International Journal of Advance Research in Science and Engineering
Vol. No.6, Issue No. 08, August 2017
www.ijarse.com
IJARSE
ISSN (O) 2319 - 8354
ISSN (P) 2319 - 8346

THE SIGNIFICANT AND MEDICAL APPLICATIONS OF GRAPHENE NANOPARTICLES

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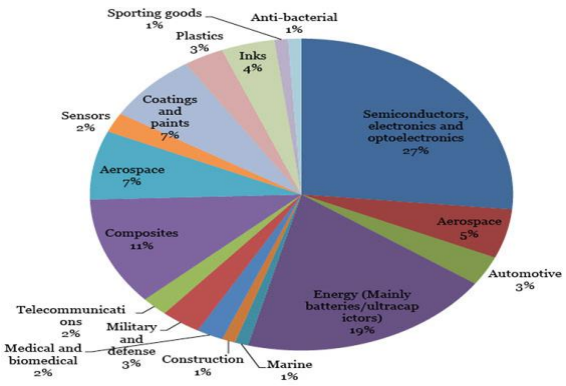
ABSTRACT

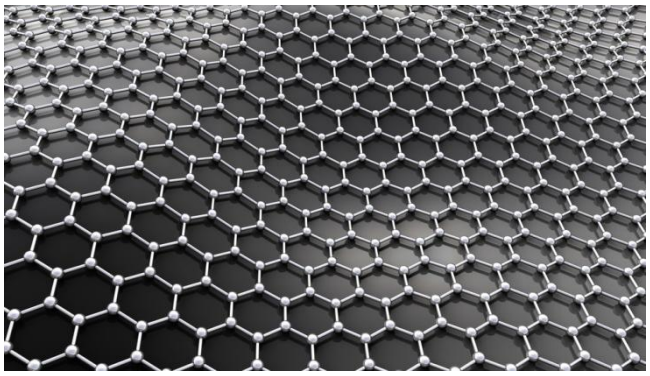
Graphene exhibits unique 2-D structure and exceptional physical and chemical properties that lead to many potential applications. Among various applications, biomedical applications of graphene have attracted ever-increasing interests over the last three years. In this review, we present an overview of current advances in applications of graphene in biomedicine with focus on drug delivery, cancer therapy and biological imaging, together with a brief discussion on the challenges and perspectives for future research in this field.

Keywords: graphene, biomedical application, drug delivery, biosensing, bioimaging.

I. INTRODUCTION

Graphene, a novel two-dimensional nanomaterial composed of sp^2-bonded carbon atoms, possesses a number of extraordinary electronic, optical, thermal and mechanical properties · With the rapid deveolopment of synthesis and functionalization approches, graphene and its related derivatives have shown outstanding potentials in many fields, such as nanoelectronics , composite materials , energy technology (for examples, fuel cell, supercapacitor, hydrogen storage) , sensors , and catalysis , which have been summarised by several review articles .

