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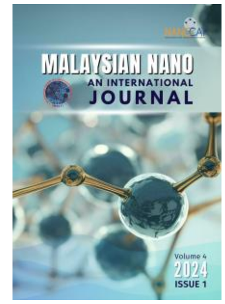

Review article

Comprehensive review on graphene, its synthesis, properties and applications in drug delivery

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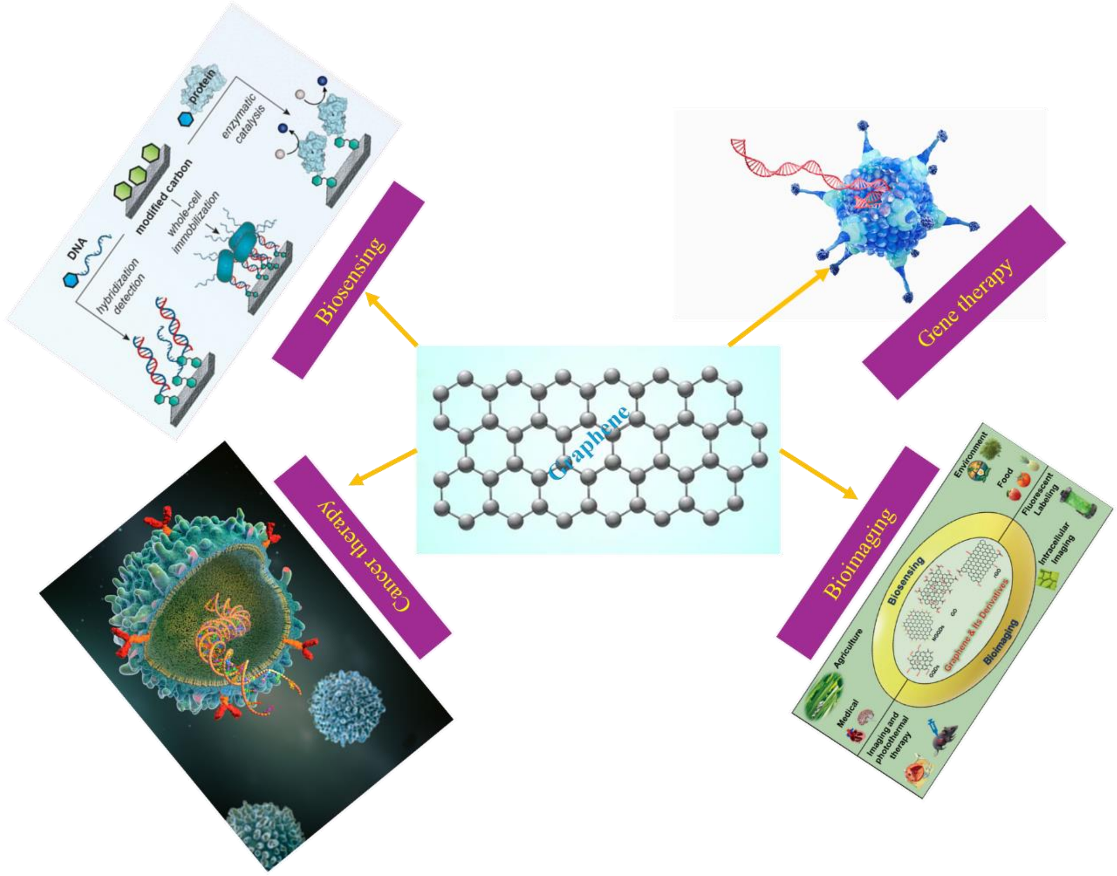
Abstract

Graphene, a single layer of carbon atoms arranged in a two-dimensional honeycomb lattice, has garnered significant attention for its exceptional properties and versatile applications. This comprehensive review delves into the synthesis, properties, and burgeoning applications of graphene in drug delivery systems. We explore various synthesis methods, including mechanical exfoliation, chemical vapour deposition, and reduction of graphene oxide, highlighting their advantages and limitations. The review discusses graphene's remarkable mechanical strength, electrical conductivity, thermal stability, and large surface area, which contribute to its efficacy as a drug delivery platform. Furthermore, we examine the biocompatibility and functionalization strategies that enable targeted and controlled drug release. Applications in cancer therapy, gene delivery, and tissue engineering are scrutinized, demonstrating graphene's potential to revolutionize these fields. Challenges such as toxicity, scalability, and regulatory considerations are also addressed, providing a balanced perspective on the future of graphene in biomedical applications. This review aims to provide a comprehensive understanding of graphene's role in drug delivery, paving the way for further research and development in this promising area.

