Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2019; 9(1); 109-113
doi: 10.25258/ijddt.9.1.18

ISSN: 0975 4415

Review Article

Biomedical Potential of Graphene oxide based Nanoformulations: An Overview

Vijay Mishra[1], Gurpal Singh[2], Nishika Yadav[1], Ravi Pratap Barnwal[3], Neha Singla[3], Kirti. S. Prabhu[4], Ashish Suttee[5]*

[1]*School of Pharmaceutical Sciences, Lovely Professional University, Punjab, India*
[2]*Department of Pharmaceutics, University Institute of Pharmaceutical Sciences, Punjab University, Chandigarh, India*
[3]*Department of Biophysics, Punjab University, Chandigarh, India*
[4]*Interim Translational Research Institute, Academic Health System, Doha, Qatar*
[5]*Department of Pharmacognosy, School of Pharmaceutical Sciences, Lovely Professional University, Punjab, India*

Received: 12th Nov, 18; Revised: 20th Feb, 19, Accepted: 8th Mar, 19; Available Online: 25th Mar, 2019

ABSTRACT

Graphene oxide is graphene-based two dimensional material and structure based on single sheet of carbon atoms arranged in hexagonal lattice or honeycomb framework. Graphene oxide is better than graphene in terms of dispersion in polar solvents due to oxygen-containing functional groups attached with carbon sheets, results as researchers to get indulged in this molecule. Graphene oxide has been attracted researchers in different fields like chemistry, physics and materials science. Graphene oxide has endless potential applications in building materials, environmental protection, electronics, medicine, pharmaceutical industries etc. In medicinal industry, graphene oxide used as antibacterial, antimicrobial and antifungal agent. Its potential activity with other nanoparticles as antifungal agent has come in light and became the main focus of going on works on graphene oxide. The antifungal property of GO-Ag composites was investigated. Furthermore, nanoparticles show great potential in the fields of biomedical, because of their antifungal properties. The GO-Ag composites act as alternative antifungal material. Moreover, antifungal activity of Reduced Graphene Oxide (rGO) nanosheets is also researched.

Keywords: Graphene; Graphene Oxide; Nanoparticle; Antifungal.

INTRODUCTION

Meanwhile, the graphene "birth" in 2004, a two-dimensional (2D) cargo materials have captivated unparalleled research attention from researchers and stimulated several applications in different fields such as energy storage, sensors, catalysis, optical/electronic devices, and biomedicine[1]. Graphene is comprised of single carbon atoms layer organized in hexagonal lattice, called as "superstar" of the 2D nanomaterial family, also explored in antimicrobial properties[2]. Amid the different catalysts utilized to transport and form energy, carbon nanomaterial have experienced profound interest in improved oxidation procedures to eliminate the organic containment. GNM have presented outstanding performance in relevance of reactions to store and generate energy for instance, hydration of fuel cells, oxidative dehydrogenation, allynes, and alcohols oxidation[3].

Graphene oxide (GO) is factor of attention in recent years due to their unique chemical and physical properties. The tremendous electrical, thermal, mechanical properties and great applications of GO make it an distinctive nanofiller for probable applications in numerous field of polymer, paper-like materials, biomedical sectors, electronic devices, composites, etc. GO comprised of functional groups containing oxygen bonded covalently like epoxide, hydroxyl, carboxyl on their basal edges and planes. These functional groups offer the robust sites of binding and interact to sculpt GO exfoliated or intercalated composites by interrelating with polar or polymers molecule for the improvement of the composites properties[4].

Graphene Oxide

The general GO structure is described simply as a graphene modified sheet including different functional groups, such as hydroxyl (−OH) carboxyl (−COOH), and epoxy (eOe). These oxygen groups confer GO hydrophilicity and their potential to enhance the hydrophobic drugs solubility, and result as highly suitable GO for the drug delivery system as compared to pristine graphene. Liu et al. studied that the efficacy of anti-cancer and the solubility of a hydrophobic drug SN38 was increased via loading the drug onto the GO grafted by polyethylene glycol (PEG)[5]. Lei et al. also reported that the doxorubicin (DOX) solubility enhanced by loading on the functionalized GO via sodium alginate and chitosan[6]. Due to the presence of oxygen reactive groups (such as –COOH, –OH), GO easily get functionalized and

Author for Correspondence: ashish7sattee@gmail.com

Table 1: Properties and applications of GFMs[9].

