressing multidrug resistance (MDR) poses a significant obstacle in the fields of drug delivery and cancer therapy (Emran et al., 2022). Carbon nanostructures (CNSs) offer a potentially effective approach for tackling this problem (Curcio et al., 2020). Exploring the Concept of Multidrug Resistance (MDR): Multidrug resistance (MDR) is a recognized phenomenon in which cancer cells acquire the ability to withstand the effects of numerous medications, resulting in diminished responsiveness to chemotherapy (Fatehi Hassanabad, 2019).

Resistance to chemotherapy frequently occurs because of the upregulation of drug efflux pumps, such as P-glycoprotein (Ughachukwu & Unekwe, 2012; Waghray & Zhang, 2018). These pumps actively expel medications from cancer cells, decreasing their intracellular concentration and reducing their therapeutic effectiveness (Takara et al., 2006).

One of the key approaches to address multidrug resistance (MDR) involves augmenting the intracellular drug accumulation within cancer cells (Emran et al., 2022). Carbon nanostructures (CNSs), due to their significant drug-loading capacity, provide a viable approach to accomplish this objective (Xue & Liang, 2012). The encapsulation of chemotherapeutic medicines within carbon nanostructures (CNSs) can enhance drug delivery to cancer cells by increasing the amount of drug payload (Montané et al., 2020). This increased drug payload has the potential to overcome efflux mechanisms that may otherwise limit the effectiveness of the treatment (C. Wang et al., 2022).

Controlled drug release

Carbon nanostructures (CNSs) can be engineered in such a way that they can facilitate the controlled release of medications (Adepu & Ramakrishna, 2021). The approach as mentioned above confers benefits in the context of multidrug resistance (MDR) scenarios as it guarantees a continuous and extended duration of cancer cell exposure to the treatment drugs (J. Wang et al., 2017). By elongating the medication release profile, carbon nanostructures (CNSs) can potentially enhance the likelihood of surmounting drug resistance (Gavas et al., 2021).

Efflux pump inhibition represents an additional pioneering strategy whereby carbon nanostructure (CNS) agents are employed for the targeted delivery of medication efflux pump inhibitors to neoplastic cells (Werle, 2008). These inhibitors can impede efflux pumps' action, inhibiting their ability to expel medicines (Alenazy, 2022). Medication retention within cancer cells can be enhanced by integrating efflux pump inhibitors with conventional chemotherapeutic medicines in carbon nanostructures (CNS)-based delivery systems (Borowski et al., 2005).

Active targeting involves ligands or antibodies that can recognize biomarkers associated with multidrug-resistant (MDR) cancer cells, enabling the targeted targeting of these drug-resistant cells (Tiwari et al., 2023; Yu et al., 2010). This can be achieved by functionalizing drug delivery systems, such as nanocarriers, with these ligands or antibodies (Seidu et al., 2022). Active targeting mechanisms guarantee the preferential accumulation of carbon nanostructures (CNS) in drug-resistant cancer cells, hence augmenting the drug exposure specifically to the resistant cell population (Bajracharya et al., 2022).

Combination therapies, which involve integrating many therapeutic modalities inside carbon nanostructures (CNSs), has been identified as a viable and efficacious approach (Panchanathan Manivasagan et al., 2022). For example, in addition to chemotherapeutic

agents, carbon nanostructures (CNS) can transport compounds for photothermal or gene therapy (Zare et al., 2021). Utilizing a multimodal strategy can potentially enhance the probability of triggering apoptosis in cancer cells, including those that have developed resistance to conventional therapeutic agents (M. Zhang et al., 2017).

The emergence of multidrug resistance (MDR) frequently stems from the presence of heterogeneous populations of tumor cells (Zare et al., 2021). Specific cells have the potential to exhibit drug resistance, whereas others do not possess this characteristic (Emran et al., 2022). The difficulty at hand can be effectively tackled through the utilization of carbon nanostructures (CNS)-based medication delivery, which guarantees the targeted distribution of therapeutic drugs to both drug-resistant and drug-sensitive cancer cell populations within the tumor (Bu et al., 2010).

Monitoring and Adaptation

Advanced carbon nanostructures (CNS)--based drug delivery systems can integrate monitoring mechanisms for evaluating the response of drugs specifically within the tumor (W. Zhang et al., 2011). The provision of real-time feedback regarding the efficacy of treatments enables the implementation of adaptive approaches, such as the adjustment of drug release profiles or the adoption of alternative therapeutic interventions (Karimi et al., 2023).

The safety and biocompatibility of CNSs must be prioritized while combating MDR (Kush et al., 2023). Conducting comprehensive preclinical and clinical investigations is imperative to assess the prolonged impacts and potential toxicity associated with carbon nanostructure (CNS) interventions (Yamashita et al., 2012).

