Journal of Controlled Release 173 (2014) 75–88

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Graphene-based nanomaterials for drug delivery and tissue engineering

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ARTICLE INFO

Article history:
Received 23 August 2013
Accepted 14 October 2013
Available online 23 October 2013

Keywords:
Graphene nanomaterials
Drug delivery
Tissue engineering
Cell–material interactions

ABSTRACT

Nanomaterials offer interesting physicochemical and biological properties for biomedical applications due to their small size, large surface area and ability to interface/interact with the cells/tissues. Graphene-based nanomaterials are fast emerging as "two-dimensional wonder materials" due to their unique structure and excellent mechanical, optical and electrical properties and have been exploited in electronics and other fields. Emerging trends show that their exceptional properties can be exploited for biomedical applications, especially in drug delivery and tissue engineering. This article presents a comprehensive review of various types and properties of graphene family nanomaterials. We further highlight how these properties are being exploited for drug delivery and tissue engineering applications.

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Contents

1. Introduction

Graphene is a sheet of two-dimensional (2D) single layer sp^2 hybridized carbon atoms with exceptional electrical, mechanical and thermal properties [1,2]. Geim and co-workers discovered graphene, the thinnest known material, in 2004 and received Noble Prize in Physics for this discovery. Since its discovery, research on graphene has increased exponentially exploring different properties and applications ranging from electronic, optoelectronic devices and photoconductive materials in solar cells to medical imaging, drug delivery and tissue engineering.

Carbon-based materials like graphite, diamond, fullerenes, nanotubes, nanowires and nanoribbons have been used for various applications in electronic, optics, optoelectronics, biomedical engineering, tissue engineering, medical implants, medical devices and sensors. Graphene is an important new addition to these carbon family materials due to its unique properties. Each carbon atom in graphite is attached to other carbon atoms in the same plane with a strong carbon – carbon

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0168-3659/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jconrel.2013.10.017

bond. However, the interlayer binding through weak Van der Waals forces makes it a soft material as opposed to diamond. Similarly, carbon nanotubes and fullerenes are other forms of carbon, which have tubular and spherical arrangements responsible for their specific properties. The strong carbon–carbon bonding in the plane, aromatic structure, presence of free π electrons and reactive sites for surface reactions make graphene a unique material with exceptional mechanical, physicochemical, thermal, electronic, optical and biomedical properties (Fig. 1).

In this review, we give a brief overview of different types of graphene materials, their properties and functionalization strategies. We then discuss the emerging biomedical applications of graphene-based materials in drug delivery and tissue engineering in detail.

2. Graphene family nanomaterials (GFNs)

Graphene family nanomaterials (GFNs) are classified based on either number of layers in the sheet or their chemical modification. Some of the widely used GFNs include single layer graphene, bi-layer graphene, multilayer graphene, graphene oxide (GO) and reduced graphene oxide (rGO). Each member of GFNs differs from the other in terms of number of layers, surface chemistry, purity, lateral dimensions, defect density and composition. Single layer graphene as the name suggests is an isolated single layer of carbon atoms bonded together in a planar 2D structure. It is synthesized by repeated mechanical exfoliation [1] or extremely controlled growth on substrates like silicon carbide [3] *via* chemical vapor deposition (CVD). Single layer defect-free graphene is difficult to synthesize in bulk. It is also difficult to suspend in solutions and isolate in gas phase due to highly reactive surface. Hence, multi-layer graphene or graphene oxides are widely used for biomedical applications.

Graphene oxide (GO) is a highly oxidized form of chemically modified graphene that consists of single atom thick layer of graphene sheets with carboxylic acid, epoxide and hydroxyl groups in the plane. The peripheral carboxylate group provides colloidal stability and pH-dependent negative surface charge [4]. Epoxide (–O–) and hydroxyl (–OH) groups present on the basal plane are uncharged but polar allowing weak interactions, hydrogen bonding and other surface reactions [5]. The basal plane also contains free surface π electrons from unmodified areas of graphene, which are hydrophobic and capable of π–π interactions for drug loading and non-covalent functionalization. Thus, GO is an amphiphilic sheet-like molecule, which can be used as a surfactant to stabilize hydrophobic molecules in a solution [6,7]. Multi-layered GO is produced by rough oxidation of crystalline graphite followed by dispersion in aqueous medium through sonication or other processes. However, repeated treatment, centrifugation and harsh environment lead to production of monolayer oxidized graphene. The presence of functional groups creates high defect density in GO thereby reducing its mechanical, electrical and thermal properties [8].