Keywords: Graphene, synthesis of graphene, drug delivery, biosensor, bioimaging

Graphical Abstract



1. Introduction

One layer of carbon atoms organized in a two-dimensional honeycomb lattice is called graphene, has revolutionized the field of nanotechnology due to its remarkable properties. This comprehensive review aims to provide an in-depth examination of graphene, covering its syn-thesis, intrinsic properties, and diverse functions, with a special focus on drug delivery systems [1]. The ability of graphene to adsorb a wide range of drugs due to its large surface area and π-π interactions is examined, along with strategies to achieve controlled drug release, thus improving the efficacy and reducing side effects. In addition, there are other biomedical ap-plications of graphene, such as bioimaging, biosensing, and tissue engineering. It explores re-cent advancements in using graphene for photothermal therapy and gene delivery, showcasing its versatility in addressing complex medical challenges [2, 3].

The review also discusses the difficulties and possible dangers of using graphene in drug delivery systems, including toxicity, biocompatibility, and the requirement for established procedures for the manufacturing and functionalization of graphene.

2. Classification of graphene:

Discovered in 2004, graphene has sparked significant interest in various fields, including electronics, materials science, and nanotechnology, due to its potential applications in flexible electronics, high-speed transistors, energy storage devices, and advanced composites [4-8]. Graphene can be classified based on its layers, quality, and production methods, here are the main classifications of graphene and their corresponding applications:

2.1 Monolayer-Graphene

Single layer of carbon atoms organized in a hexagonal lattice makes up monolayer graphene, possesses several distinctive structural properties that contribute to its unique characteristics and applications. Despite its atomic-scale thickness, monolayer graphene is remarkably strong and flexible. It is among the strongest materials known due to its tensile strength, which exceeds 130 GPa. Graphene's high electron mobility and conductivity make it ideal for ultra-fast transistors in electronics, potentially enabling future generations of smaller, faster, and more efficient devices [9, 10]. Monolayer graphene's flexibility and transparency make it suitable for flexible electronic devices, such as bendable displays and wearable electronics. Graphene-based sensors can detect a wide range of substances, from gases to biomolecules, due to graphene's high surface area and sensitivity to changes in its environment. Graphene-based electrodes in supercapacitors can store and deliver energy quickly, offering high power density and extended cycle life. Graphene additives improve the activity of lithium-ion batteries by increasing their capacity, charging speed, and lifespan [1].

2.2 Few-Layer Graphene (Few-Layer Graphene Nanosheets) (FLG)

Few-layer graphene consists of a small number of graphene layers stacked on top of each other, typically up to ten layers thick. The specific number of layers can affect its electronic and mechanical properties. Few-layer graphene may contain defects such as vacancies, grain boundaries, and edge structures (zigzag or armchair), which can affect its mechanical, electrical, and chemical properties. Functionalized FLG is investigated for targeted drug delivery systems due to its biocompatibility and ability to carry therapeutic molecules. FLG scaffolds support cell growth and tissue regeneration, offering potential applications in regenerative medicine and biomedical implantation. FLG membranes effectively filter contaminants from water due to their nanoporous structure and high mechanical strength. FLG-based sensors are used for real-time monitoring of pollutants in air and water, contributing to environmental protection efforts [11].

2.3 Graphene Oxide (GO)

Graphene sheets have functional groups (hydroxyl, epoxy, carboxyl) containing oxygen. Graphene oxide, which is made up of sp^2 hybridized carbon atoms organized in a hexagonal lattice, maintains the layered structure of graphene. Functional groups that contain oxygen, like hydroxyl (-OH), epoxy (-O-), and carboxyl (-COOH), are affixed to the graphene sheet, causing disruption to its π-conjugated structure. [12]. Because graphene oxide contains oxygen functional groups that interfere with the π-electron system and prohibit charge carriers from freely flowing across the sheet, graphene oxide is an electrical insulator. GO and rGO derivatives are explored as catalyst supports because of their surface area, tunable surface chemistry, and ability to enhance catalytic activity and selectivity in chemical reactions. GO can be functionalized with drugs and biomolecules for targeted drug delivery systems. Its biocompatibility and ability to interact with biological molecules make it suitable for controlled release and therapeutic applications. GO-based biosensors detect biomolecules and pathogens with high sensitivity and specificity, offering applications in medical diagnostics, environmental monitoring, and food safety [13].

