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Graphene toxicity and future perspectives in healthcare and biomedicine

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Highlights

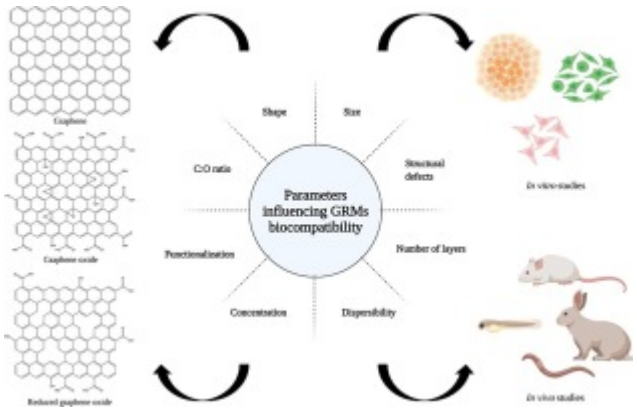
- Brief presentation of the current technology readiness level of graphene related materials (GRMs);
- Advances in industrial synthesis routes of GRMs;
- An overview of the latest *in vitro* and *in vivo* studies for GRMs;
- Limitations of GRMs and their negative effects on biological systems.

Abstract

Graphene and graphene related materials (GRMs) are foreseen to provide advantages that bring about distinctive applications influencing the landscape of different sectors of society. The escalating exploitation of graphene related materials demands a comprehensive evaluation of the potential impact of these materials on human health. Divergent results related GRMs such as biocompatibility, biodegradability, beneficial

effect on cell proliferation and differentiation rate but also apoptosis, necrosis, autophagy, oxidative stress, physical destruction, DNA damage, and inflammatory response were indicated by different studies. The current paper is grounded to the context and recent advancement in various graphene and GRMs synthesis control, reproducibility, and limitations. Furthermore, we discuss human hazard assessment of GRMs using *in vitro* and *in vivo* models and emphasize the structure–activity relationships that cause the toxicity of these materials, highlighting the key parameters that trigger the biological effect such as synthesis route, the number of graphene layers, the average size of GRMs layers, ingested amount, carbon/oxygen atomic ratio (functional groups density on the surface of GRMs), functionalization. Based on current understanding GRMs family vary considerably and it is not a valid statement that all GRMs are hazardous, nor is it true that all GRMs are harmless, hereby we provide a brief overview regarding GRMs biodegradability as a doorstep in introducing these 2D materials in the biomedical field.

Graphical abstract



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Introduction

A broad foundation of knowledge about graphene and the mechanism on which new devices and therapies can be built was laid based on several studies that were reported since 2004 when graphene was first isolated and characterized by Novoselov et al. [1]. In 2015 a roadmap for graphene was brought to the spotlight [2], a massive effort of 64 scientists to collect and summarize advancement of knowledge related to graphene up to that point. Expectations regarding the prize decrease, more forceful targets, as well as the need of forwarding reliable quality management were recently emphasized by Döscher et al. [3], [4] in the recent published updated review on graphene and graphene related

materials (GRMs). Aspects related to the latest developments and on the industrialization progress and future expectations in this context were also tackled by Döscher and co-workers. Several authors have put a great effort in addressing the biomedical applications of GRMs that were discussed in valuable review studies highlighting the importance of these materials in regenerative medicine [5], anticancer therapy, protein functionalization [6] and drug delivery systems [7] to name a few. Moreover, Ionita et al. [8] anticipated GRMs to provide advantages that bring about unique and novel applications rather than simply an improved substitute to existing materials poised to achieve extraordinary real-world benefits. To date, several products based on GRMs were developed, such as sports equipment (tennis rackets, skis, bicycle wheels and frames, cycling helmets, cycling shoes, fishing rods), earphones, inks, lubricants, or sensors [9], [10]. An European consortium called Graphene Flagship [10], advanced the production and commercialization of all these products with the goal of increasing the technology readiness level (TRL) of GRMs-based products. Under Graphene Flagship the number of spin-off companies and commercial products [10] increased significantly in recent years which, in turn, determined the increase of TRL. However, some of these products are not yet mass-produced and TRL is at different stages depending on the industry. Among the first commercialized products using GRMs are sports equipment, considering that these type of applications are based on existing technologies and require considerable fewer research efforts compared to energy storage and energy conversion applications, or to biomedical applications. The rapid advancement of knowledge and applications, which have expended continuously, indicated an enormous scientific progress, while graphene market is expected to grow substantially and reach $876.8 million by 2027 and $2 billion by 2035 [11]. Lately, researchers focused more and more on the applicability of GRMs in the biomedical field while also starting to consider the potential harmful consequences of these two-dimensional (2D) materials in regard to human health and environment [12], [13].