Reduced graphene oxide (rGO) can be obtained by thermal, chemical and UV treatment of GO under reducing conditions with hydrazine or

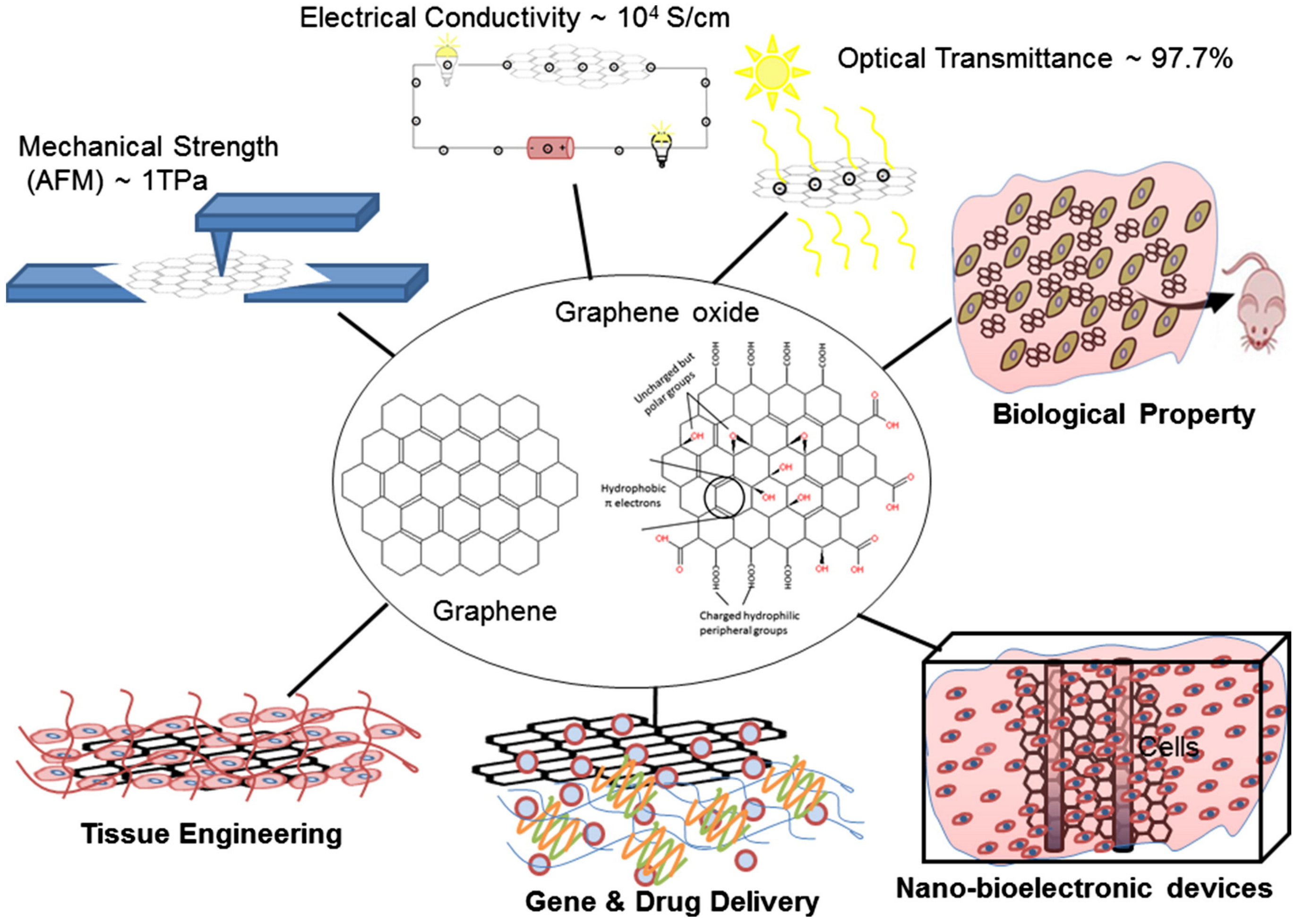

Fig. 1. Schematic overview of various applications of graphene. Graphene-based nanomaterials have been explored for various non-medical and biomedical applications due to their excellent mechanical, electrical and optical properties.

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