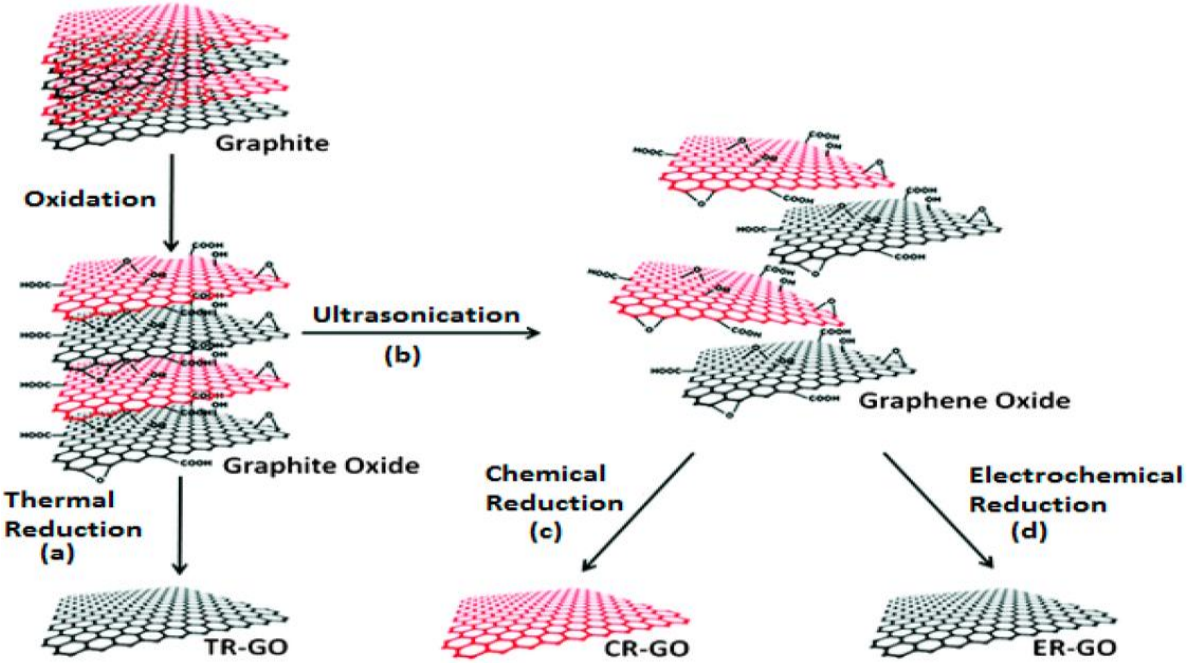




Beyond the applications aforementioned, the biomedical application of graphene is a relative new area with significant potential. Since the seminal report on use of graphene oxide (GO) as an efficient nanocarrier for drug delivery by Dai et al. in 2008, the first study on graphene for biomedical applications, a lot of interesting work has been carried out to explore the use of graphene for widespread biomedical applications, ranging from drug/gene delivery, biological sensing and imaging, antibacterial materials, to biocompatible scaffold for cell culture. The intensive research on the bioapplications of graphene and its derivatives is due to many fascinating

IJARSE
ISSN (O) 2319 - 8354
ISSN (P) 2319 - 8346

properties, such as high specific surface area (2630 m^2/g), exceptional electronic conductivity (mobility of charge carriers, 200,000 $cm^2 V^{-1} s^{-1}$), thermal conductivity (~5000 W/m/K), mechanical strength (Young's modulus, ~1100 Gpa) of graphene, and, intrinsic biocompatibility, low cost and scalable production, and facile biological/chemical fictionalizations of GO .



Synthesis and Characterization Ofgraphene−Nanoparticle Hybrid Materials

Because of the many unique and advantageous properties of graphene and its derivatives, GO and rGO, a significant amount of effort has been invested in utilizing these materials either by themselves, or in combination with other interesting nanoma-terials such as nanoparticles. As mentioned previously, graphene−nanoparticle hybrid materials can be broadly categorized into two main classes on the basis of their structural morphology. They can exist as (1) graphene−nanoparticle composites, where nanoparticles are decorated or grown on sheets of graphene or its derivatives, and (2)graphene-encapsulated nanoparticles wherein nanoparticles are wrapped by graphene or its derivatives. The main difference between these two classes can be found in the relative size ratio that exists between the diameter of the nanoparticles and the lateral dimensions of the graphene sheets. Specifically, when the diameter of the nanoparticles is in the range of a few nanometers to about a hundred nanometers, the nanoparticles are generally small in comparison to the graphene sheets and can easily be decorated onto the sheets, thereby forming graphene−nanoparticle composites. On the other hand, when the size of the nanoparticles is larger and becomes more comparable with the graphene sheets, the small 2D sheets can be wrapped around the nanoparticles resulting in graphene-encapsulated nanoparticles. In this section, we will begin bybriefly describing the primary methods used to produce graphene, GO, and rGO. This will be followed by an in-depth analysis of the various methods that have been developed for the synthesis of graphene−nanoparticle hybrid structures, with particular emphasis on the properties and characteristics that result from these different procedures.