2.4 Three-Dimensional Graphene

Three-dimensional graphene (3D graphene) refers to graphene structures that extend into three dimensions, deviating from the flat, two-dimensional nature of traditional graphene sheets. 3D graphene can form various structures such as foams, aerogels, sponges, and frameworks with interconnected networks of graphene sheets or graphene-based materials. It typically exhibits a high surface area with interconnected pores at the nanoscale, which enhances its accessibility for molecules and ions. 3D graphene retains the exceptional mechanical strength of graphene due to its carbon-carbon bonds and sp^2 hybridization, making it stronger than steel at a fraction of the weight. It maintains flexibility and can be compressed, folded, or shaped into complex geometries without losing its structural integrity [14]. 3D graphene exhibits high electrical conductivity, like that of pristine graphene, due to its graphene-based structure with delocalized π-electrons. It has excellent electrochemical properties, making it suitable for applications in energy storage devices (e.g., supercapacitors) and electrochemical sensors. 3D graphene structures are chemically stable under various environmental conditions, exhibiting resistance to corrosion, oxidation, and degradation. 3D graphene materials typically have a large specific surface area due to their porous structure, enhancing their capacity for adsorption and interaction with molecules [15]. 3D graphene-based materials serve as efficient catalyst supports because of their large surface area, tunable pore structure, and exceptional mass transport properties [16]. They are used in various catalytic processes for energy conversion, environmental remediation, and chemical synthesis. 3D graphene structures are highly sensitive to gases because of their large surface area and porous nature. They are used in gas sensors for detecting and monitoring pollutants, hazardous gases, and volatile organic compounds (VOCs). Functionalized 3D graphene is employed in biosensors for detecting biomolecules, pathogens, and specific analytes with high sensitivity and specificity. This application finds use in medical diagnostics, environmental monitoring, and food safety [17]. 3D graphene serves as a reinforcement in composite materials to enhance mechanical strength, thermal conductivity, and electrical properties. It is incorporated into polymers, ceramics, and metals for applications in aerospace, automotive, construction, and sporting goods industries. 3D graphene-based membranes are used in water purification technologies due to their high surface area, nanoporous structure, and selective permeability. They effectively filter out contaminants, ions, and particulates from water, making them suitable for desalination, wastewater treatment, and clean water production.3D graphene scaffolds support cell adhesion, proliferation, and differentiation, making them promising for tissue engineering applications. They are used in regenerative medicine to create implants, scaffolds, and drug delivery systems. Functionalized 3D graphene materials are explored for targeted drug delivery due to their biocompatibility, ability to encapsulate drugs, and controlled release properties [18].

3. Structural form of graphene and its properties

Graphene possesses a range of distinct properties that set it apart from other materials. These properties contribute to its unique potential for various applications in electronics, energy storage, composite materials, and more. Graphene production costs have been a significant barrier to its widespread commercial adoption. Several factors influence the price of graphene, including production methods, quality, economies of scale, market demand and supply, and research and development costs. Current large-scale production techniques, such as chemical vapor deposition (CVD) and liquid-phase exfoliation (LPE), are costly and require specialized equipment and processes. High-quality graphene, with fewer defects and consistent properties, commands a higher price due to the difficulty in achieving uniformity in production [14].

3.1 Layered Structure:

Graphene nanosheets refer to graphene structures that are typically a few layers thick, often up to several tens of layers. These nanosheets exhibit properties like single-layer graphene but with some differences due to their increased thickness. Here are some key aspects of the structure of graphene nanosheets. It consists of multiple layers of graphene stacked on top of each other. The number of layers can vary, typically ranging from a few layers (few-layer graphene) to several tens of layers [19].

