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Graphene-based nanosheets for delivery of chemotherapeutics and biological drugs☆

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ABSTRACT

Graphene-based nanosheets (GNS), including graphenes, graphene oxides and reduced graphene oxides, have properties suitable for delivery of various molecules. With their two-dimensional structures, GNS provide relatively high surface areas and capacity for non-covalent π-π stacking and hydrophobic interactions with various drug molecules. Currently, GNS-based delivery applications extend to chemotherapeutics as well as biological drugs, including nucleic acid drugs, proteins, and peptides. Surfaces of GNS have been modified with various polymers, such as polyethylene glycol and biopolymers, which enhance biocompatibility and increase drug loading. Anticancer drugs are prominent among chemotherapeutic agents tested, and have been loaded onto GNS with relatively high loading capacities compared with other nanocarriers. For enhanced distribution to specific tissues, GNS have been covalently or non-covalently modified with targeting ligands, including folic acid, transferrins, and others. In this review, we cover the current status of GNS for delivery of anticancer chemotherapeutics and biological drugs, with a focus on nucleic acid drugs. Remaining challenges for the application of GNS for drug-delivery systems and future perspectives are also addressed.

Contents

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1. Introduction

Graphene is a kind of carbon allotrope, exemplified by fullerenes and carbon nanotubes, with a flat single layer of graphite containing stacked layers of carbon atoms with a honeycomb lattice [1]. Graphene is reported to have various extraordinary properties, including a unique structure and mechanical, thermal, and optical characteristics [2,3]. Graphene-based nanosheets (GNS) with nanoscale lateral sizes include graphene nanosheets [4] (Fig. 1A), graphene oxide (GO) nanosheets [5] (Fig. 1B), and reduced graphene oxide (rGO) nanosheets [6] (Fig. 1C). GNS have been intensively exploited as nanocarriers for a variety of drugs, including chemicals [7] and biological drugs [8]. GNS in particular have been proposed as a potential nanocarrier of water-insoluble anticancer chemotherapeutics [9,10].

Although the initial physical exfoliation method for preparing graphene single layers—a novel approach using adhesive tape—was very simple, its applicability to large-scale, industrial production of graphene layers is limited [11]. Therefore, chemical exfoliation methods, including oxidation of graphite resulting in GO and rGO [12,13], have become more commonly used for bulk scale production. GO can be dispersed as a single layer in water owing to the hydroxyl (—OH), epoxide (—O-), and carboxylic acid (COOH) functional groups on their surface and edges, but this impairs the planar hydrophobic structure of the graphene surface, resulting in the loss of its intrinsic properties. Reduction of GO to produce rGO restores a surface that mimics the original planar graphene layer with carboxyl groups on their edges [6].

In this review, we provide an overview of significant advances in graphene-based nanomaterials for delivery of chemical and biological drugs, address current challenges, and highlight future perspectives.

2. Physicochemical properties of GNS for drug delivery

2.1. Interaction with drug molecules

Among the various types of delivery systems, GNS features a unique two-dimensional planar surface. This two-dimensional feature of GNS confers a higher capacity for drug loading than other types of drug-delivery systems [14]. GO and rGO have been more extensively studied for delivery of drugs than pure graphene. The relative paucity of studies on graphene nanosheets for drug delivery likely reflects the poor water dispersity of these nanosheets. Graphene nanosheets are composed of sp2-hybridized carbon in a honeycomb lattice with nanoscale lateral sizes. Aksay and colleagues reported that the mean thickness of a stack of 140 graphene sheets was ~1.75 nm [14]. The surface area of graphene as a dry powder, measured by the Brunauer–Emmett-Teller method, has been found to be 600–900 m^2/g [14]. Although the high surface area of graphene nanosheets makes it possible to load drugs with high capacity, the hydrophobicity of these nanosheets and difficulties associated with handling them present limitations to their application in drug delivery. Because they lack functional groups on their surfaces [4], pure graphene nanosheets mainly interact with drug molecules through π-π stacking and hydrophobic interactions.

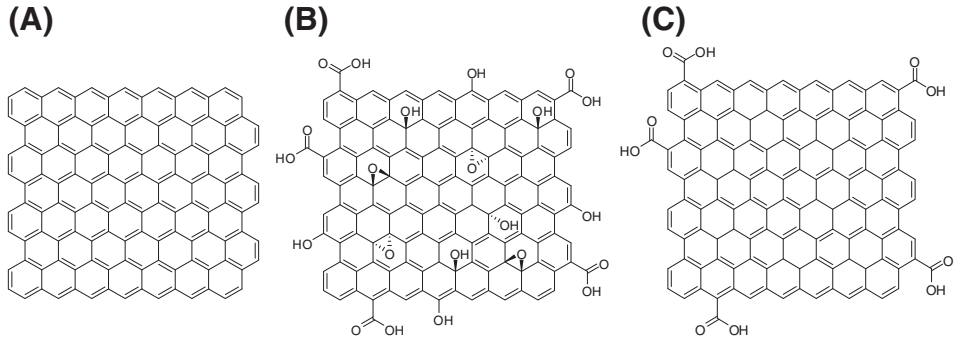

Fig. 1. Structures of GNS. Structures of graphene (A)[4], GO (B)[5], and rGO (C)[6] are presented.