Review Article

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Graphene: Recent Advances in Engineering, Medical and Biological Sciences, and Future Prospective

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Abstract

Graphene, a two dimensional carbon allotrope, has been appeared as an interesting material of the 21st century, and received a worldwide attention due to its extraordinary thermal, optical, and mechanical properties. Graphene and its derivatives are being studied in different fields of science from medicine and pharmaceutics to engineering and industries. Graphene materials have been mainly explored in electronics, clean energy devices, biosensors, and environmental remediation. In biomedicine field, their antimicrobial activity and capacity as drug delivery or gene delivery platforms and tissue engineering scaffolds have been reported. This article provides an overview of graphene and its recent advances in different fields including biomedicine and industries.

Keywords: Biomedicine, Clean energy, Drug delivery, Graphene, Sensors.

1. Introduction

Since 2010 that Andre Geim and Novoselove won noble prize in physics for groundbreaking experiments regarding the two dimensional (2D) material graphene, graphene has attracted the attention of many researchers all over the world (1). Graphene is a single- or few-layered sheet of Sp_2-bonded carbon atoms synthesized from graphite (2). In graphite, van der Waals forces keep graphene sheets tightly together (3). Carbon allotropes include 0D fullerenes, 1D carbon nanotubes, 3D graphite, and graphene, which is 2D one (Figure 1) (4). Due to their unique physical and chemical properties, graphene and its derivatives (graphene oxide (GO), reduced graphene oxide (RGO), carboxylated GO, and GO-nano composites) have attracted tremendous attention in different fields of science such as energy technology, biotechnology, biopharmaceuticals, medicine,

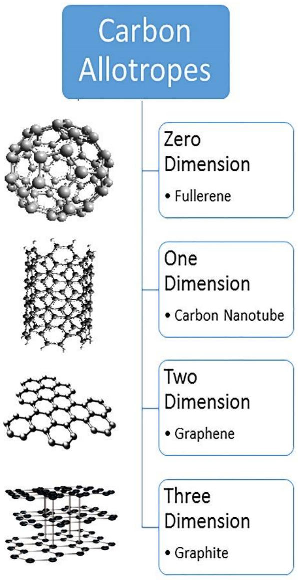

Figure 1. Different types of carbon allotropes.

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electronics, *etc* (5). These properties include high surface area, excellent electrical conductivity, strong mechanical strength, unparalleled thermal conductivity, scalable and low cost method of synthesis, and ease of functionalization (6, 7). Here in, we will describe graphene applications in industries and biomedicine, and its perspective will be discussed.

2. Applications in engineering and industries

Recent years have witnessed many breakthroughs in research on graphene, as well as a significant advance in the mass production of this material. Here, we review recent progresses in graphene research for various engineering and industrial applications.

2.1. Electronics

Graphene provides an ideal system to study the transport behavior and interactions of π-electrons. Its 2D monolayer structure permits direct access to the whole material, a requirement for high-tech applications of graphene, particularly in electronics (8).Possibility of production of large quantities at low cost, the ease to functionalize, and compatibility with various substrates make them an attractive candidate for high yield manufacturing of graphene-based electronic and optoelectronic devices, such as field effect transistors, chemical/bio sensors, organic solar cells, flexible touch screens, photodetector, phototransistors, emitters, transparent electrodes in photovoltaic devices and electronic skin (9-11).

2.2. Sensors

Surface adsorption, large specific surface area, best surface to volume ratio, and high electron mobility make monolayer graphene a promising candidate for different sensors, including chemical, electrochemical, photoelectrical, electric field, and magnetic field sensors and especially biosensors (12-15) .

Charge transfer between the adsorbed molecules and graphene is proposed to be responsible for the chemical response. As molecules are adsorbed to the surface of graphene, the location of adsorption causes a charge transfer with graphene as a donor or acceptor, thus changing the carrier density, and electrical resistance of graphene, which can be detected as a value for calculating a variable (6). Graphene has been extensively attracted attention in biosensing, since 2008 when Mohanty et al. detected bacterium, DNA, and proteins by graphene electronic devices (16, 17).The significant sensitivity of graphene-based biosensors also provides opportunities for detecting infectious organisms and disease biomarkers at concentrations that cannot be measured by current conventional methods. The majority of papers are focused on the application of graphene immunosensors for detection of cancer markers. Biomarker detection is relatively complex in biological samples such as blood (18). Despite many publica¬tions on graphene-based biosensors, the advan¬tages of these biosensors over the conventional bioassays should be explained and their reliability and reproducibility need more studies.