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IJARSE
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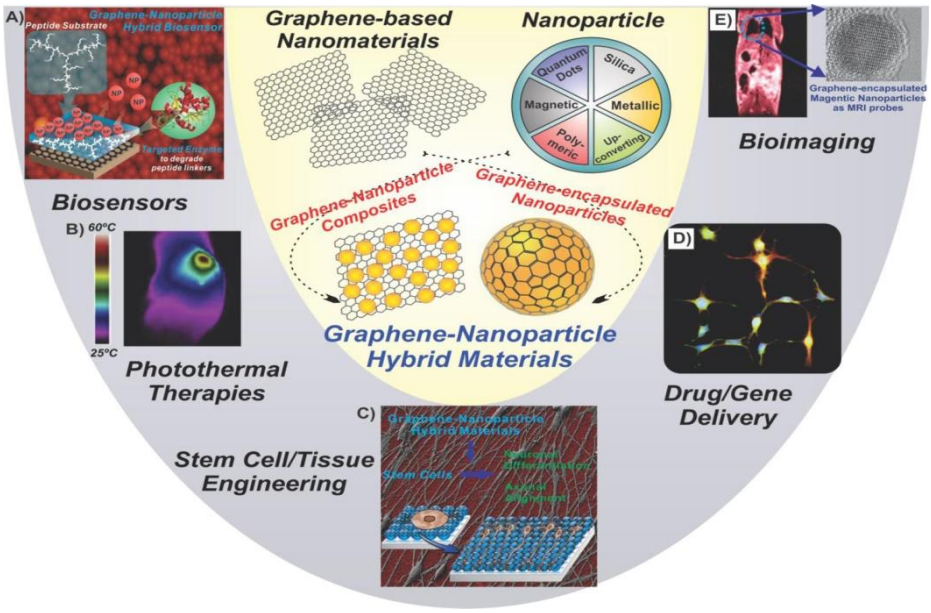
II. MEDICINAL APPLICATIONS



III. DRUG DELIVER

GO, produced by vigorous oxidation of graphite by Hummers method , is an ideal nanocarrier for efficient drug and gene delivery. GO used for drug delivery is usually 1-3 layers (1-2 nm thick), with size ranging from a few nanometers to several hundred nanometers . The unique structural features, such as large and planar sp^2 hybridized carbon domain, high specific surface area (2630 m^2/g), and enriched oxygen-containing groups, render GO excellent biocompatibility, and physiological solubility and stability, and capability of loading of drugs or genes via chemical conjugation or physisorption approaches. Moreover, the reactive COOH and OH groups GO bears facilitate conjugation with various systems, such as polymers , biomolecules (biotargeting ligand , DNA , protein , quantum dots , Fe_3O_4 nanoparticles , and others), imparting GO with multi-functionalities and multi-modalities for diverse biological and medical applications.

Inspired by the ideas for carbon nanotubes-based drug delivery , Dai *et al.* explored for the first time nanoscale GO (NGO) as a novel and efficient nanocarrier for delivery of water insoluble aromatic anticancer drugs into cells . In their approach, NGO was first conjugated with an amine-terminated six armed polyethylene glycol (PEG) molecule, followed by loading of a water insoluble anticancer drug, SN38 onto NGO surface by simple non-covalent adsorption via π-π stacking. The PEG-functionalized NGO loaded with SN38 exhibited high cytotoxicity for HCT-116 cells, 1000-fold more potent than CPT-11. In another work, the same group studied targeted delivery of chemical drugs into cells by using a Rituxan ($CD20^+$ antibody) conjugated NGO-PEG This work further demonstrated that the drug release from the GO surface was pH dependent, suggesting the possibility of pH-controlled drug release. The pH-sensitive drug release behavior from many different GO-based drug delivery systems was also studied later by Chen et al. , Shi and colleagues , Misra et al. , and our group . Apart from pH-activated drug release, recently Pan and colleagues developed a thermo-responsive drug delivery cargo, poly(N-isopropylacrylamide) grafted graphene sheets.