Property	Applications
Optical	Anti-reflective coatings
	Surfaces are refractive index tailored
Mechanical	Developed resistance of wear
	Advanced properties of anti-corrosion
	Novel materials structure, composites
Magnetic	Increased storage media density
	Nanomagnetic particles lead to enhance the detail in images (Magnetic Resonance)
Energy	High energy density and durable batteries
	Electrocatalysts for high-efficiency full cells
	Ultra-high performance solar cells
	Catalysts for combustion engines to improve efficiency
Thermal	Improves the efficacy of the coolants
Electronic	High ability of performance and smaller compounds (i.e. mobile phones)
	Great conductive materials
Biomedical	Sensor acts to detect the diseases (quantum dots)
	The release of drug delivery systems is programmed
Environmental	Cleans up pollution and contamination of soil (e.g. biodegradable polymers, oil)
	Industrial emissions treatment
	Filtration or purification of water
Personal care	Sunscreens (inorganic)
	Protection of dye

modified and therefore results in great application in the improved delivery of drug[7].

Guo et al synthesized graphene oxide–MnO2–fluorescein (GO–MnO2–FL) nanocomposite and used for detection of Glucocorticoid-Suppressible Hyperaldosteronism (GSH). GSH can deduct MnO^2 to Mn^{2+} and restrict the transfer of energy between GO–MnO_2 and FL, resulting to the important fluorescence improvement of composite. The GSH fluorescence-based biosensing has the detection limit of 1.53 μM and a broad range of detection of 10 μM–2 mM[8].

Properties of Graphene Oxide

GO have elastic modulus, great thermal conductivity of 5.1×10^3 Wm^{-1} K^{-1}, maximum electrical conductivity (intrinsic) contrast to other carbon nanomaterials (6×10^5 Sm^{-1}), elevated aspect flakes ratio (lateral dimensions to thickness ratio of 104 and more) and excellent intrinsic flexibility are some most significant graphene family materials (GFMs) characteristics. These properties yield functional properties to GO-based NMs such as electrical or semi-conductivity, exclusive photonic transportation, least permeability, anisotropic transport, and quenching of fluorescence. Because of various major reasons GFMs applications are growing rapidly. GO is most popular derivatives of graphene, exhibits different properties and reflects different biomedical and non-biomedical applications. An important GO feature is its chemical reactivity and capacity for functionalization chemically.

Fabrication methods of Graphene Oxide

In earlier few years, graphene oxide (GO) synthesized by means of chemical exfoliation and oxidation of graphite pristine involving the Staudenmaier, Brodie, or Hummers method.

- Brodie was the first researcher who found that oxidizing mixture ($KClO_4$ + fuming HNO_3) can fabricate GO only by graphitizable carbons which contain graphitic structure regions.
- Then Staudenmaier reported that the GO form when the graphite heated with HNO_3, $KClO_4$, and H_2SO_4.
- Later more, Hummers and Offeman discovered most convenient and easy method of fabricating GO using $KMnO_4$ and H_2SO_4.

Exfoliation is a significant step in the synthesis of GO and usually attained in aqueous solution by means of an ultrasonic method using various solvents. The usual procedures include contact of graphite powders to specific solvents, furthermore, exposing to sonication method. Recently, alternative methods also introduced for reduction and exfoliation of GO simultaneously to achieve graphene nanosheets (GNs), for instance, chemical method, microwave, thermally treatment, and plasma[10].

Biomedical applications of Graphene Oxide

Anti-bacterial activity

Graphene quantum dots (GQDs) are zero-dimensional grapheme nanomaterials derivative, possess alike peroxidase-mimic characteristic, and subsequently used to prompt the antibacterial action of H_2O_2 at reduced concentrations[1]. GO displayed higher antibacterial property and lesser cytotoxicity as compared to rGO because of the presence of different charges and groups on their surfaces. Additionally, GO exhibit improved antibacterial efficiency toward both Gram-positive *Staphylococcus aureus* (S. aureus) and Gram-negative *E. coli*. Pham et al studied the viability of bacteria on graphene films per altered roughness (facilitated by densities of edge and orientation of sheet). Researchers resulted that the "graphene nano rough" (GN-R)-coated surface attains improved bactericidal efficacy in contrast to "graphene nano-smooth" (GN-S)- and graphite (GT)-coated ones, concluding that graphene edges density is