2.3. Clean Energy Devices

Solar cells, rechargeable lithium ion batteries (RLBs), and electrochemical double layer capacitors (EDLCs) are believed to provide clean energy with almost zero waste emission (19). Graphenebased solar calls reveal high performance, low prices, reproducibility and long-term stability (20). Graphene-based electrode materials with appropriate defects and alignment pattern of graphene sheets displayed enhanced capacitive activity and better cycling performance compared to that of graphite in RLBs. The encapsulation of metal or metal oxide nanoparticles with graphene can improve significantly the cycling performance of the particles as anode in RLBs (21). An enhanced power density of EDLC can be achieved via the incorporation of graphene into the electrodes (22).

2.4. Environmental remediation

Environmental pollution by both water soluble toxic pollutants, as well as greenhouse gases, is causing great alarm all over the world. Graphene-based materials show high adsorption capacity for water and air pollutants. Graphene functionalized composites show enhanced performance in adsorption via strong π-π interactions. The important pollutants in water include anions and heavy metal cations. Air pollutants include toxic gases and particulates, can cause significant damages to the environment and human health (23). Multiple studies have investigated the graphene materials on the adsorption and degradation of pollutants for water and air remediation (24-27).

3. Applications in biomedicine

Since the first report of drug delivery using pegylated graphene oxide by Liu et al. (28), graphene-based materials have been intensively investigated in biomedicine and show a great potential, as well as the capability to adsorb a variety of aromatic biomolecules through a π-π stacking interaction or electrostatic interaction. Biomedical applications utilize the properties of graphene in several ways and also their toxicity as a major concern will be described.

3.1. Drug delivery

The major advantage of graphene over other nano materials is its ultrahigh surface area and sp2 hybridized carbon area, which makes it a good candidate for drug delivery by loading large amounts of drug molecules (29). GO is the most useful derivative of graphene in biomedicine. Lots of studies have investigated GO for drug delivery. GO can add advantages to drugs, such as improvement of solubility or potency. For example, a pegylated GO (GO-PEG) was designed as a carrier for anticancer drug SN38with an aromatic structure. Aromatic drugs are insoluble in water. The hydrophobic aromatic molecules of SN38 were non-covalently attached to GO-PEG via stacking. The resulting GO-PEG-SN38 complex showed excellent water solubility, while maintaining its high cancer cell killing potency similar to the free SN38 in organic solvents. The efficacy of GO-PEG-SN38 was far higher than irinotecan (28). Another example is loading doxorubicin (DOX) on GO with high loading efficacy. The hydrophilicity and solubility of DOX were increased in this system (30). A mixture of anticancer drugs, DOX and camptothecin (CPT), was loaded on the folic acid-conjugated GO (FA-GO) via π-π stacking and hydrophobic interactions. FA-GO loaded with the two anticancer drugs showed a remarkably higher cytotoxicity compared to GO loaded with only a single drug (31).

3.2. Gene delivery

Viral gene carriers have some disadvantages, such as mutagenicity, oncogenicity, several host immune responses, and high cost of production (32). Non-viral carriers were developed to solve these problems. One of these carriers is GO, which has been widely used to interact with DNA through π-π stacking interactions (33). Usually GO grafted biocompatible polymer, using PEI (poly ethylene imine), chitosan or PEG appears more efficient and biocompatible in gene deliver. The PEI-functionalized GO-encapsulated gold nanoparticles were used to delivery DNA into HeLa cells and exhibited much lower cytotoxicity and transfection efficiency (65% efficiency and 90% viability)(34). Bao and his co-workers reported the synthesis of chitosan-based functionalized GO (GO-CS) as a gene carrier, which showed reasonable transfection efficiency in HeLa cells at certain nitrogen/phosphate ratios (35). GO, as the cooperative vehicle in delivery of drugs and genes, was also investigated. PEI was covalently linked to GO via a facile amidation process. PEI-GO enabled loading of siRNA via electrostatic adsorption and DOX via π-π stacking, and the anticancer efficiency was meaningfully enhanced(36). PEI functionalized GO nanosheets with vascular endothelial growth factor-165(VEGF) gene was formulated and incorporated in the low-modulus methacrylated gelatin hydrogel. Hydrogels were injected intramyocardially to the rat models. Results showed a proliferation in myocardial capillary density at the injected region and a decrease in scar area (37). Yue *et al* raised a GO-PEG- PEI nanocarrier for the delivery of Cas9/single-guide RNA (sgRNA) complexes for gene editing. The results demonstrated that the nanocarrier can be used successfully for efficient gene editing in human AGS cells with an efficiency of ~39% and protect sgRNA from nucleases (38).