The exploration of GO-based drug delivery expands from anticancer drugs to other drugs for non-cancer diseases treatment. Most recently, Rana et al. reported the delivery of an anti-inflammatory drug, Ibuprofen, by

IJARSE
ISSN (O) 2319 - 8354
ISSN (P) 2319 - 8346

using a chitosan-grafted GO. In this case, the loading rate of Ibuprofen on the GO sheet was determined to be 9.7%. Furthermore, the work demonstrates that controlled drug release can be achieved by adjustment of pH value.

To enhance the anticancer effect, Yang and colleagues designed and prepared a magnetic- and bio- dual targeting drug delivery cargo based on GO-Fe_3O_4 nanoparticle hybrid. The *in vitro* experiments indicated specific targeting of the multifunctional drug carriers by SK3 human breast cancer cells. Clearly, *in vivo* study is desired to demonstrate the performance of this external magnetic field-guided and bio-targeted drug delivery system.

IV. GENE DELIVERY

Gene therapy is a novel and promising approach to treat various diseases caused by genetic disorders, including cystic fibrosis, Parkinson's disease, and cancer. Successful gene therapy requires a gene vector that protects DNA from nuclease degradation and facilitates cellular uptake of DNA with high transfection efficiency . The major challenge facing the development of gene therapy is lack of efficient and safe gene vectors . Recently Liu et al. and our group studied gene delivery using polyethylenimine (PEI)-modified GO (PEI-GO). GO conjugated with positively charged PEI allows condensation of plasmid DNA onto the surface of GO sheet through electrostatic interaction arising from the cationic polymer. Liu and colleagues examined the transfection efficiency of GO-PEI-10K and GO-PEI-1.2K and compared with the unbound polymers PEI-10K and PEI-1.2K, respectively. Their experiment indicates that grafting PEI to GO not only significantly lowered the cytotoxicity of the cationic polymer, but also improved the transfect ion efficiency of the polymer. We also found much higher luciferase expression in HeLa cells with PEI-GO/pGL-3 complexes (2.75×10^9 RLU/mg protein) than that of PEI/pGL-3 complexes (2.07×10^9), and high DNA transfection efficiency by PEI-GO in HeLa cells even in the presence of 10% FBS .

V. CANCER THERAPY

Much success has been made on exploration of graphene in drug delivery by in vitro test, as we discussed above. For clinical cancer and other disease treatment, the in vivo behavior of graphene loaded with drugs must be investigated. Liu and colleagues for the first time studied in vivo tumor uptake and photo thermal therapy with PEGylated GO using xenograft tumor mouse models. They observed very high tumor uptake of the PEG-modified GO due to highly efficient tumor passive targeting of GO caused by EPR effect. Moreover, under the low-power near-infrared (NIR) laser irradiation on the tumor, a highly efficient tumor destruction was achieved, taking the use of strong absorbance of GO in the NIR reg

VI. BIOSENSING AND BIOIMAGING

Biosensing

Graphene derivatives, including pristine graphene, GO, chemically reduced GO (rGO) and doped graphene have been intensively studied for their widespread applications in biosensing and detection of biomolecules such as thrombin , ATP , oligonucleotide , amino acid , and dopamine