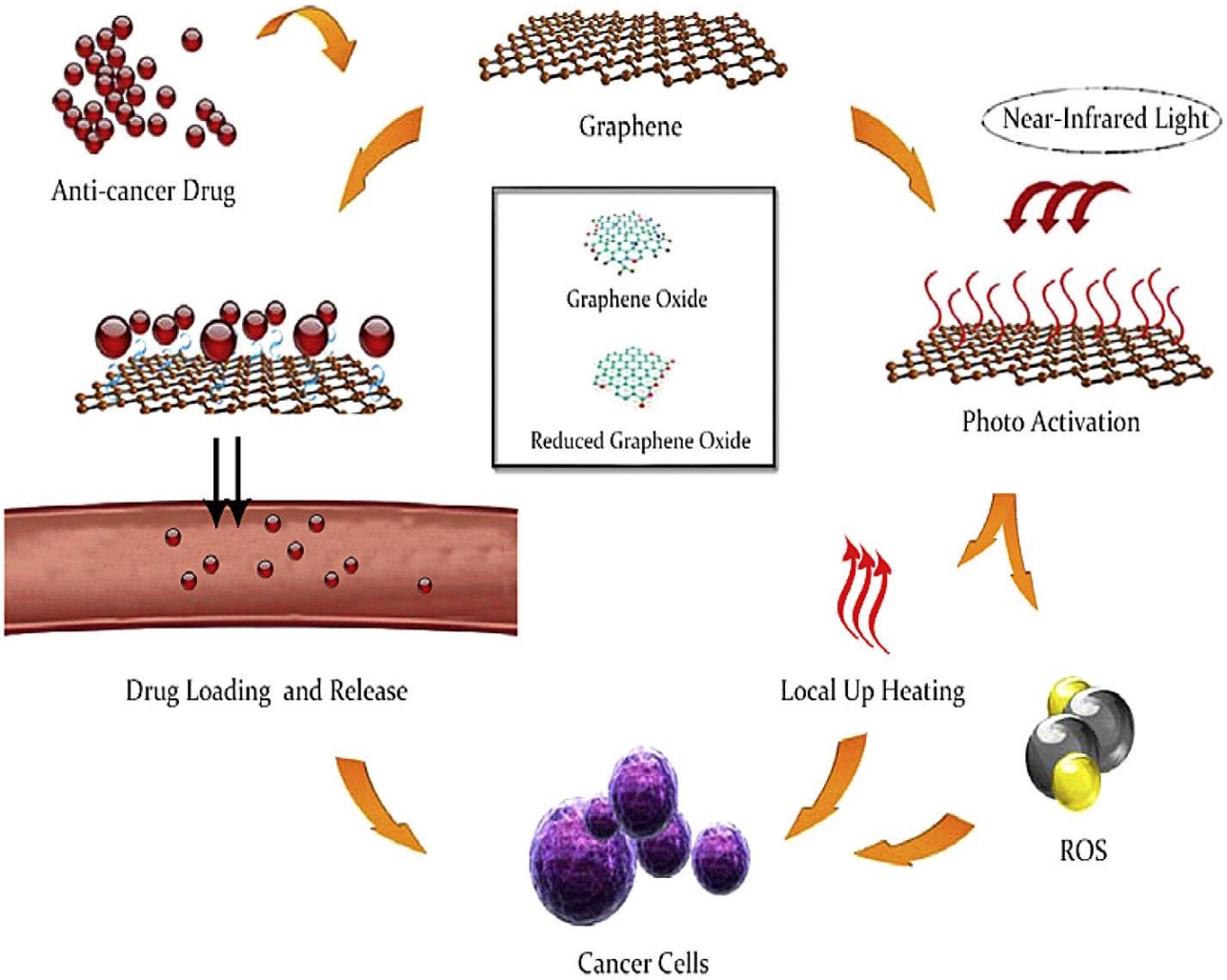

Figure 1: Schematics of the anti-cancer function of graphene-based nanomaterials, either as drug carriers or photothermal agents[17].

the main parameter which contributes to the efficacy of antibacterial property[11].

