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Review article

# Reinforcing nanomedicine using graphene family nanomaterials

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ABSTRACT

Graphene is an allotrope of carbon which consists of single layered $sp^2$ hybridized carbon arranged in honey comb lattice. The fascinating properties such as ultrahigh surface area, high electrical and thermal conductivity and optical property made graphene a major point of research interest. Apart from their application in the field such as nanoelectronics, energy storage, engineering of nanocomposite materials, transistors, sensors, diodes, catalysis; they are also investigated in the field of nanomedicine. This review mainly focus on the applications of graphene in nanomedicine including drug delivery, cancer therapy, cellular imaging, gene therapy, photodynamic and photothermal therapy, antimicrobial activity, biosensing and tissue engineering, along with a short description of their unique physicochemical, biological properties and safety profile.

## 1. Introduction

Graphene based nanomaterials possess unique physicochemical and biological properties leading to the exploration of their applications in many fields such as engineering, drug delivery, gene therapy etc. Graphene represents the thinnest form of carbon. In 2010, Andre K. Geim and Konstantin S. Novoselov were honored with Nobel Prize (Physics) for its discovery. Among the various members belonging to carbon family; graphene made a unique position due to its extraordinary physicochemical, thermal, optical, mechanical and biological properties. The research on graphene and its derivatives are still going on; which further expanded their application range [1]. The planar structure of graphene ensures effective loading of a variety of substances like metals, drugs, fluorescent probes, nucleotides and other biomolecules, there by promising their application in drug delivery, gene delivery, biosensing, bioimaging, tissue engineering etc. [2–4]. The main feature that makes graphene superior in drug delivery application is their large surface area, which is four times higher than that of other nanomaterials investigated for drug delivery [2,5,6].

Graphene family nanomaterials (GFN), consisting of single layered graphene, multiple layered graphene, the oxidized form of graphene (graphene oxide, GO) and reduced form of graphene oxide (rGO) (Fig. 1). In addition to the purity and surface chemistry, difference can be noted in defect density and composition of each member of GFN. Single layered graphene is having higher surface area. When the number of layers increases, the surface area decreases and the rigidity increases. Lateral dimensions of graphene affect the cellular uptake, renal clearance, blood-brain barrier transport etc. [1,2,5–8]. Owing to the difficulties associated with synthesis of single layered defect free graphene, and their high reactivity, multilayered graphene or GO are commonly investigated for biological applications [1,9,10].

GO, being the oxidized form of graphene is rich in oxygen containing functional groups on their surface. The carboxyl groups are responsible for the negative charge having a pH dependency in addition to providing stability for their colloidal dispersions. The surface reactions are facilitated by epoxide and hydroxyl group on the basal plane. The reduction in the thermal, mechanical and electrical properties of GO is associated with high defect density created by the functional groups [1,9,11]. GO on reduction, resulting in the formation of rGO, with reduced oxygen content, improves the electrical conductivity and optical absorbance [1,7,9,12].

*Abbreviations:* GFN, graphene family nanomaterials; GO, graphene oxide; rGO, reduced graphene oxide; TLR4, toll-like receptor 4; PEG, polyethylene glycol; CPT, camptothecin; SN-38, 7-ethyl-10-hydroxy camptothecin; PNIPAM, poly *N*-isopropyl acrylamide; NGO, nano graphene oxide; CCK-8, cell counting kit-8; KGM/SA, konjac glucomannan/sodium alginate; CLSM, confocal laser scanning microscopy; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; QDs, quantum dots; GQDs, graphene quantum dots; Ce6, chlorine e6; HA, hypocrellin A; BPEI, branched poly ethylenimine; Bcl-2, B-cell lymphoma 2; PEI, poly ethylenimine; VEGF, vascular endothelial growth factor; Ge IMA, methacrylated gelatin; MIC, minimum inhibitory concentration; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; hASCs, human adipose derived stem cells; GNP, graphene nanoplatelets; BMP-2, bone morphogenetic protein-2; SPR, plasmon reference chip

