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Carbon Based Multifunctional Nanomaterials for Biomedical Applications: A Brief Overview

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Abstract

Carbon based nanomaterials (CBNs) serve as efficient carries in drug delivery. Due to their high propensity to cross cell membranes CNTs are identified as multipurpose innovative carriers in drug delivery applications. The unique electronic and mechanical properties of carbon based nanostructures can be tailored using control-label chemical Functionalization. The potential long-term toxicity concerns of CBNs are still not completely addressed. Innovative ideas and solutions are required to develop carbon nanostructures based efficient and economically viable biomaterials.

Keywords: Carbon based nanomaterials; Functionalization; Drug delivery; Multifunctional nanomaterials; Biomedical; Toxicity and safety

Abbreviations: CNTs: Carbon Nanotubes; CBNs: Carbon Based Nanomaterials; SWNTs: Single Walled Carbon Nanotubes; AMB: Amphotericin B; AMBD: Amphotericin B With Sodium Deoxycholate

Introduction

Rapid advances in nanotechnology in the last two decades aid in several fascinating developments in the health care industry. Conventional surgical treatments are hindered by the accessibility of the tumorous cells and damage risks in the vicinity of vital organs. Also, selective chemotherapy and radiation techniques are limited. In this context, nanomedicine provides a means of targeted drug delivery. Since the dimensions of the biological body cells are of the order of nanoscales, quantity of the drug required to cure the cells is small. Due to the nanoscale dimensions of the carbon based nanomaterials (CBNs), they can easily reach the body cells. Therefore, employing the CNTs avoid additional solvents in the drug delivery. Thus, the disease diagnosis and treatment process transformed painless in the recent years.

Sp^2 hybridized carbon based nanomaterials such as zero dimensional Fullerenes (0D) [1], one dimensional (1D) carbon nanotubes (CNTs) [2] and two dimensional (2D) graphene [3], play a vital role in developing efficient biomaterials. Furthermore, excellent mechanical, electrical and chemical characteristics of the CBNs as well as their ability to hybridize with a wide range of organic and inorganic materials preferred them in developing several novel and efficient composite materials for various applications including biomedical. Therefore, based on the multifunctional nature, CBNs are promising in advanced biomedical applications. As a result, CBNs attracted enormous interest of the materials research community.

Applications

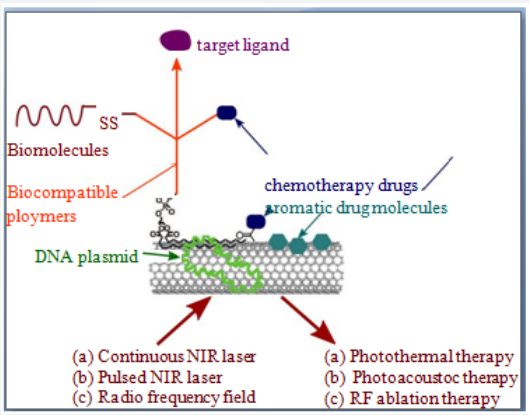

Figure 1: Approaches for CNT based drug delivery and cancer therapy [4].

Fullerenes and their derivatives can serve as drug delivery vehicles. Under certain circumstances they act as nano-drugs as well [4,5]. CNTs have been successfully employed in numerous applications, including electronics, composite materials, fuel

cells, sensors, optical devices and biomedicine [6]. CNTs are identified as multipurpose innovative carriers in drug delivery applications due to their high propensity to cross cell membranes [7]. Because of high surface to volume ratios, CNTs are the prime choice in drug de-livery. Various strategies developed to load small molecules such as chemotherapeutic cancer drugs on CNTs via either covalent conjugation , as non-covalent adsorption are explained in the schematic (Figure 1).

