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Review

Graphene and graphene oxide as new nanocarriers for drug delivery applications

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ABSTRACT

The biomedical applications of graphene-based materials, including drug delivery, have grown rapidly in the past few years. Graphene and graphene oxide have been extensively explored as some of the most promising biomaterials for biomedical applications due to their unique properties: two-dimensional planar structure, large surface area, chemical and mechanical stability, superb conductivity and good biocompatibility. These properties result in promising applications for the design of advanced drug delivery systems and delivery of a broad range of therapeutics. In this review we present an overview of recent advances in this field of research. We briefly describe current methods for the surface modification of graphene-based nanocarriers, their biocompatibility and toxicity, followed by a summary of the most appealing examples demonstrated for the delivery of anti-cancer drugs and genes. Additionally, new drug delivery concepts based on controlling mechanisms, including targeting and stimulation with pH, chemical interactions, thermal, photo- and magnetic induction, are discussed. Finally the review is summarized, with a brief conclusion of future prospects and challenges in this field.
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1. Introduction

The development of new and effective drug delivery systems with the ability to improve the therapeutic profile and efficacy of therapeutic agents is one of the key issues faced by modern medicine. Advances in nanoscience and nanotechnology, enabling the synthesis of new nanomaterials, have led to the development of a number of new drug delivery systems [1,2]. The recent discovery of graphene has been accompanied by increasing research attention to explore this new material for drug delivery applications. Graphene, a single layer of sp^2-hybridized carbon atoms arranged in a honeycomb two-dimensional (2-D) crystal lattice, has evoked enormous interest throughout the scientific community since its first appearance in 2004 [3]. Due to its unique structure and geometry, graphene possesses remarkable physical–chemical properties, including a high Young's modulus, high fracture strength, excellent electrical and thermal conductivity, fast mobility of charge carriers, large specific surface area and biocompatibility [4,5]. These properties enable graphene to be considered as an ideal material for a broad range of applications, ranging from quantum physics, nanoelectronics, energy research, catalysis and engineering of nanocomposites and biomaterials [5–9]. In the area of nanomedicine, graphene and its composites have emerged as new biomaterials that provide exciting opportunities for the development of a broad range of applications, including a new generation of biosensors, nanocarriers for drug delivery and probes for cell and biological imaging [10–14].

Graphene is a basic building block for other graphitic materials with different geometries (Fig. 1), which can be wrapped into spherical structures (zero-dimensional fullerenes), rolled into one-dimensional (1-D) structures (carbon nanotubes, CNTs) or stacked into three-dimensional (3-D) layered structures (graphite) [3]. In this way, graphene is analogous to fullerenes and CNTs, which vary in wall number, diameter, length and surface chemistry. Graphene consists of a layer with a π-conjugated structure of six-atom rings, which can be conceptually viewed as a planar aromatic macromolecule. This planar structure offers an excellent capability to immobilize a large number of substances, including metals, drugs, biomolecules and fluorescent probes and cells [10–15]. Therefore, it is not surprising that graphene has generated great interest in nanomedicine and biomedical applications, where suitably modified graphene can serve as an excellent drug delivery platform for anti-cancer/gene delivery, biosensing, bioimaging, antibacterial applications, cell culture and tissue engineering [11,12,14–18]. Compared with CNTs, graphene exhibits

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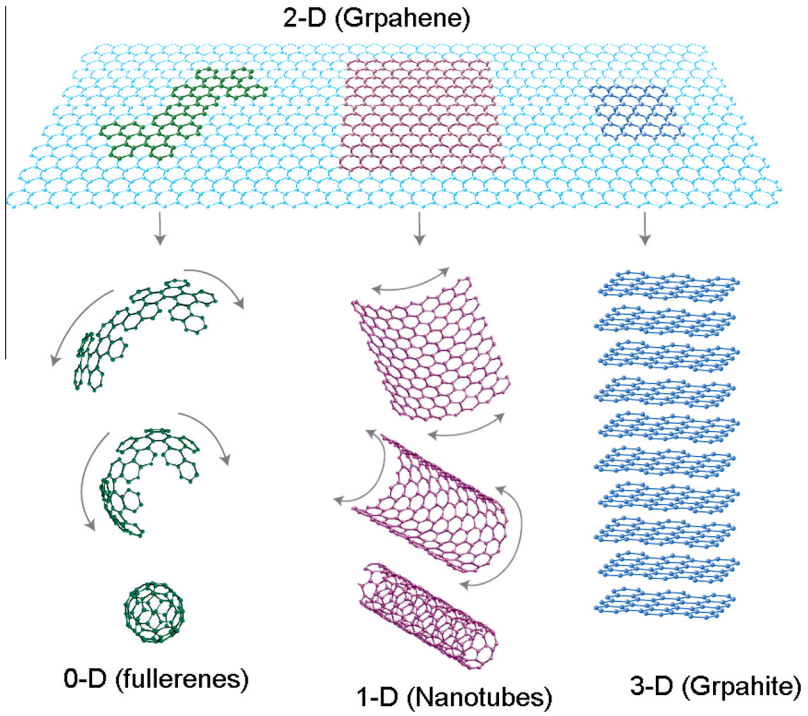

