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Perfluorocarbons–graphene oxide nanoplatforms as biocompatible oxygen reservoirs

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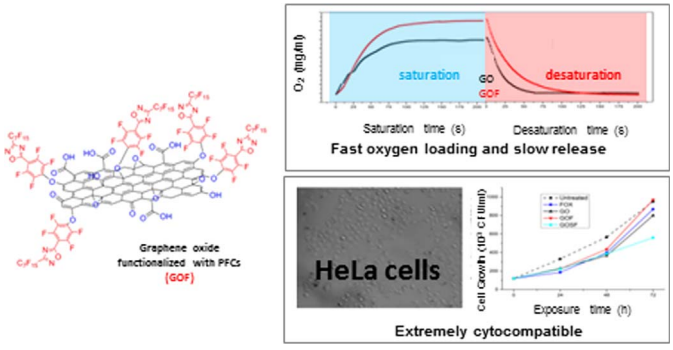
GRAPHICAL ABSTRACT



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ABSTRACT

3-Pentadecafluoroheptyl,5-perfluorophenyl-1,2,4-oxadiazole (FOX) molecules were attached onto a graphene oxide (GO) via a facile aromatic substitution in alkaline environment. This approach allows achieving high degree of functionalization under mild conditions. The covalent attachment of perfluoromoieties onto GO lamellae was confirmed by spectroscopic analyses. The performance of these nanoplatforms (GOF) as oxygen reservoirs was assessed at different concentrations and temperature. The results revealed that under physiologic conditions GO and FOX synergistically operate for increasing oxygen uptake and release, either from a thermodynamic and a kinetic point of view. Even at low concentrations, GOF showed values in terms of oxygen content at saturation and diffusion rate higher than those of other materials currently proposed as O_2-reservoirs in tissue engineering, for cell oxygenation during the regeneration of vascularized tissues. Furthermore, GOF displayed a high cytocompatibility. These findings open new, intriguing scenarios for a further application field of graphene-derived materials.

1. Introduction

The rising concern towards oxygen delivery methods involves the formulation of advanced materials addressed to a wide range of applications, such as biomaterials for tissue engineering and wound healing, membranes for environmental remediation, gas sensing devices, and materials for energy storage [1–3]. Indeed, since oxygen regulates all the metabolic processes, as well as most of electrochemical reactions, its diffusion kinetics plays a vital role in a widespread range of fields [4,5]. For instance, in tissue engineering currently developed

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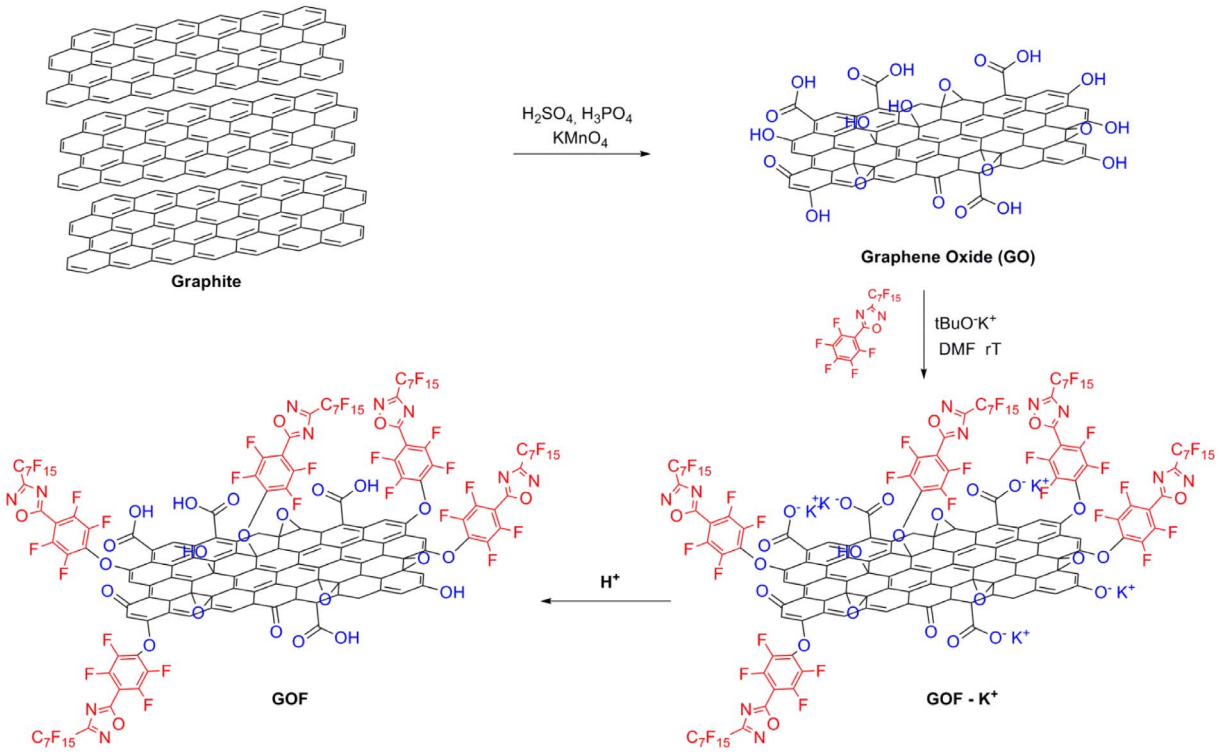