The photo-thermal therapy is a popular technique for cancer treatments. Single walled carbon nanotubes (SWNTs) generate significant amount of heat upon excitation with near-infrared light (NIR, l=700-1100nm). Therefore, the photo-thermal effect can be employed to induce thermal cell death in a noninvasive manner. Moon et al. [8] demonstrated the *in vivo* obliteration of solid malignant tumors by the combined treatments of SWNTs and NIR irradiation. Furthermore, the effect of electronic structure (metallic versus semiconducting behaviour) of SWNTs in regulating antimicrobial activity is studied in [9]. A permeable, single-walled carbon nanotube based filter for the effective removal of bacterial and viral pathogens from water at low pressures is proposed in [10]. While developing the filter, the authors used the key properties of SWNTs, such as: small diameter and high surface area, tendency to aggregate and form highly porous structures and the antibacterial properties

Carbon nanotubes possess hydrophobic surfaces, which are not soluble in aqueous solutions. Functionalizing CNTs with other functional groups can make them hydrophilic. Functionalization is the chemical process of attaching the functional groups to the CNT surfaces. The unique electronic and mechanical properties of SWNTs can be tailored using controllable chemical functionalization [6]. Benincasa et al. [11] efficiently employed functionalized CNTs (f-CNTs) for the transportation of micellar dispersed Amphotericin B (AMB) with sodium deoxycholate (AMBD) in the treatment of serious invasive fungal infections. The authors tested the antifungal activity of two conjugates between f-CNTs and AMB, against a collection of reference and clinical fungal strains, and reported that the measured minimum inhibition concentrations for f-CNT-AMB conjugates are either comparable to or better than those displayed by AMB and AMBD. Functionalized CNTs can be also used as molecular carriers for in vitro and in vivo drug delivery, primarily employed for cancer treatment [12].

Multiwalled carbon nanotubes (MWNTs), strongly absorbs the near-infrared (nIR) radiation and efficiently convert absorbed energy to released heat which can be used for localized hyperthermia applications Ghosh et al. [13] demonstrated that DNA-encasement increases heat emission following nIR irradiation of MWNTs, and DNA-encased MWNTs can be used to safely eradicate a tumor mass in vivo. They reported that DNA-encased MWNTs are more efficient at converting nIR irradiation into heat compared to nonencased MWNTs and hence, DNA-encased MWNTs can be used safely and effectively for the selective thermal ablation of malignant tissue in-vivo. A controlled drug release system for transporting Ibuprofen using functionalized multiwall carbon nanotubes is discussed in [14]. Raffa et al. [7] reported that length of nanotubes influence their uptake and shorter (sub-1mm) MWNTs are easier to be internalized through an energy-independent pathway.

CNTs are also employed in developing novel bio-sensors to detect various biological targets and as nano-probes for biomedical imaging [4,12,15]. Banerjee et al. [6] explored the covalent chemical strategies for the functionalization of carbon-nanotube surfaces. The authors reported their observations from a structural perspective, the breadth and types of reactions SWNTs can undergo in solution phase, not only at the ends and defect sites but also along the sidewalls. Moreover, prevailing themes in nanotube functionalization have been involved with dissolution of tubes. Su et al. [16] developed graphene quantum dot (GQD) based nanoprobe for targeted drug delivery, sensing, dual-modal imaging and therapy, by conjugating the carboxyl-terminated GQD with Fe_3O_4@SiO_2 followed by functionalization with cancer targeting molecule folic acid. They reported a lumino magnetic Fe_3O_4@SiO_2 @GQD-FA/DOX nanoprobe cancer diagnosis and therapy. A review of carbon nanotubes for multifaceted applications in human healthcare industry is available at [17].