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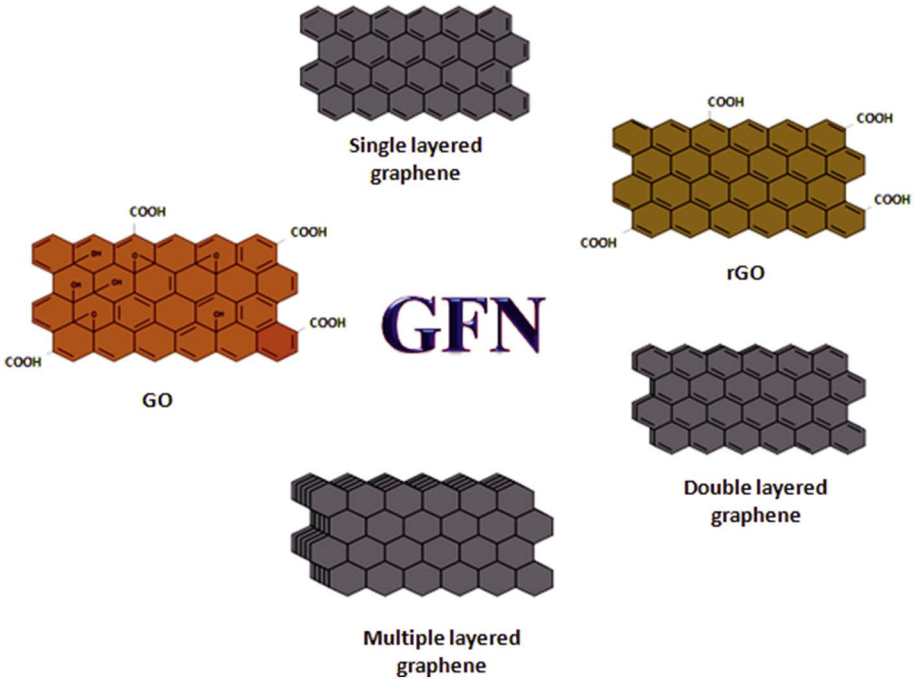


**Fig. 1.** Graphene family-nanomaterials: single layered graphene, double layered graphene, graphene oxide (GO), reduced graphene oxide (rGO) and multiple layered graphene.

## 2. Properties of graphene

### 2.1. Physicochemical properties

Graphene consisting of 2D $sp^2$ hybridized carbon atoms joined together by sigma bond. Each carbon atom of graphene possesses a free π electron, which contributes to the formation of electron network, thereby promoting the electrophilic substitution rather than nucleophilic substitution. Introduction of defects in the planar structure of graphene further enhances their chemical reactivity. These properties in addition to large surface area made graphene an investigation point in drug delivery applications [13].

### 2.2. Thermal and electrical properties

Graphene has excellent thermal and electrical conductivity due its strong carbon-carbon bonding. The single layered defect free structure of graphene is responsible for its high thermal conductivity. The defects developed during the chemical modification reduce the electrical conductivity of graphene [14]. Their unique thermal and electrical properties resulted in their use in the development of electronic and biomedical devices.

### 2.3. Optical properties

Graphene shows good light absorption property, with a maximum absorption at 268 nm. The light transmittance decreases with the conversion of GO to graphene. The higher transmittance of insulated GO in contrast to pristine graphene or rGO is attributed to their different electronic structures [15]. Properties such as absorption of light and image contrast are influenced by the presence of layer in graphene; with increased number of layers enhancing both properties. The nanoribbons and quantum dots of graphene are luminescent in nature, whereas loosening of π electron network results in photoluminescence [1]. Photoluminescent properties of nano GO in the visible and infrared region break ground their application in cellular imaging [16]. In addition to photoluminescent property and high light transmittance, the charge mobility character of graphene contributes to their application in magnetic resonance imaging and biomedical imaging [1].

### 2.4. Mechanical properties

Graphene is one of the strongest materials, having mechanical strength about 1100 GPa. Mechanical properties of GO, which are lower in comparison to graphene, can be enhanced by cross linking of individual particles [17,18]. Conjugation of graphene with polymers enhances the modulus and hardness for its biological applications. Incorporation of carbon nanotubes or nanodiamonds in to the polymer composite further enhances the stiffness and hardness [19,20].

### 2.5. Biological properties

Graphene family nanomaterials can be used for delivery and detection of DNA and RNA, owing to its adsorption character. Graphene possessing positive charge is capable of interacting with negatively charged nucleotides; there by protecting them from nuclease enzymes [21–23].

## 3. Safety profile of graphene

The non biodegradable nature of graphene contributes to its health hazards and environmental hazards [16,24]. GO and rGO are biocompatible and biodegradable due to their water dispersibility, potentially less toxicity in human cell type and safer for biological applications [25]. Graphene having large surface area interact with the biological tissues and triggers the production of reactive oxygen species; leading to toxic effects, which further depends on the concentration, shape and time of exposure [26]. An important concern regarding use of GO is that it decreases the activity of macrophages by interacting with toll-like receptor 4 (TLR4) and produces oxidative damage [27]. The safety profile of a graphene based nanosystem has been evaluated in zebrafish. The developed curcumin loaded Polyethylene glycol (PEG) functionalized GO-nanocomplex was found to be excreting from the body rapidly, without effecting their growth [28]. The functionalization of graphene with polar groups minimizes their hydrophobicity and thereby potential toxicity [29].