3.2 Hexagonal Lattice:

Each layer of graphene within the nanosheet retains the characteristic hexagonal lattice structure of carbon atoms bonded together in a two-dimensional plane. This structure gives graphene its exceptional mechanical strength and electrical conductivity [20].

3.3 Intercalation and Stacking:

Adjacent layers of graphene in nanosheets can have different orientations and stacking arrangements. The stacking order and interlayer interactions influence the electronic properties and mechanical behavior of graphene nanosheets [21].

3.4 Defects and Functionalization:

Graphene nanosheets can contain defects such as vacancies, grain boundaries, and edges that affect their properties. Functional groups can also be introduced onto the surface or between layers through chemical modification, which can tailor their chemical and physical properties for specific applications [22].

3.5 Size and Morphology:

Graphene nanosheets can vary in size from a few nanometers to micrometers in lateral dimensions. Their morphology can be influenced by the synthesis method used, affecting their surface area and dispersibility in solvents or matrices.

4. Different properties of graphene

Graphene nanosheets are highly versatile materials with properties that make them suitable for a large number of uses, including electronics, energy storage, composites, sensors, and biomedical devices. Understanding their structure and how it relates to their properties is crucial for optimizing their performance in specific applications. Graphene is incredibly strong, with a tensile strength over 100 times greater than steel of the same thickness. This property makes it one of the strongest materials known. Graphene exhibits high electrical conductivity, with electron mobility surpassing that of traditional conductors like copper. It can conduct electricity more efficiently at room temperature [23]. It possesses excellent thermal conductivity, allowing it to conduct heat better than most materials. It is an efficient heat conductor, making it potentially useful in thermal management applications. Despite being a single atomic layer thick, graphene is optically transparent, absorbing only around 2.3% of visible light. This property makes it suitable for transparent conductive films in applications such as touchscreens and solar cells. Graphene is extremely thin and flexible, yet it retains its strength and other properties even when bent or folded. Its low density contributes to its lightweight nature [24]. It is impermeable to gases and liquids, even helium atoms, due to its dense atomic structure. This property makes it potentially useful for applications requiring barriers against gases and liquids can be synthesized in different ways [25]. The properties of graphene can be different depending on the synthesis method. Some of the synthesis methods of graphene are as follows:

4.1 Mechanical Exfoliation (Scotch Tape Method):

Graphene nanosheets can vary in size from a few nanometers to micrometers in lateral dimensions. Their morphology can be influenced by the synthesis method used, affecting their surface area and dispersibility in solvents or matrices.

4.2 Chemical Vapor Deposition (CVD):

One of the most popular processes for producing high-quality graphene on a big scale is CVD. It entails subjecting a metal substrate-usually copper or nickel-to a gas that contains carbon, like methane, at temperatures as high as around 1000 °C. Carbon atoms dissolve in the metal and then precipitate on the surface in the form of a graphene layer. The metal substrate is then etched away, leaving graphene on top [27].

4.3 Liquid Phase Exfoliation (LPE):

LPE involves exfoliating graphite or graphite oxide in a solvent using sonication or other mechanical means to obtain graphene flakes dispersed in the solvent. This method can produce graphene in large quantities and is suitable for producing graphene dispersions for ink formulation and composite materials [28].

4.4 Graphite Oxide Reduction:

Chemical oxidation techniques can be used to convert graphite into graphene oxide (GO), which is an oxidized form of graphene. Reduction of graphene oxide, either chemically or thermally, produces reduced graphene oxide (rGO), which is a form of graphene with defects and functional groups attached. This method allows to produce graphene-like materials with adjustable properties [29].

4.5 Electrochemical Exfoliation:

In this method, graphene is electrochemically exfoliated from graphite electrodes in a suitable electrolyte solution. This approach allows to produce graphene with controlled thickness and properties, making it potentially useful for electronic and sensing applications.

The desired graphene quality, quantity, and planned uses determine which synthesis process is best. Each approach has pros and cons. Research on graphene synthesis is still ongoing to improve manufacturing methods and discover new uses for this amazing substance [30].

