European Journal of Pharmaceutics and Biopharmaceutics 104 (2016) 235–250

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Review article

Graphene in therapeutics delivery: Problems, solutions and future opportunities

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ARTICLE INFO

Article history:
Received 17 November 2015
Revised 12 April 2016
Accepted in revised form 18 April 2016
Available online 22 April 2016

Keywords:
Graphene
Drug delivery
Graphene oxide
Targeted drug delivery
Graphene nanomaterials
GFN
Gene delivery

ABSTRACT

Graphene based nanomaterials are being used experimentally to deliver therapeutic agents to cells or tissues both *in vitro* and *in vivo*. However, substantial challenges remain before moving to safe and effective use in humans. In particular, it is recognised that graphene molecules undergo complex interactions with solutes, proteins or cellular systems within the body, and that these interactions impact significantly on the behaviour or toxicity of the molecule. Approaches to overcome these problems include modification of the graphene or its combination with other molecules to accentuate favourable characteristics or modify adverse interactions. This has led to an emerging role for graphene as one part of highly-tailored multifunctional delivery vehicles. This review examines the knowledge that underpins present approaches to exploit graphene in therapeutics delivery, discussing both favourable and unfavourable aspects of graphene behaviour in biological systems and how these may be modified; then considers the present place of the molecule and the challenges for its further development.

Contents

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http://dx.doi.org/10.1016/j.ejpb.2016.04.015
0939-6411/

1. Introduction

Since the isolation of graphene in 2004, potential uses of the material have expanded rapidly, and a wide range of biomedical applications are now proposed [1–23]. In this review, the physical and chemical properties of what will be referred to as *the graphene family of nanomaterials (GFNs)* [24] will be reviewed in the context of their potential role in therapeutics delivery – which includes drugs, biopharmaceuticals and genetic material.

The use of graphene in therapeutics delivery is based upon its particular properties. Its high surface-area to volume ratio, polyaromatic structure and the ease with which various forms can be functionalised offers capacity and flexibility for cargo loading, transport and targeting to tissues. Additionally, the ability to combine hydrophilic and hydrophobic regions on the surface of GFN flakes supports both their solubility within aqueous environments and their subsequent interaction with lipids in cell membranes. However, it is also recognised that graphene may have potential adverse interactions within biological environments that are highly relevant to biomedical applications. In particular, interactions between graphene and protein elements in biological fluids may significantly affect the physical properties of the molecule, potentially inducing damaging responses by the host immune system, while the membrane interactions and chemical properties of graphene have the potential to cause direct toxicity to target cells or to normal "bystander cells".

The review examines those qualities of GFNs that may make them attractive as therapeutics delivery vehicles, before considering how the varied properties of different graphene forms may affect their performance. Present and possible future applications in drug delivery are then considered.

2. Properties of graphene

2.1. The graphene family of nanomaterials

Graphene was first isolated using mechanical exfoliation in the now famous "scotch-tape" method [25] and is the first truly two-dimensional material. Each carbon atom of pristine graphene is bound to three others in a flat structure (sp^2 hybridised). This structure is the basis of many carbon materials, from graphite to carbon nanotubes (CNTs) and fullerenes, and underlies the distinctive honeycomb lattice structure of the molecule [16,28] (Fig. 1). The benzene-like structure of the hexagonal components of the lattice allows it to be thought of as a giant aromatic poly-molecule [16]. Even without further functionalisation, this structure confers properties that are useful in therapeutics delivery: aromatic molecules may bind to graphene through non-covalent interactions between their carbon rings (π–π stacking), and the large relative surface-area of the 2D geometry permits a single graphene flake to be decorated with a raft of different aromatic groups [26]. For pristine graphene, π–π stacking and hydrophobic interactions are the major source of binding for drugs and other molecules; however, for other graphene forms the additional presence of chemical functional groups provides a greater range of possible interactions (Fig. 3) [26,27].

2.2. Structural features and solubility of graphene

For use in therapeutics delivery, GFN flakes must be dispersed within biological fluids. In its pristine form graphene is hydrophobic; therefore, solubilisation is achieved through exfoliation of graphite layers in the presence of a non-polar solvent or surfactants

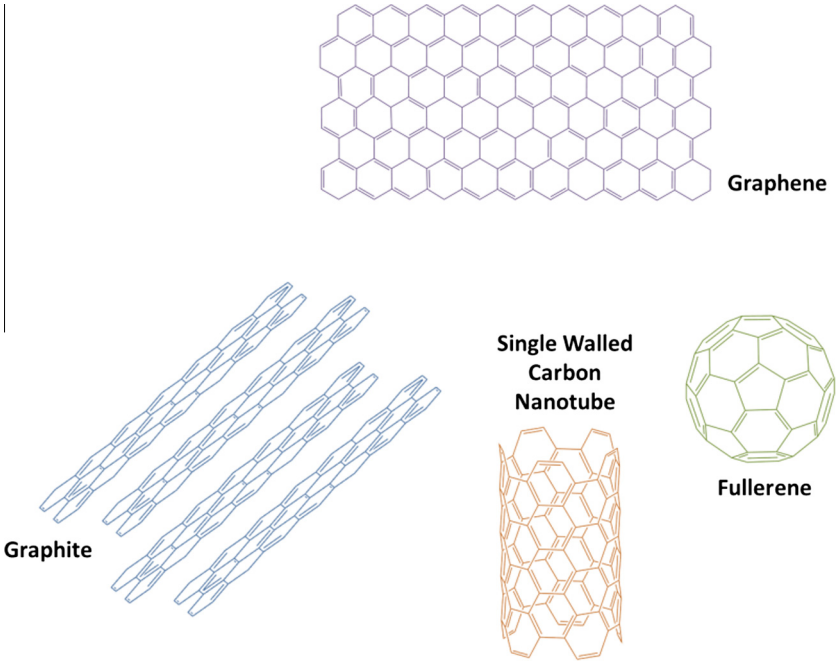

Fig. 1. sp^2 hybridization in graphene and other carbon allotropes. The honeycomb structure recognisable in the above materials derives from the sp^2 hybridized bonds between their constituent carbon atoms; graphene is often described as the structural precursor to graphite, CNTs and fullerenes.