Fig. 1. Mother of all graphitic forms. Graphene is a 2-D building material for carbon materials with other dimensions including zero dimensions (fullerenes), one dimension (carbon nanotubes) and three dimensions (graphite) (with permission from Ref. [3]).

some important qualities such as low cost, facile fabrication and modification, a higher surface area with two external surfaces and the absence of toxic metal particles. Thus, graphene has begun to threaten the dominance of CNTs in many applications, including drug delivery, demonstrating lower toxicity and superior biocompatibility [19]. In the case of drug delivery, an example is that the loading ratio (weight ratio of loaded drug to carriers) of graphene nanomaterials (GNMs) could reach 200%, which is considerably higher compared with nanoparticles and other drug delivery systems [20,21]. Dai's group in 2008 pioneered work first demonstrating that polyethylene glycol (PEG)-functionalized graphene oxide (NGO) can be used as a novel drug nanocarrier to load anti-cancer drugs via non-covalent physisorption and has in vitro cellular uptake capacity [22,23]. Graphene and graphene oxide (GO) and other graphene derivatives have been widely explored in the last 5 years for drug delivery applications by many other research groups. A significant increase in research efforts in this new emerging field is clearly visible via hundreds of related publications per year, including a few recent reviews [11,13,16].

In this review we summarize and discuss the most recent advances and developments in the applications of graphene and GO for drug delivery. Firstly, we briefly describe the key parameters essential to develop nanocarriers for drug loading, based on surface modifications and functionalization of graphene and its derivatives, followed by discussion related to their toxicity and biocompatibility. Secondly, we present the most outstanding examples of the latest advances in their use for drug delivery applications, including delivery of different therapeutics such as anti-cancer drugs, DNA, genes, the concepts for targeting delivery, controlled and stimulated drug release (pH, temperature, photo and magnetic) and the design of graphene nanohybrids for combined therapy and imaging. Finally, we conclude this review with a summary of recent developments and the prospective outlook for future trends in this research field.

2. Graphene and GO as drug nanocarriers: the concept and challenges

In the past two decades various nanomaterials of different sizes, shapes and chemical composition, including metal and metal oxide nanoparticles, polymeric micelles, lyposomes, dendrimers and carbon nanotubes, have been explored as nanocarriers for the delivery of therapeutic agents [1,2,24,25]. Among them, graphene and GO, with their advantageous properties, have recently emerged as new and competitive drug delivery systems with the potential to be applied for systemic, targeting and local drug delivery systems. The scheme of GO and graphene as nanotherapeutic drug delivery platforms to carry different therapeutics from small drug molecules, antibodies, DNA, proteins and genes is presented in Fig. 2. The properties of GNMs, which are relevant for their drug delivery and biological applications, include surface area, layer number, lateral dimension, surface chemistry and purity. The surface area of graphene ($2600\ m^2\ g^{-1}$) is four magnitudes higher than the surface of any other nanomaterials explored for drug delivery [26]. Basically, a monolayer of graphene represents an extreme case where every atom is exposed on the surface, which allows significantly higher drug loading capacity compared with other nanomaterials. The number of layers of GO and graphene sheets and their thickness are important for several reasons. A larger number of layers will reduce surface area but will increase the rigidity of GNM nanocarriers required for cell penetration. Lateral dimensions of GNMs do not have an effect on specific surface area and drug loading, but could have size limitations relevant to cell uptake, renal clearance, blood-brain-barrier transport, biological degradation and other biological phenomena dependent on particle dimensions. The lateral dimensions and the shape could also have a significant impact on toxicity; even the toxicity and cellular uptake of 2-D plate-like nanostructures are not explored or well understood. Based on previous studies of nanoparticles and carbon nanotubes,

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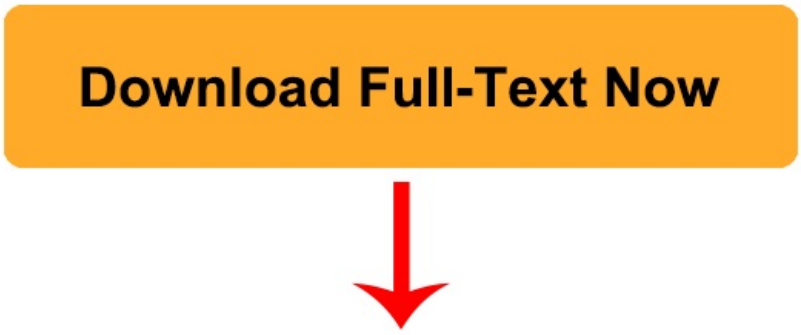

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