GRM-based medical devices have a long way until they can be commercially available worldwide, because there is a higher need for testing and understanding fully the GRMs behavior in biological systems. Moreover, the development of biomedical products usually requires an additional planning phase, i.e., clinical tests, compared to other type of products [14], that increase significantly the cost and timeline of commercialization. Based on current GRMs products development and existing challenges, scientists predict that GRMs will be available in the energy sectors in 5–15 years [15], while in the medical market in 15–30 years (Fig. 1) [4].

Before further advancements in GRM-based technology can be achieved, there is a need for several aspects to be elucidated to avoid misunderstandings and to facilitate the communication between scientists all over the world. Ferrari et al. [16] offered a list of acronyms to standardize the nomenclature related to the graphene family, seven years

later this continues to be an issue, not only in academic centers, but also in industry with commercial products. Aspects related to reliable quality management, stability, reproducibility, functionalization, and toxicity need to be taken into account before high-quality commercial products can be manufactured on a mass scale. The current state of the emerging GRMs supply industry is described as “Graphene Zoo”, referring to the vast diversity of mostly small, start-up type suppliers offering various types and grades of graphene and GRMs (graphene nanoplateletes (GNPs), graphene oxide (GO), etc.). This situation often creates a perception of general immaturity and insufficient reliability among potential customers. Individual and joint efforts of graphene producers concentrate on relieving themselves and their products of such generalization. The success of GRMs as a biomaterial with medical applications is highly dependent on fully understanding its negative effects, not only the positive ones. The current paper presents an overview of the short- and long-term impact of GRMs when in contact with the human body. Considering the 15 years effort of intensive studies [17], [18], [19] we shall be able to start having some answers regarding the GRMs biocompatibility.

Section snippets

Graphene synthesis – control, reproducibility, and limitations

Usually, graphene synthesis is performed by two approaches: top-down and bottom-up. On one hand, the top-down method consists in exfoliating one graphene layer from a graphitic material by interrupting the weak van der Waals forces binding the graphene sheets together [20]. Top-down synthesis of graphene is achieved by micromechanical and electrochemical exfoliation of graphite (graphite oxide) often combined with chemical and electrochemical reduction strategies, solvent-based exfoliation, and …

Grms biocompatibility

Most published works dealing with graphene and graphene related materials have focused on beneficial features and positive aspects of physical and biological behavior. Several studies (including ours) focused on biocompatibility, biodegradability, cell proliferation and differentiation rate, while negative outcomes seem to be overshadowed or not enough investigated.

Biocompatibility of GRMs is a crucial assessment for future application in biomedical devices. When it comes to this topic, both…

GRMs biodegradability

Biodegradability represents the capacity of microorganisms to change the initial structure of a material by enzymatic or metabolic means into harmless compounds. GRMs biodegradation is a very important issue both in toxicology and in nanomedicine because in order to be safely used, they have to be entirely removed from the organism once they have served their goal. Many discussions regarding this topic suggest that graphene biodegradation is related to its lateral dimension, number of layers,…

Conclusions and future perspectives

GRMs have been thoroughly investigated in the last decade due to their unique and exceptional properties and changed the medical field as we know it. However, there is still work to be done in order to find the ideal synthesis method, functionalization, modulating specific characteristics and scale up needed for each application. Furthermore, *in vitro* and *in vivo* studies have to provide extensive evaluation of the potential impact of GRMs on human health before this can be used at its full…

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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