Toxicity and Biodegradability

The toxicity and biodegradability of carbon nanostructures (CNSs) are critical factors that significantly impact their application, particularly in biomedicine and drug delivery systems (Garriga et al., 2020). Understanding and addressing these concerns is essential for the safe and effective use of CNSs in clinical settings (W. H. De Jong & Borm, 2008).

Toxicity of Carbon nanostructures (Du et al., 2013; Kobayashi et al., 2017; Liu et al., 2013). CNSs can be internalized by cells, potentially leading to cytotoxic effects such as oxidative stress, inflammation, and cell death. The unique shape and size of CNSs may cause physical interference with cellular components and biological processes (Farmand et al., 2022).

Factors Influencing Toxicity

- Size and Shape: Longer CNSs have been associated with higher toxicity, similar to the effects of asbestos fibers (S. S. Gupta et al., 2022).
- Chemical Surface Modifications: Functionalization of CNSs can influence their toxicity. For example, covalently functionalized CNSs are generally less toxic than their non-functionalized counterparts (Jain et al., 2011).
- Purity: The presence of metal catalyst residues from CNS synthesis can contribute to their toxicity (Bhat et al., 2022).

In Vivo and In Vitro Studies

Research has shown varying degrees of toxicity in both in vitro (cell culture) and in vivo (animal) studies. These studies help determine the safe concentration and exposure levels of CNSs (Di Ianni et al., 2022; Savage et al., 2019).

Biodegradability of Carbon nanostructures

CNSs are inherently resistant to biodegradation due to their strong carbon-carbon bonds, which poses a challenge to their elimination from the body and the environment (M. Chen et al., 2017). Functionalizing CNSs with biodegradable groups or polymers can facilitate their breakdown in biological systems (Bianco et al., 2011; Peng et al., 2020). Compositing CNSs with biodegradable materials can improve their overall biodegradability (Lin et al., 2011). Studies are exploring how enzymes and other biological agents can degrade CNSs. For instance, certain enzymes capable of breaking down carbon structures have shown the potential to degrade CNSs (Ibrahim et al., 2023).

Regulatory and Safety Considerations (Wim H. De Jong et al., 2022; Riego Sintes et al., 2012; Sousa et al., 2020)

- Safety Assessments: Comprehensive toxicity and biocompatibility assessments are required for medical applications of CNSs, following regulatory guidelines.
- Long-Term Effects: Understanding the long-term effects of CNSs in biological systems is crucial, particularly their accumulation and potential chronic toxicity (Riego Sintes et al., 2012).
- Environmental Impact: The environmental impact of CNSs, particularly their persistence and accumulation, is an area of ongoing research and concern (Sousa et al., 2020).

Regulatory and Clinical Translation (Đorđević et al., 2022; Foulkes et al., 2020; Hua et al., 2018)

- Regulatory Approvals: Rigorous clinical trials and regulatory approvals will be required to bring CNT-based drug delivery systems to the market. This includes proving their safety, efficacy, and advantages over existing delivery systems (B. Gupta et al., 2024).
- Collaboration and Funding: Collaborations between academia, industry, and regulatory bodies, along with adequate funding, are necessary to advance the research from laboratory settings to clinical applications (Tanaka & Lopez, 2024).
- Ethical and Legal Considerations: As with any emerging technology, ethical and legal considerations surrounding the use of CNSs in medicine must be carefully considered, particularly regarding patient safety and data privacy (Baran, 2016).

Future Perspectives

- Integration with Other Technologies: Integrating CNSs with other nanotechnologies, such as nanoparticle systems or biosensors, could lead to more sophisticated drug delivery systems (Masoudi Asil et al., 2023; Saito et al., 2022).
- Personalized Medicine: Leveraging CNSs for personalized drug delivery, where treatment is tailored to the individual's genetic makeup and disease profile, holds great promise (Alghamdi et al., 2022).

Research has shown that CNSHs can penetrate cell membranes efficiently, which is beneficial for intracellular drug delivery (Park et al., 2019; Tan et al., 2015). This property is beneficial for delivering drugs to cancer cells, where they can exert their therapeutic effect more directly (Gavas et al., 2021). Moreover, the high thermal conductivity of CNSHs has been utilized in photothermal therapy, where they convert near-infrared light into heat, causing localized destruction of cancer cells (Lagos et al., 2022).

CONCLUSION

Carbon nanostructures, such as CNSHs, represent a promising frontier in the field of targeted anticancer drug delivery due to their versatile tunable characteristics, capacity for functionalization, and adeptness in traversing biological barriers. Nonetheless, the translation of CNS-based therapies from experimental stages to clinical applications necessitates comprehensive investigations into their enduring safety profiles, environmental repercussions, and the ethical considerations associated with their utilization.

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