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Review

Graphene oxide — A platform towards theranostics

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ABSTRACT

Due to the abundance of its utilization in various applications, ranging from electronics to biomedicine, recent data witnessed manifold increase in the commercial potential of graphene oxide based biomaterials. Major contribution of such increased potential comes from the work on graphene oxide which carries unparalleled advantage over graphene itself and/or reduced graphene oxide. Few reviews have been published in previous years which have highlighted the capacity of graphene oxide in drug delivery and photothermal therapy application. But this review exclusively provides an outlook for the role of graphene oxide based magnetic composites in constituting a theranostic system through previously inaccessible options. These composites have been exploited for their use in drug delivery applications, biosensing, bioimaging and phototherapy. This review discusses the potential challenges and advantages of using graphene oxide based magnetic nanocomposites systems to explore much needed length and breadth of theranostics, not fully elaborated so far.

Contents

1. Introduction

Graphene is a single sheet of an atom thickness having sp^2 hybridized carbon atoms, arranged in a honeycomb like lattice [1]. In this lattice like structure, each carbon atom is attached to another carbon atom in the same plane *via* covalent carbon/carbon bond. While the interlayers are arranged through weak Van der Waal forces. These forces are responsible for softness of this material. Presence of aromatic structure, free π-π electrons and reactive sites on the periphery are the reasons for its diverse usage [2,3].

Graphene exists in many forms such as graphene sheets, graphene oxide (GO) and reduced graphene oxide (rGO) [4–6]. Properties which makes GO a material of choice in the field of biomedicine especially theranostics include its biocompatibility and biodegradability [7,8], its large surface area (2630 m^2/g approximately) [9] and high aspect ratio for modifications [10], its un-matched thermal conductivity *i.e.* 5000 W/m/K [11], its tendency to disperse well in aqueous medium, its better colloidal stability compared to other carbon based materials [12], its capability of traversing the plasma membrane and its cost effectiveness and scalability [13].

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Existing challenges for successful commercial applications of GO include reproducibility of the functionalized GO layers or composites [14,15] and limited and/or contradictory data available on *in vitro* and *in vivo* toxicity of graphene as biomaterial [16–18] However, despite all the hurdles and difficulties in capping a suitable system for biomedical usage, GO has 62.6% research weightage towards biomedical applications in contrast to its non-medical usage [19–22]. Many of these research products ranging from synthesis procedures to their real-time applications are being patented thereby signifying their potential usage in everyday life [23–28].

There are two kinds of modifications that are generally carried out to functionalize GO nano-sheets namely, covalent and non-covalent modifications [29,30]. Covalent functionalization occurs due to mutual sharing between adjoining chemical moieties whereas non-covalent modifications include electrostatic, hydrophobic, physisorption, hydrogen bonding and π-π stacking. Presence of various functional groups such as epoxide, hydroxide and carboxyl groups provide endless possibilities to tailor covalent linkages to make desired system [31,32]. Both these modification techniques have been employed with variations and both have their own downsides. For example non covalent interactions are weak therefore show instability to external environment *in vitro* and *in vivo* while covalent modifications allow less quantity of drugs (aromatic) to be uploaded since GO sheets are also occupied by the coated polymers or other functional moieties [33–36].

1.1. Graphene oxide composites

Remarkable properties of GO are mainly associated with chemical modifications & its combine effect with various entities such as polymers and magnetic nanoparticles (Fig. 1). Since GO tends to aggregate under the physiological conditions (due to the presence of salts, ions and proteins) thereby reducing the proposed effectiveness, these modifications not only help retain its effectiveness but also reduce toxicity of the other component.

Most of the composites include chemical moieties that provide biocompatibility (*e.g.* poly ethylene glycol (PEG), poly vinyl chloride (PVC)) [37–39], thermo/stimuli responsiveness (*e.g.* poly (*N*-isopropylacrylamide) (PNIPAM) [40,41], enhance mechanical properties (PMMA, PVC) [42–44], used for the surface coating of the biomaterials (*e.g.* dextran, polyamide 11) [45] and enhance colloidal stability (Sulfonic acids, Oleylamine) [46] (Fig. 2).

Therefore, a lot of research highlights the use of GO in drug delivery application [35,48,49], magnetic resonance imaging (MRI) [50–52], fluorescence imaging [53], antibacterial activity [54], biosensors [55–60] and hyperthermia [61,62]. Despite of all this available literature, there is a dearth of knowledge towards GO based magnetic nanocomposites and its role in theranostics [63,64].