5. Uses of graphene in drug delivery

Because of its special qualities, graphene and its derivatives, such as graphene oxide (GO) and reduced graphene oxide (rGO), have demonstrated encouraging potential in the field of drug delivery. Key uses of graphene in medication delivery include the following:

5.1 Targeted Drug Delivery Systems:

Functionalization: Functionalization of graphene and its derivatives with targeting ligands (such as antibodies, peptides, or aptamers) and therapeutic agents (drugs, genes, proteins) to specifically target diseased cells or tissues. Figure 1 shows the molecular pathways for graphene nanoparticle delivery to cancer cells and potential antitumor effect.

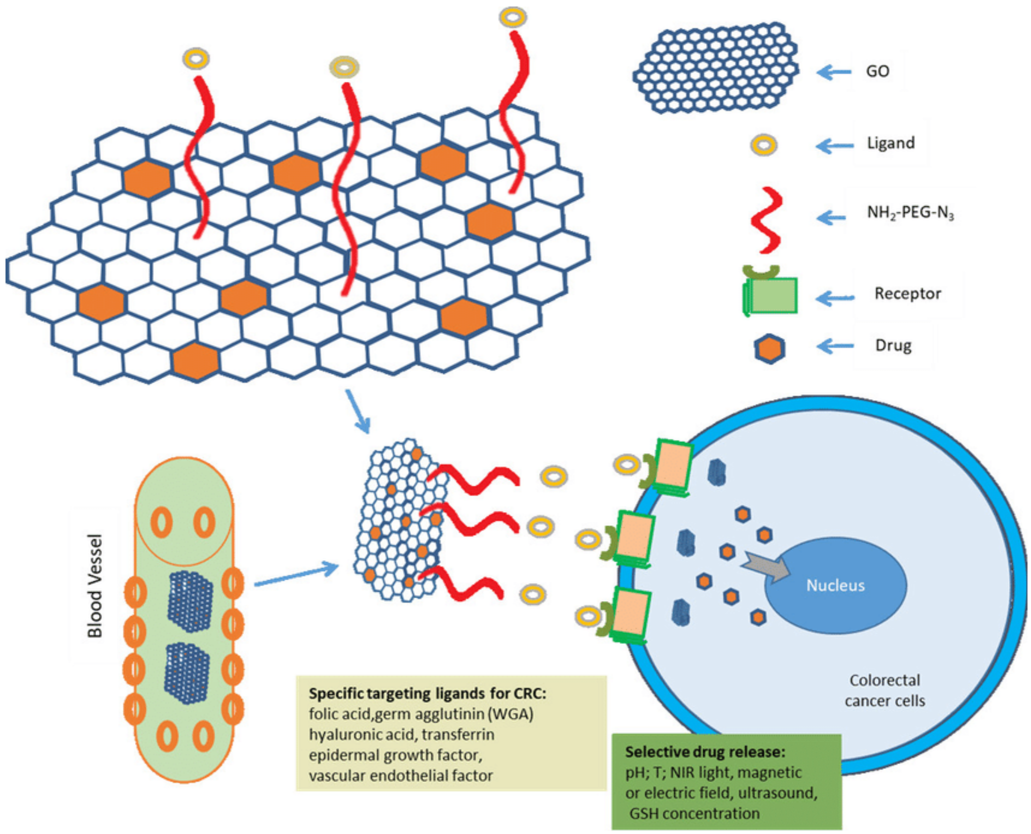


Figure 1: Schematic illustration of the molecular pathways for nanoparticle delivery to cancer cells and potential antitumor effects [31]

Enhanced Permeability and Retention (EPR) Effect: Graphene-based nanomaterials can exploit the EPR effect, where nanoparticles accumulate preferentially in tumors due to leaky vasculature, enhancing therapeutic efficacy while minimizing side effects.

5.2 Controlled Release Systems:

Gatekeeper Systems: Graphene and GO can be used as gatekeeper systems to encapsulate drugs within their nanosheets. The release of drugs can be controlled by external stimuli such as pH, temperature, light, or magnetic fields, improving drug bioavailability and reducing toxicity. Figure 2 shows the modified graphene for control release drug system.

