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Review

Advanced review of graphene-based nanomaterials in drug delivery systems: Synthesis, modification, toxicity and application

Qi Zhang [a,b,1], Zhuona Wu [a,b,1], Ning Li [c], Yiqiong Pu [a], Bing Wang [a,b,*], Tong Zhang [a,b,*], Jiansheng Tao [b,**]

[a] Experiment Center for Teaching and Learning, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
[b] School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
[c] Division of Life Science, HKUST Shenzhen Research Institute, Shenzhen 518057, China

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ABSTRACT

The discovery of graphene, a notable achievement in the field of novel carbon nanomaterials, has triggered the worldwide exploration of the biomedical applications of this material since 2004 because of its unique properties. The two-dimensional planar structure, large surface area, chemical stability, mechanical stability, and good biocompatibility of graphene are promising for applications in drug delivery systems (DDSs). In this review, we briefly discuss the characteristics, synthesis, and modification of graphene. We also investigate its toxicity and its applications in DDSs, with several representative examples. This review presents a comprehensive summary of graphene-based nanomaterials from their characteristics to their synthesis and applications, as well as their *in vitro* and *in vivo* evaluation in medicine. This paper provides a guiding strategy for the selection of optimal approaches to the fabrication of nanocarriers that are suitable for medical treatments and to controlling the toxicity within therapeutic safety limits. The promising achievements made with graphene-based nanomaterials indicate several possibilities for further biomedical research, as well as theoretical and applied development.

Contents

Abbreviations: 0-D, zero-dimensional; 1-D, one-dimensional; 2-D, two-dimensional; 3-D, three-dimensional; AASA, atomic absorption spectrophotometer analysis; AFM, atomic force microscope; ATR-IR, attenuated total reflectance-infrared spectroscopy; CS, chitosan; CNT, carbon nanotube; CPT, camptothecin; CVD, chemical vapor deposition; DDS, drug delivery system; DLS, dynamic light scattering; DMF, *N*, *N*-dimethylformamide; DOX, doxorubicin; EA, elemental analysis; ECC, electrochemical characterization; EIS, electrochemical impedance spectra; FA, folic acid; FDA, the United States Food and Drug Administration; FSHR, follicle-stimulating hormone receptor; FTIR, fourier transform infrared spectroscopy; GFNs, graphene family nanomaterials; GnPs, graphene platelets; GO, graphene oxide; GQD, graphene quantum dot; HA, hyaluronic acid; iGOs, isocyanate-treated graphite oxides; LSD, lateral size distribution; MMP, mitochondrial membrane potential; MRI, magnetic resonance imaging; MTX, methotrexate; NIR, near-infrared; PAA, poly (acrylic acid); PAH, polycyclic aromatic hydrocarbon; PDT, photodynamic therapy; PEG, Polyethylene glycol; PEI, polyethylenimine; PSS, poly(sodium 4-styrenesulfonate); PTT, photothermal therapy; PVA, poly(vinyl alcohol); RAFT, reversible addition fragmentation transfer; RES, reticuloendothelial system; RGD, arginine-glycine-aspartic acid; RGO, reduced graphene oxide; ROS, reactive oxygen species; RV, resveratrol; SEM, scanning electron microscope; SQID, superconducting quantum interference device; TBA, tetrabutylammonium; TEM, transmission electron microscope; Tf, transferrin; TGA, thermogravimetric analysis; UnC, uniaxial compression; UV, ultraviolet and visible spectrum; VB12, vitamin B_{12}; XPS, X-ray photoelectron spectroscopy; XRD, X-ray diffraction; ZPD, zeta potential distribution.

* Corresponding authors at: Experiment Center for Teaching and Learning, Shanghai University of Traditional Chinese Medicine, No. 1200, Cailun Road, Pudong New District, Shanghai, China.
** Correspondence to: J. Tao, School of Pharmacy, Shanghai University of Traditional Chinese Medicine, No. 1200, Cailun Road, Pudong New District, Shanghai 201203, China.
E-mail addresses: annabel_cn@163.com (B. Wang), zhangtdmj@hotmail.com (T. Zhang), taojs@sohu.com (J. Tao).
[1] These authors contributed equally to this work.