Toxicity and safety issues

In biological applications, particularly *in-vivo,* care must be taken to ensure that the toxicity of the nanomaterial is thoroughly characterized and the material behavior is well understood. The potential long-term toxicity concerns of CBNs are still not completely addressed. Zhang et al. [18] compared the cytotoxicity level of graphene to the CNTs in the neuronal PC12 cells. They concluded that the toxicity depends on shape and composition, where graphene is found to have a lower toxicity than CNTs. However, subsequently the toxicity of Graphene is observed to be inversely proportional to the concentration [19], In other words, graphene exhibits a higher toxicity at low concentrations compared to CNTs [19]. Further investigations on PEG-coated graphene nano sheets in mice and subsequent photo-thermal treatment of cancerous tumors are reported non-toxicity of graphene [20]. On the other hand, sharp Graphene nanosheet edges are observed to cause considerable damage to the cell membrane of bacteria [21], although the antibacterial property is useful. Moreover, compared to hydrophobic pristine graphene, hydrophilic carboxyl-functionalized Graphene are able to be internalized in cells without any toxic effects [22]. Wide ranges of morphologies, coatings and hybrid structures of graphene sheets exists in the literature. However, detailed and long-term studies are still required before the implementation of important in-vivo biomedical applications.

Several reports, based on the experiments on animals [20,23,24], have suggested that well-functionalized CNTs and Graphene are safe within certain dosage. A few preliminary tests [22,25] showcased that the CNTs are biologically benign

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to certain cells, tissues, and organs under certain conditions. While further studies have indicated that CNTs are potential hazards which can cause both acute and chronic effects to many living systems [22]. However, the observation periods are generally no longer than six months, which may not be sufficient to estimate the long-term safety aspects of the CBNs. Therefore, the effect of the CBNs on the immune, reproductive and nervous systems are yet to be systematically investigated. In this context, pre-clinical toxicity studies are required before adopting the carbon nanostructures based cancer therapies can be finally translated into practice. Nevertheless, based on the current knowledge, the biological effects of CNTs are observed to be sample specific and must be assessed on a case-to-case basis. Therefore, the nanotoxicity of CNTs requires continuous extensive investigations by the regulatory bodies, before the CNTs can be used in practice in functional biomaterials and biomedical devices.

Conclusions and future prospects

Carbon based nanostructures in drug delivery and bio sensing applications, apart from the issues associated with toxicity and safety in living biological systems, are addressed in this overview. Intense research in the last two decades provided specificity, selectivity, reproducibility and robustness to the carbon based nanostructures for biological applications. As a result, carbon based nanostructures are successfully applied in many areas of biomedical research, like: drug delivery systems, tissue scaffold reinforcements and cellular sensors [26]. Some of the parameters that influence the delivery performance of CBNs include: shape and size, number of layers, removal of the catalyst during synthesis, apart from the functionalization. However, toxicity of CNTs and Graphene in living biological systems is still an issue to be addressed at macroscopic, cellular and intracellular levels.

During the last decade, CBNs are extensively explored as nanoscale drug carriers for potential applications in biomedicine and cancer treatment. The unique physical properties of CBNs made them the potential candidates in novel cancer therapies such as photo-thermal therapy, photo acoustic therapy and radiofrequency (RF) ablation treatment of tumours. Compared to traditional drug delivery systems, such as biodegradable organic macromolecules, inorganic nanomaterials like CNTs and Graphene may not have clear advantages when they are exclusively used as drug carriers, as their degradation in the biological systems is meager. However, the unique physical properties of the sp2 hybridized CBNs enable a range of novel cancer therapies such as photo thermal, photo acoustic and RF ablation, which could be combined with therapeutic drugs and genes co-delivered by CNTs/Graphene, overcoming the multi-drug resistance problem in current cancer chemotherapies for improved tumor treatment efficacy.

To summarize, we discussed the promising future applications of CBNs for biomedicine, particularly: drug delivery, tissue engineering and cancer therapy. The benefits of CBNs are presented along with toxicity of CBNs and their harmful effects on biological systems. There are many challenges that must be addressed before CBNs can be integrated into the biomedical devices. The following points are required to be addressed:

i. Advanced methodologies to increase the sensitivity of CBNs towards the single molecule detection.

ii. Efficient loading and unloading techniques for drug delivery to improve the overall performance of CBNs as carriers.

iii. Modification of CBNs to promote cell adhesion and growth.

iv. Experiments to accurately estimate the toxicity of cabon nanostructures based biomaterials.

Therefore, innovative ideas and solutions are required to develop cabon nanostructures based efficient and economically viable biomaterials.

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