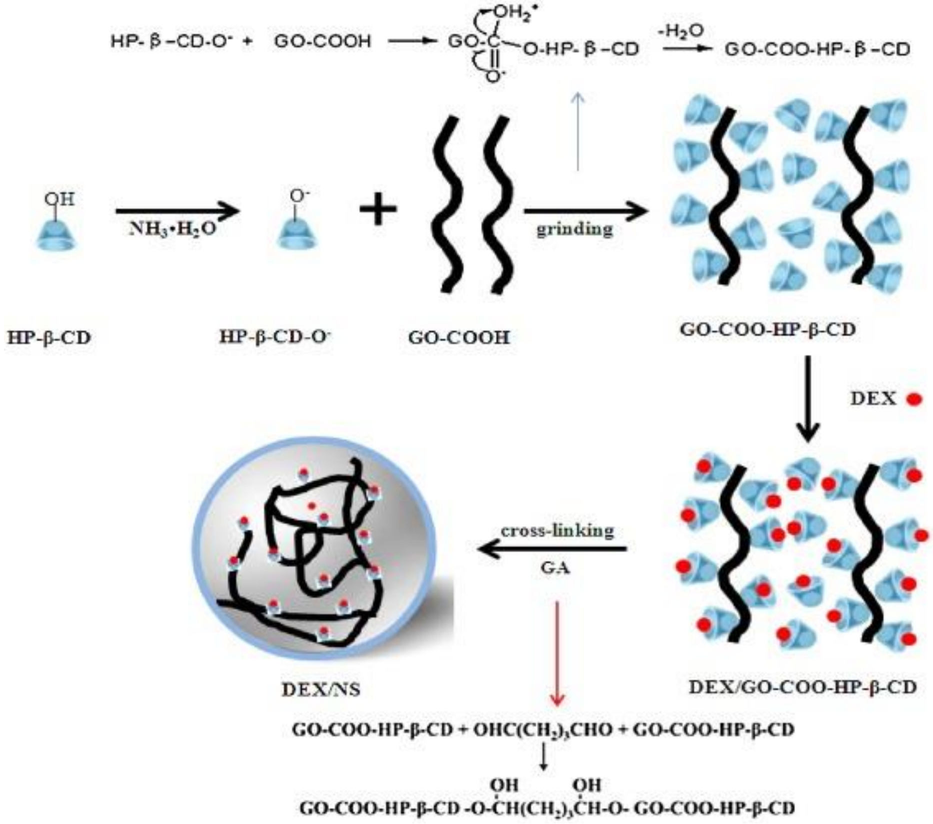


Figure 2: Schematic diagram of the construction of DEX-loaded GO-COO-HP-β-CD nanosphere [32].

Layer-by-Layer Assembly: Multilayer films of graphene oxide can be assembled to encapsulate drugs in a controlled manner, allowing for sustained release profiles tailored to specific therapeutic needs.

5.3 Imaging and Therapeutic Combination:

Theranostic Platforms: Graphene-based nanomaterials can be used for both diagnostic imaging (e.g., MRI, fluorescence imaging) and therapeutic purposes simultaneously. This allows for real-time monitoring of drug delivery and therapeutic response. Figure 3 shows the combined targeted chemo/PTT for colorectal cancer treatment in presence of graphene.

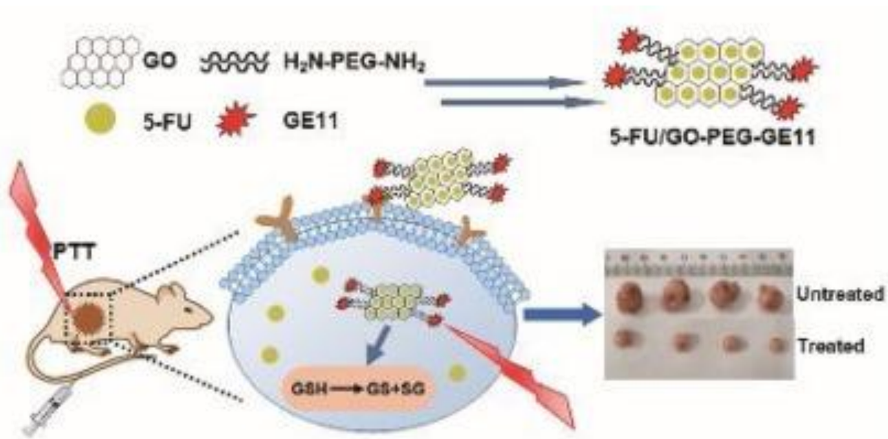


Figure 3: Schematic Illustration of the Combined Targeted Chemo/PTT for Colorectal Cancer Treatment [33].