3.3. Photothermal therapy of cancer

GO application has been a progress in photothermal therapy of cancer treatment due to its strong intrinsic near-infrared (NIR) absorbance(39). For instance, GO-iron oxide nanocomposite was investigated to combine tumor bioimaging with photothermal therapy. As a result, solid tumors were effectively ablated by irradiation with 808 nm NIR laser(40). In another study, DOX-loaded PEGylated nanoGO was designed to deliver both the heat and drug to the tumorigenic region to combine chemotherapy and photothermal treatment in one system. Results demonstrated that the designed approach was significantly superior to chemotherapy or photothermal treatment alone(41). Therefore, irradiating GO with NIR light after its intracellular uptake by cancer cells can be used as a noninvasive technique for cancer therapy in combination with its advantages as an appropriate nanocarrier for antineoplastic drugs.

3.4. Tissue engineering

Graphene has high elasticity, strength, flexibility, planar geometry, and surface roughness (42). Thus, it can be used as a reinforcement material in hydrogels, biodegradable films, electrospun fibers and other tissue engineering scaffolds especially for neural and bone tissue engineering (43, 44). GO-chitosan hydrogel scaffolds prepared by covalent linkages of chitosan amino groups with carboxylate groups of graphene improved cell adhesion, differentiation, and proliferation. These scaffolds have better mechanical and biological properties and a lower degradation rate (45). Further, chitosan functionalized graphene did not show toxicity on murine fibrosarcoma L929 cell line (46). In another study, GO-chitosan scaffolds exhibited significant improvements in cell adhesion, differentiation, proliferation, and calcium phosphate deposition by mouse pre-osteoblast MC3T3-E1 cells (47). In Wang et al. study, a fluorinated graphene induced higher proliferation and neuronal differentiation (48).

3.5. Implants and artificial organs

Graphene exhibits a considerable potential for enhancing the surface bioactivation of materials to improve their biomedical applications (49). For example, in Podila et al. study, Graphene was grown on copper substrates via chemical vapor deposition and then transferred onto nitinol substrates. It was found that graphene coating on nitinol substrates could be functional for implant materials and improved the biological response compared to the uncoated nitinol (50). Another study demonstrated that the average mineral apposition rate of the bone and the biomechanical properties of graphene-coated polyethylene terephthalate based artificial ligaments (G-PET-AL) groups were significantly higher than those of the PET-AL graft group. The results indicated that in the G-PET-AL group, there was more newly formed bone than that in PET-AL group (51).

3.6. Application in dentistry

In recent years, the development of graphene nanopowder in a polymer matrix has opened a new capacity in the science of dental materials. Graphene-silver nanopowder has been used as a filler in new dental composites. Sava *et al.* investigated the water absorption and solubility in distilled water and artificial saliva of three composites, two with different percentages in graphene-silver nanopowder and one commercial composite Herculite XRV Ultra (Kerr). The results revealed that the composite with greater amount of graphene presented better results regarding water absorption and flexural strength (52). Kulshrestha and coworkers suggested graphene/zinc oxide nanocomposite as a coating agent for dental implants and simultaneously inhibition of *Streptococcus mutans* biofilms (53). Rosa *et al.* investigated the effect of GO-based scaffolds on dental palp stem cells proliferation and differentiation and indicated that GO provided an up-regulation and enhancement of odotogenic gene expression in dental palp stem cells (54). Moreover, GO has been utilized as an effective bleaching agent. In a study, rGO- cobalt tetraphenylporphyrin (CoTPP) composites were applied as a catalyst for tooth bleaching. H_2O_2 with CoTPP/rGO under photoactivation increased the bleaching effect of H_2O_2 and diminished the treatment time(55).

4. Perspectives on graphene

Graphene may be one of the most useful materials ever discovered. Despite the advantages of graphene, it still faces many challenges in different aspects, from synthesis and characterization to application in various fields, which need to be solved by effective collaborations between chemistry, physics, pharmaceutical sciences, biology, and medicine. Growth in the commercialization of graphene has been significant, especially in the last ten years. There are more than 70 companies that produce graphene powder at a capacity of 100 tons per year, and graphene thin films (with a production capacity of 50,000 m^2 per year) for touch-panel and wearable electronic devices (56). Biomedical devices are still not among the graphene devices coming to the market, because there are still many unresolved issues and challenges in graphene-based biomedical devices such as solubility and cytotoxicity. Few studies have been designed to investigate the toxicological profile of graphene *in vitro* and *in vivo*. Cytotoxicity is the most vital concern about graphene based biomedical devices which are related to variable factors including dose, shape, surface chemistry, exposure route and purity and is still in need of further investigation. We hope that this review, which provides an outlook on some applications of graphene could help scientists from different research areas to realize opportunities in graphene field research.

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Conflict of Interest

None declared.

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