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Review

A review of ligand tethered surface engineered carbon nanotubes

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ABSTRACT

Carbon nanotubes (CNTs) have emerged as fascinating materials, exhibiting promising potential in receptor based targeting owing to their unique physicochemical properties (cell membrane penetration, high surface area and drug payload, biocompatibility, easy surface modification, photoluminescence property, and non-immunogenicity etc). The hydrophilicity, a major constrain associated with the first generation of CNTs *i.e.* pristine CNTs, could be overcome using functionalization techniques. In the last two decades variety of functionalized CNTs (*f*-CNTs) *i.e.* oxidized, amidated, acylated, surfactant and biopolymer-assisted, and biomolecules modified have been developed and utilized as effective, safe, nano sized, and smart systems to deliver a wide range of bioactives in the biological system. The purpose of this review is to examine the various aspects of conjugation and associated conjugation chemistry of various targeting ligands to CNTs for their respective biomedical applications. The various biomolecules have been easily tethered to CNTs surfaces including proteins and amino acid, enzymes, nucleic acid (DNA and siRNA), aptamers, vitamins, monoclonal antibodies, peptides (NGR, RGD and Aniopep-2) and so on, for targeting purposes.

1. Introduction

During the last few decades, increasing attention has been paid to drug targeting concepts using nanotechnology to improve the overall therapeutic efficacy by reducing the side effects with minimizing degradation or elimination of drugs. It represents a viable option for cancer theragnostics owing to the size and spatial as well as temporal placement of drug at desired site(s).

In current scenario nanotechnology is a multidisciplinary, rapidly expanding scientific zone and has achieved breakthrough in molecular biology, diagnostics and imaging, bio-engineering, nanomedicines, and therapeutics. According to a statistical data nanotechnology will exceed the impact of the Industrial Revolution on society and is projected to become a US $2.6 trillion business in 2014 [1], while Global nanotechnology announced a comprehensive global outlook on the nanotechnology industry. According to this new report the global nanotechnology market to reach US $30.4 billion by 2015 [2,3]. Nanotechnology unfolds avenues to explore its impact on various fields and has certainly a great impact on the future of medical practice as well bio-nanomedicines [3–8]. Great progress has been made in the arena of nanomaterials such as liposomes [4,5], dendrimers [9–13], nanostructured lipid carriers (NLCs) [14], carbon nanotubes (CNTs) [4,15–25] and polymer-mediated therapeutic delivery strategies to target at the specific sites [26] for boosting the safety and therapeutic efficacy. These above mentioned nanomaterials have emerged as the most lucrative segment of which a large number of related nanotechnologies are already commercialized and earning revenues for the public sector [1].

2. Origin and historical perspective of carbon nanotubes

The CNTs were originally discovered and fully described by Sumio Iijima (Japanese Microscopist) in his TEM observation [27], while some scientists believed that it was earlier discovered by Bacon [28,29].

In 1952, two scientists L.V. Radushkevich and V.M. Lukyanovich published a clear TEM image of 50 nm diameter tubes made of carbon but unfortunately this discovery remained unnoticed worldwide because of langue as well as region restriction [30]. In 1970's, a different kind of CNTs were produced and imaged directly using high resolution transmission electron microscopy (HRTEM) and referred as single-walled carbon nanotubes (SWCNTs) [31]. The circular (armchair nanotubes), spiral, and helical arrangement (chiral tube) of the carbon nanotubes are shown in Fig. 1 [32].

In this sequence different methods for production of CNTs were come in existence like hyperion catalysis [33], capping with fullerene hemispheres [34] and arc discharge method [35]. In 1993, single-atomic layer walled carbon nanotubes (SWCNTs) was reported [36,37]. Since its discovery CNTs have been continuously

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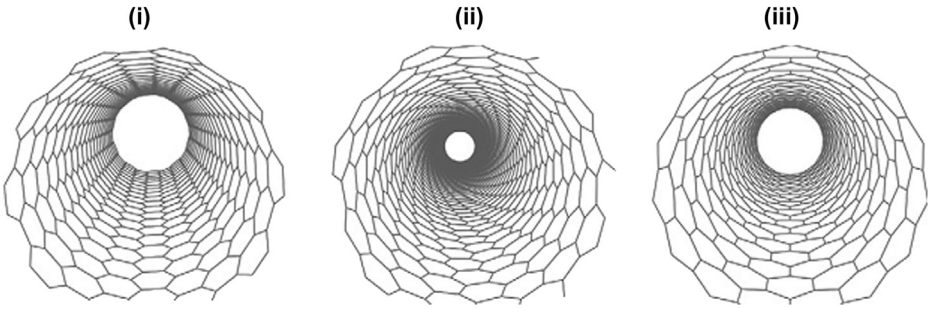

Fig. 1. Schematic representation of three typical types of SWCNTs. (a) Armchair (10, 10), (b) Chiral (13, 6), and (c) Zigzag (14,0) (Reprinted with permission from Ref. [21] Elsevier Pvt. Ltd.).

used in targeted/controlled drug after surface modification in biomedical applications [38–54]. Our group has made modest contribution in the field of pharmaceutical applications of CNTs.