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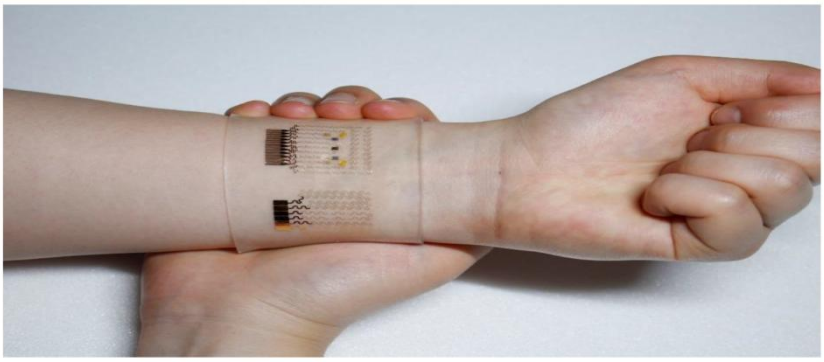
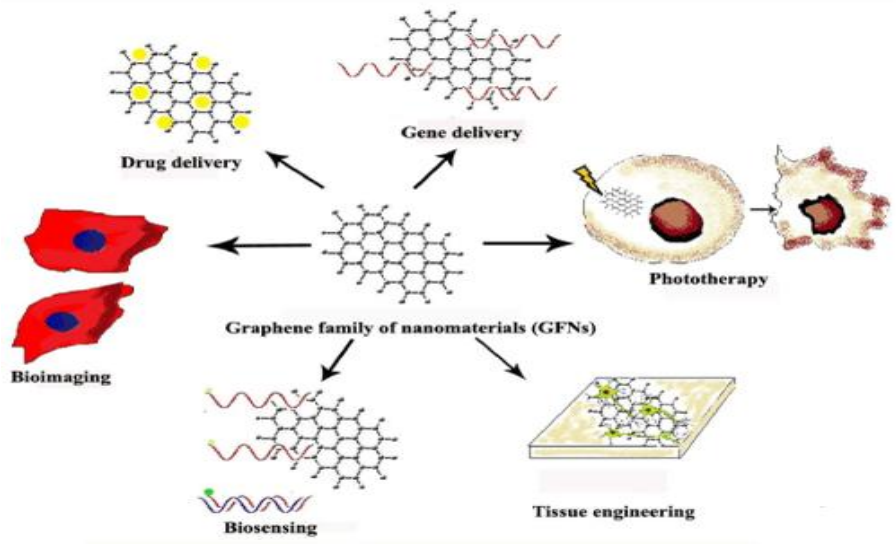
ISSN (O) 2319 - 8354
ISSN (P) 2319 - 8346

Skin-based Diabetes Monitoring and Therapy



on Bioimaging

Exploration of feasibilities of GO in biological imaging with optical and magnetic modalities has just started recently . Dai et al. for the first time examined cellular uptake of PEG-modified GO loaded with chemical drugs using intrinsic fluorescence of GO in the NIR region. Later, another group studied gelatin-grafted rGO labeled with a fluorescence dye for cellular imaging and drug delivery.



Other Applications

VII. GO-BASED ANTIBACTERIAL MATERIALS

Fan et al. prepared macroscopic freestanding GO and rGO paper from their suspension by vacuum filtration technique, and found that these papers exhibit strong antibacterial effect. Considering the scalability and low cost of the graphene-based antibacterial paper, this work opens new opportunities for the use of GO in environmental and clinical applications.

VIII. GO-BASED SCAFFOLD FOR CELL CULTURE

Min group studied the behavior of NIH-3T3 fibroblasts as a model of mammalian cells growing on a supported film of GO . Their work suggests that GO film induces no significantly harmful effect on the mammalian cells

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ISSN (O) 2319 - 8354
ISSN (P) 2319 - 8346

with respect to adhesion, and exhibits remarkably high gene transfection efficiency, 250% that of cells grown on a cover glass substrate. The result indicated the potential application of GO as a surface coating material for implant.

IX. CONCLUSIONS AND PERSPECTIVES

As in many other fields, the research on biomedical applications of graphene has seen dramatic progress, and is expanding rapidly, yet mostly in its initial stage. The advances made in this area so far are exciting and encouraging, the challenges we face, however, are also very huge and must be overcome. One of such challenges is thorough and profound understanding of graphene-cell (or tissue, organ) interactions, especially the cellular uptake mechanism. Such knowledge certainly facilitates development of more efficient graphene or GO-based nanoplatform for drug delivery, biosensing and other applications, which, however, is still lacking at the moment. The toxicity of graphene and GO, at in vitro and in vivo level, is another major concern. At the current stage there are only a few publications in this regard. The preliminary results indicate that the physicochemical properties such as flat shape and charges, are closely related to the cytotoxicity, and affect in vivo biodistribution and fate of GO . The mechanisms of the in vitro biotoxicity caused by graphene are related to oxidative stress and damage of cell membrane.

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