Combined Therapy: Graphene can be combined with other therapeutic agents (e.g., chemotherapy drugs, photothermal agents) to achieve synergistic effects, enhancing therapeutic outcomes against cancer and other diseases.

5.4 Biocompatibility and Biodegradability:

Graphene oxide and reduced graphene oxide are generally considered biocompatible and can be functionalized to further improve their biocompatibility and reduce potential toxicity. Surface modifications can be applied to graphene-based materials to enhance their stability and biodegradability in vivo, ensuring minimal long-term accumulation and clearance from the body. Figure 4 shoes various direct and indirect mechanical forces and their mechanisms that synergistically work with graphene nanoparticles to enhance transdermal drug delivery.

Figure 4: Various direct and indirect mechanical forces and their mechanisms that synergistically work with nanoparticles to enhance transdermal drug delivery [34]

5.5 Transdermal Drug Delivery:

Graphene-based nanomaterials are explored for transdermal drug delivery applications due to their ability to penetrate the skin barrier effectively.

They can enhance the delivery of therapeutic agents across the skin for localized treatment of skin diseases or systemic delivery. Figure 5 shoes the applications of GOs in biotechnology.

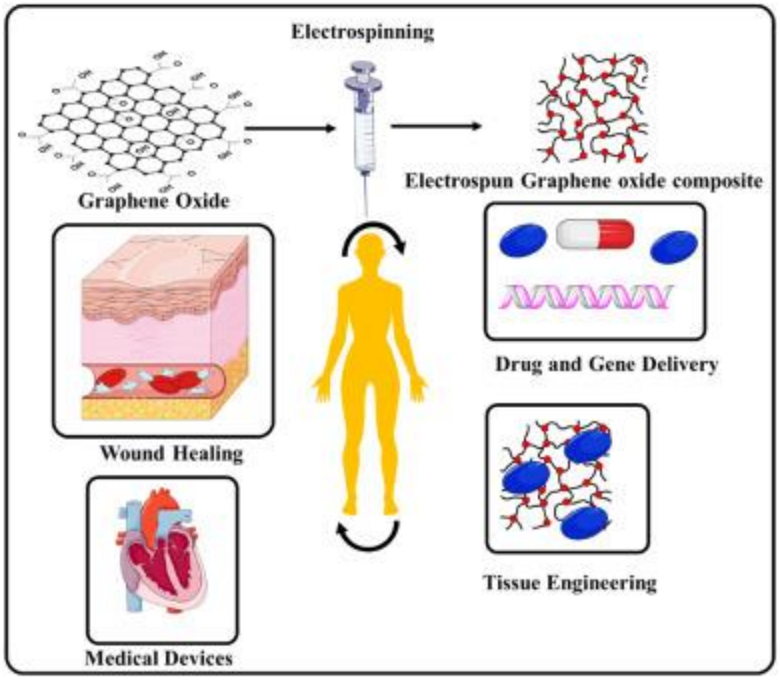


Figure 5: Applications of GOs in Biotechnology [35]

Graphene-based materials hold significant promise in revolutionizing drug delivery strategies by offering targeted and controlled release systems, enhanced therapeutic efficacy, and potential applications in personalized medicine and combination therapies. Continued research and development efforts are essential to further explore their capabilities and overcome existing challenges for clinical translation. Because of their exceptional heat and electrical conductivity, biocompatibility, high specific surface area, and variety of surface oxygen-containing groups, graphene and its derivatives have garnered a lot of attention in the last five years. They have also demonstrated significant promise in the administration of drugs. For instance, GO has been used to introduce aromatic medicinal compounds into cells through interactions known as π-π stacking. In addition to delivering the anticancer medication doxorubicin (DOX) into target cells, functional graphene quantum dots (GQDs) allow for real-time monitoring of drug release and cellular uptake without the use of external dyes. In the previous work, π-π stacking interactions were used to directly conjugate related graphene-based carrier medicines to graphene materials. The simplicity and high drug loading capacity of this method's preparation procedure are its main advantages; nonetheless, it can be challenging to control the final graphene-drug nanohybrids' stability and biocompatibility [36]. Subsequently, certain useful small compounds were used to enhance the nanocarriers' biocompatibility and stability. For example, Zhou et al. found that co-loading 7-ethyl-10-hydroxycamptothecin and Hypocrellin A onto the surface of GO dramatically increased the activity of Hypocrellin A, a photosensitive anticancer medication, compared to just modifying