This review entails the compilation of studies carried out on the GO composites used in theranostics from 2010 to 2017 (Fig. 3). In contrast to previous studies, this information is sorted and lately discussed to evaluate the potential challenges and advantages of using GO based magnetic nanocomposites for theranostics.

2. Graphene oxide for theranostics (therapeutics and diagnostics)

2.1. Drug delivery applications of graphene oxide (therapeutics)

Maintaining the efficacy of therapeutic drugs is a major driving force behind drug delivery research. In order to maintain the efficacy of drugs, long term sustained release of drug through blood circulation is required. SN 38 is considered as water insoluble drug and its dispersion is an issue which hampers its potency to attack colon cancer cells. Dai et al., used PEG conjugated graphene nanosheets with non-covalent adsorption of SN38 [38]. This non-covalent adsorption was driven by hydrophobic interaction and π-π stacking. Through this system, they were able to attain controlled release along with high potency *i.e.* IC 50 value 6 nM for Human Colon Cancer Cell line (HCT cells) in comparison to its pro-drug, a hydrophobic analogue Camptothecin (CPT-11). Further this group used PEG-NGO for the targeted delivery of Rituxan (CD 20 antibody) and Doxorubicin (DOX) (Fig. 4). This system exhibited pH dependent drug release [65].

Zhang and colleagues tested the ability of graphene nanosheets to carry multiple anticancer drugs at a time. This approach was one of its kind and significant to reduce drug resistance occurring for many cancer treatments thereby reducing their efficacy over time. They used NGO functionalized with sulfonic acid groups which was decorated later

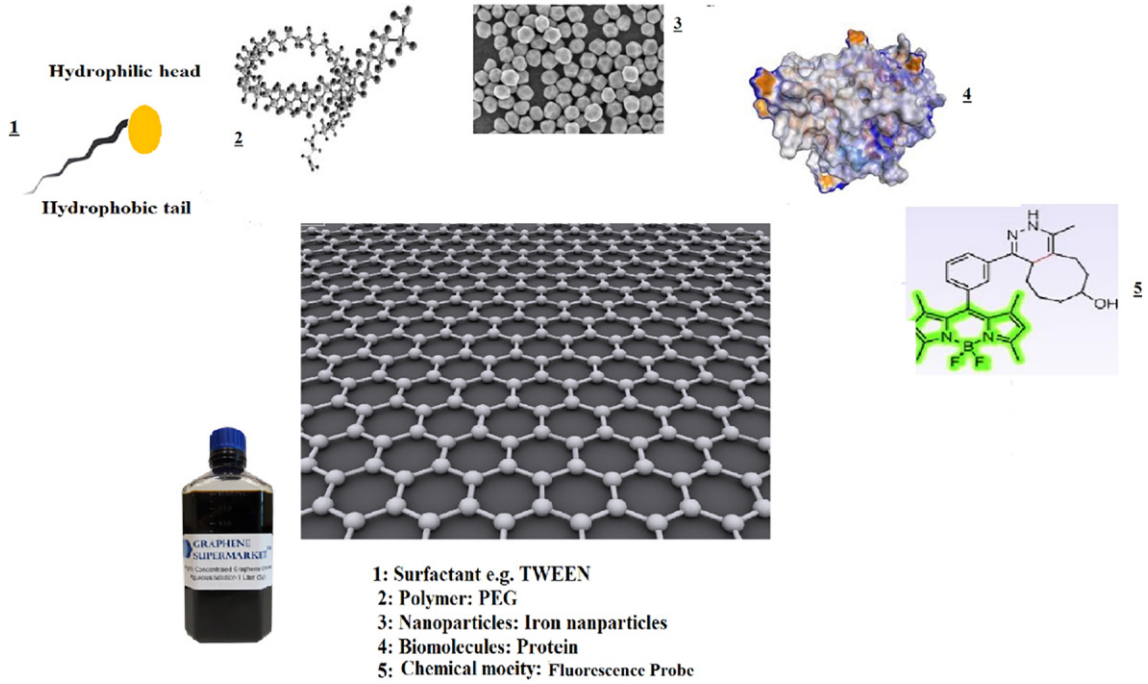

Fig. 1. Depiction of modifications that can be made to modify GO.