Fig. 1. Synthetic pathway to GOF.

biomaterial scaffolds are not capable to mimic and/or replace highly vascular tissues, since the limited O_2 diffusion at the center affects the tissue survival and functioning. In wound healing, O_2 is vital on one hand for cell proliferation and cell motility, and on the other hand for its well-known antibacterial activity [4,5].

Among the compounds traditionally used to improve oxygen exchange, perfluorocarbons (PFCs) are gaining a significant interest. Originally introduced as blood substitutes due to their impressive ability to carry respiratory gases, especially oxygen, in biological conditions and because of their biological inertness, PFCs are the most promising oxygen carriers for biological applications and, more generally, they could be suitable for entrapping other gases of particular concern, such as CO, CO_2 and NO [4–6].

Indeed, PFC-based biomaterials could be advantageous in directing stem cell differentiation into various cells types, since the amount of O_2 dissolved within a given PFC is linearly dependent on O_2 partial pressure (according to Henry's law) [4–6]. This crucial factor allows an oxygen storage and delivery particularly sensitive by cell demand. Otherwise, other oxygen carriers, such as peroxides, release O_2 by a chemical reaction independent of the environmental O_2 concentration and show several drawbacks related to their cytotoxicity. Nevertheless, PFCs are found to pack less densely on surfaces, leading to poorer van der Waals interactions with water which results in a strong hydrophobicity [7]. This drawback hinders the direct use of PFCs in biologic aqueous environments, if not conjugated to a more hydrophilic structure. In the past years, PFCs were added to biomaterials under the form of emulsions stabilized by surfactants. This approach shows several cons, related to the cytotoxicity of surfactants (at the doses required) and to the dramatic loss of mechanical performance of biomaterials [4]. More recently, chitosan and other biomaterials were conjugated to PFCs to obtain amphiphilic hybrid structures capable to drag and release oxygen throughout scaffolds. However, a more convenient pathway to improve the oxygen affinity of a larger class of biomaterials (e.g. polylactic acid, polycaprolactone, polyethylene oxide) may involve the conjugation of PFCs with graphene oxide lamellae. This approach brings several advantages. First, graphene oxide is amphiphilic, prone to further derivatization routes and indeed more cytocompatible with respect to graphene, although more studies still must be done to effectively assess its environmental and biological interactions [8,9]. Nevertheless, GO was recently used as a filler for PLA and PCL for bone tissue regeneration, since it promotes stem cell differentiation, even providing the biocompatibility of both the scaffolds and the degradation products of the scaffolds, owing to the high water retention ability and hydrophilic nature [10].

Moreover, adding GO to a biopolymer matrix generally leads to increased mechanical properties and allows the preparation of polymer-GO systems by melt processing, solvent casting, electrospinning and multi-step technologies [11–13].

We already prepared a nanohybrid material by combining together GO, Silica and fluorinated moieties, showing remarkable oxygen affinity, due to both the silica nanoparticles and perfluorinated chains [14]. In that case we obtained a material with twofold oxygen affinity with respect to other fluorinated systems reported in the literature [14–16].

Aim of this study is to explore the possibility to combine the intriguing features of GO and fluorinated materials by synthesizing a novel nanohybrid built by highly oxygenated GO decorated by 3-pentadecafluoroheptyl,5-perfluorophenyl-1,2,4-oxadiazole molecules.

Compared to our previous study it is interesting to explore the role of the fluorinated moiety directly linked to the GO surface without the support of silica nanoparticles, in order to understand the role and importance of each component of the hybrid material in study.

In order to achieve a significant degree of functionalization, we followed the already applied methodology, by anchoring the perfluorinated moieties, through a nucleophilic aromatic substitution, involving both epoxy and –OH moieties, and differently from other synthetic approaches which employ the –COOH as reactive grafting functionality. This pathway allows significant extents of functionalization, since –OH and epoxy are more abundant with respect to carboxyl groups. The choice to impart a high degree of fluorofunctionalization is motivated by the possibility to enhance oxygen affinity in materials even at low loading levels of fluorinated GO, based on the simple