3. Nature and classification of carbon nanotubes

In the existing circumstances, CNTs, the third allotrope of carbon and fullerene family member CNTs, comprised of thin graphite sheets of condensed benzene rings rolled up into the seamless tubular hollow cylinder, nanoneedle shape, have attracted great interest in biomedical and healthcare applications [1,4,5,16,17,20,55]. The ends of CNTs exhibit a resemblance to hemispherical buckyballs connected by a graphene cylinder and depending upon their atomic structure the properties of individual CNTs may vary [7]. Excellent electrical, mechanical and thermal properties including the special features like nanosize diameter, ultra light weight, ultrahigh surface area, aspect ratio (length/diameter) in the range of 1:1000, photoluminescence, rich surface chemistry, non-immunogenicity, biocompatibility and excretion by biliary pathway, neutral electrostatic potential and extremely high drug cargo ability are expected to make CNTs as attractive vehicle for drug delivery [4–6,16,17,56,57]. All types of CNTs materials are commercially available (Carbon Nanotechnologies; Cheaptubes; Sigma Aldrich, Nanoshell etc) and can also be easily synthesized by electric arc-discharge (EAD), laser ablation (LAB), electrolysis and high-pressure co-conversion (HiPCO), catalytic chemical vapor deposition (CCVD) and CoMoCat process. The properties of CNTs may vary depending upon the types of methods employed in the synthesis of CNTs [4,6,7,58–60].

CNTs are considered as promising nano drug delivery vectors, because these are observed to easily cross cell membranes and exhibit fair blood circulation half-lives in order of hours [4,6,7,49,55,57]. Three possible mechanisms of CNTs–drug interaction are: (1) absorption of the active components of drug within the CNTs mesh, (2) surface modification of drug molecules, peptides, nucleic acids on the exterior surface of the CNTs using covalent or non-covalent linkage, and (3) the use of CNT channels as catheters [55].

3.1. Classification of carbon nanotubes

Carbon nanotubes (CNTs) are mainly classified into four categories (Fig. 2) depending upon their diameter, lengths and presence of walls: (i) single-walled carbon nanotubes (SWCNTs), (ii) double-walled carbon nanotubes, (iii) triple-walled carbon nanotubes (TWCNTs) and (iv) multi-walled carbon nanotubes (MWCNTs) [4,6,7,22,23,61,63].

(i) Single-walled carbon nanotubes

Single-walled carbon nanotubes (SWCNTs) consist of only single graphitic sheet seamlessly wrapped into a cylindrical tube structure with a diameter between 0.4 and 2.5 nm. SWCNTs have diameter close to 1 nm, with a tube length that can be several million times longer because of their simplest geometry [1,4,6].

(ii) Double-walled carbon nanotubes

Double-walled carbon nanotubes (DWCNTs) belonging to second class of carbon nanotubes resemble SWCNTs due to the similarities in their morphology and properties. DWCNTs are coaxial nanostructures, containing exactly two concentric graphene cylinders. It is a synthetic blend of SWCNTs and MWCNs. Only the outer wall can be modified, while the properties of the inner tubes would remain unchanged and preserve its intrinsic properties. The smallest nanotubes possessing less than 1 nm diameter can never be DWCNTs [62,63].

(iii) Triple-walled carbon nanotubes

Triple-walled carbon nanotubes (TWCNTs) are characterized by the presence of three walls [61].

(iv) Multi-walled carbon nanotubes

Multi-walled carbon nanotubes (MWCNTs) consisting multiple rolled layers (concentric tubes) of graphene (2–10) are more than one atom thick with >10 nm external diameter. Generally two models, Russian Doll and Parchment models are used to describe the structure of MWCNTs. In Russian model, graphite sheets are arranged in concentric cylinders, while in Parchment model, a single graphite sheet is rolled in around itself, resembling a scroll of parchment or a rolled newspaper [1,4–7,22,56,64,65].

The pristine (raw synthesized) CNTs are not suitable for drug delivery due to their intrinsic hydrophobic nature, thus surface engineering is essential. In last two decade surface decoration of CNTs made a concrete foundation in the development of new drug products, which could be witnessed by many research papers continuously published every year. We believe that in coming years engineered CNTs will make a promising and alternative approach for the treatment of various diseases. Apart from drug delivery, surface engineered CNTs have also been used in the field of photodynamics, gene therapy, imaging and diagnostic, catalysis, sensor, and in nano-electronics etc. Jain and co-workers exhaustively reviewed the appraisal toxicities associated with the pristine and functionalized carbon nanotubes [7]. This research group also explored the safety and efficacy concerns of carbon nanotubes using cancer cell lines [56].