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1. Introduction

Carbon is one of the most abundant elements in nature; carbon atoms can form complicated networks that are fundamental to organic chemistry and the existence of life [1]. Carbon is a unique material that can exist in forms that range from zero-dimensional (0-D) to three-dimensional (3-D) [2]. In addition, allotropes of carbon have various properties, from hard (diamond) to soft (graphite), from insulative (diamond) to semi-conductive (graphite) and conductive (graphene), and from light absorbing (graphite) to diaphanous (diamond) [3–5].

Graphite and its allotropes, such as graphene, graphene oxide (GO), carbon nanotubes (CNTs), and reduced graphene oxide (RGO), have attracted extensive interest for use in quantum physics [6], nanoelectronics [4,7], catalysis [8], nanocomposites [9], and sensor technology [10] because of their unique structure and geometry. Graphite and its allotropes possess outstanding physicochemical properties, including high fracture strength and Young's modulus, excellent electrical and thermal conductivity, quick charge carrier mobility, large specific surface area, and good biocompatibility [11–14] and have thus been widely used in medical science and biotechnology, including in sensitive biosensors [15], drug delivery systems (DDSs) [16], and near-infrared (NIR) fluorescence imaging techniques [17–19].

The allotropes of carbon have various structures and properties but share a common two-dimensional (2-D) structure called graphene, which was first prepared in 2004 [20]. Graphene can be transformed into spherical structures (0-D fullerenes), tubulate structures (one-dimensional carbon nanotubes, 1-D CNTs) or layered structures (3-D graphite) (Fig. 1) [21]. The free-standing 2-D crystal of graphene is composed of six-atom rings in a honeycombed network with one-atom thickness; thus, graphene can function as a planar aromatic macromolecule [22], which results in several unique properties. Since a single layer of graphene was first prepared in 2004 using a sticky tape and a pencil [20], several efficient production methods for graphene have been developed, such as micromechanical exfoliation, chemical vapor deposition (CVD), epitaxial growth, and chemical synthesis [23]. In addition, GO can be mass produced with high throughput, low processing

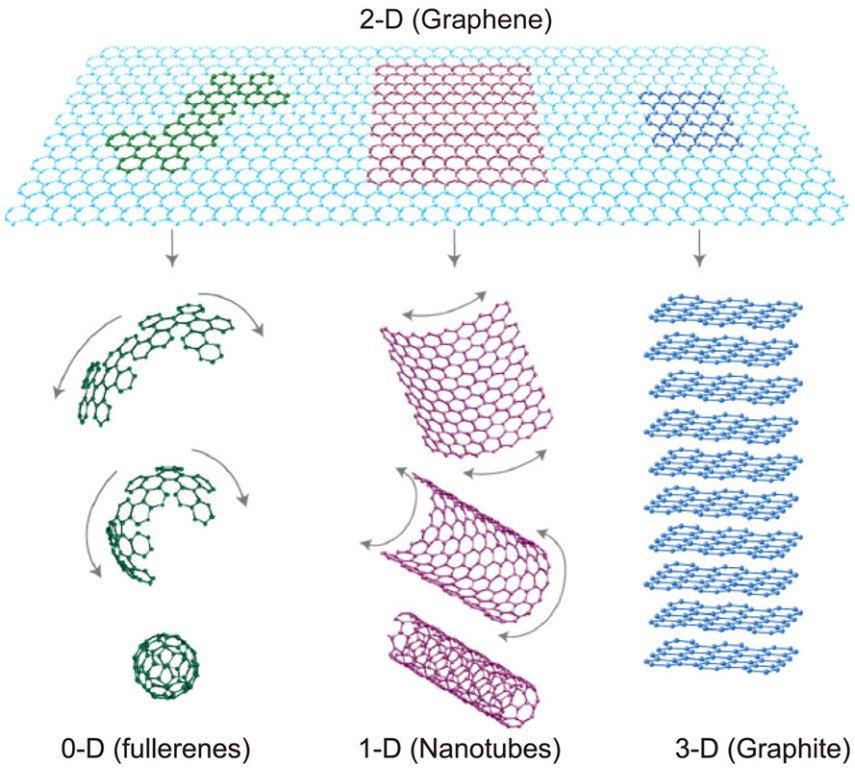

Fig. 1. Common structure of all graphitic forms, which can be changed into 0-D fullerence, 1-D nanotubes, and 3-D graphite (Ref. [21]) (Adapted from Nat. Mater. 2007,(61): 183–191, with permission from Nature Publishing Group).