Hypocrellin A alone [37]. In another study, Park et al., conjugated the reduced graphene oxide (rGO) with folic acid (FA) through noncovalent functionalization. The as prepared rGO/FA conjugate showed high dispersion stability in physiological media and enabled the accumulation of hydrophobic DOX [38]. Liu and colleagues reduced exfoliated graphene oxide (GO) with soluble starch to create starch-functionalized graphene nanosheets (starch-GNS). The starch-GNS demonstrated a high drug loading capacity and good biocompatibility in its produced state. According to the experimental data, 12 μg of hydroxycamptothecine may be loaded via physisorption using 150 μg of starch-GNS [38].

Small molecule-modified GQDs could also be utilized for simultaneous drug delivery cellular imaging. For example, Qiu et al. modified GQDs with arginine-glycine-aspartic acid (RGD) and FA, respectively. The DOX loaded RGD- or FA-modified GQDs could not only deliver drugs to target cells effectively, but also monitor the process of cellular uptake the drug in real-time without employing external dyes [38]. Huang and co-workers developed multifunctional paramagnetic GQDs (folate-GdGQDs) for simultaneous dual-modality bioimaging and tutor targeted drug delivery. The synthetic folate-GdGQDs exhibited a strong therapeutic activity by loading DOX though π-π stacking and hydrophobic interactions, and the fabricated nanocarriers could release about 80% of DOX at pH 5.0 after 48 h. Moreover, the folate-GdGQDs also showed an excellent biocompatibility and good targeting ability for noninvasive cancer diagnosis with T1-weighted magnetic resonance (MR) and fluorescence imaging [38].

6. Challenges and Future Directions

Graphene holds tremendous promise for future applications in drug delivery because of its exceptional properties like high surface area, biocompatibility, and the ability to be functionalized for targeted delivery and controlled release. However, several challenges need to be addressed to fully realize its potential in this field. Addressing long-term safety and potential toxicity of graphene-based materials is critical to ensure they are safe for medical use. Developing scalable production methods and overcoming challenges in large-scale manufacturing are necessary to make graphene-based drug delivery systems commercially viable. Meeting stringent regulatory requirements is essential for the clinical translation and commercialization of graphene-based drug delivery technologies. Continued research to ensure safety and biocompatibility, advancements in scalable production techniques, and successful navigation of regulatory landscapes will be key to realizing the potential of graphene in drug delivery. With these advancements, graphene-based systems could revolutionize targeted therapy, controlled drug release, and personalized medicine

[39]. Functionalization techniques have been pivotal in overcoming biocompatibility issues, enabling targeted and controlled release of therapeutics. Graphene-based drug delivery systems have shown promising results in cancer therapy, gene delivery, and tissue engineering, showcasing their versatility and efficacy [40]. However, challenges such as potential toxicity, scalability of production, and regulatory hurdles must be addressed to fully harness graphene's capabilities in clinical settings.

7. Conclusion

In conclusion, graphene stands out as a groundbreaking material with immense potential in drug delivery applications, owing to its exceptional structural, mechanical, and electronic properties. This comprehensive review has highlighted the diverse methods of graphene synthesis, from mechanical exfoliation to chemical vapor deposition, each offering distinct advantages and challenges. The exceptional qualities of graphene, such as high surface area, remarkable strength, and excellent conductivity, make it a prime candidate for enhancing drug delivery systems. Future research should focus on refining synthesis methods to ensure consistency and safety, exploring novel functionalization approaches, and conducting extensive in vivo studies to better understand the long-term effects and efficacy of graphene-based drug delivery systems. By addressing these challenges, the biomedical community can unlock the full potential of graphene, paving the way for innovative and effective therapeutic solutions.

Conflicts of interest

The authors declare that they have no conflict of interest.

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