Bain and co-workers reported that GO shows lower candidacidal property in treated macrophages at with two promising enlightenment. First, exocytosis of the GNMs as well non-lytic Candida expulsion can explain their lesser detected activity of fungicide. The fungal cells release follows the macrophage phagocytosis, known as "non-lytic" expulsion, also been described for various fungal pathogens, such as Candida albicans[12]. Second explanation refers to the after exocytosis of cargo-material, as macrophages are least capable to ingest cells of Candida[13].

Cancer Therapy

The continuous rise in cancer death rate and morbidity needs highly effective approaches for cancer management. The traditional chemotherapy frequently fails to cure cancer or extended rate of survival because of their side effects, toxicity, and lack capacity of targeting[14]. GO derivatives like GO treated base and carboxylated GO (GOCOOH) been sightseen in cancer immunotherapy because of their amended properties[15]. GO treated base is achieved by washing the GO from sodium hydroxide, defined as a process which removes the fragments of oxidation from GO lattice, enhancing their loading capacity of loading drug[16]. Lee et al. formed GO layered with conjugates of Pluronic® F-127-FA with altered densities of folic acid (FA). In vitro, the authors proved that by increasing the density of FA on GO surface enhances the materials internalization through cancer cells. Though,, in vivo, FA decorated GO with densities of 0, 10 and 25% showed similar accumulation of tumor. As result, FA functionalized GO with densities of 50% and 100% yield similar performance, presenting the maximum uptake of the tumor. Furthermore, the photothermal effect of GO mediated by 50% FA formed a hyperthermia to 60 °C and eradication of tumor in 2 mice. Alternatively, GO having densities of 0 and 25% FA lead to tumors growth reduction on irradiation, and only generate hyperthermia near 47 and 50°C, respectively[17].

Toxicity

GO and rGO can cause toxicities, like hematotoxicity and cytotoxicity[18-20]. Many studies done regarding the safety of rGO, GO, and their derivatives revealed cytotoxicity of dose-dependent[21]. GO, in vivo toxicity was reported as dose-dependent. Akhavan et al. performed a study and displayed the GO effect of dose-dependent on the capability of mice reproduction[22]. The author found, GO

involved in the spermatogenesis and improved the ROS generation in the mice semen, resulting in the spermatozoa destruction. Their toxicity also affected by alternative factors, like size. Liao et al. formed GO of different sizes and concluded that GO of smallest size yields highest hemolytic property[18]. Excitingly, GO hemolytic activity reduced on aggregation of GO and approximately destroyed by a coating of chitosan. Sasidharan et al. studied that water-insoluble rGO accumulate on the membrane of a cell in a large extent, persuading high ROS stress then leads to cell death[23]. Formerly, functionalized the rGO using carboxyl to form it water soluble also the toxicity eliminated in a large amount, representing that the solubility of water can also affect the rGO toxicity.

CONCLUSION

The developments of GFM have been taken to a stimulating climax in the biomedical field for their various properties. The large surface of graphene provides the capability to bind or absorb more therapeutics to treat and detect different diseases, like cancers. Functionalization by chemical reaction or physical interaction with active groups may attain enhanced reduced toxicity, biocompatibility, and targeting. Although the presently available outcomes all support further nanomaterials improvement of in clinical studies. By small size, accountable functionalization of the surface, tremendous biocompatibility, and appeared to be less dangerous.

REFERENCES

1. Sun W, Wu FG. Two-Dimensional Materials for Antimicrobial Applications: Graphene Materials and Beyond. Chemistry-An Asian Journal; 2018 Jul 17. doi: 10.1002/asia.201800851.
2. Tegou E, Magana M, Katsogridaki AE, Ioannidis A, Raptis V, Jordan S, Tegos GP. Terms of endearment: Bacteria meet graphene nanosurfaces. Biomaterials 2016; 89:38-55.
3. Higgins D, Zamani P, Yu A, Chen Z. The application of graphene and its composites in oxygen reduction electrocatalysis: A perspective and review of recent progress. Energy & Environmental Science 2016; 9:357-390.
4. Baishya P, Maji, TK. A comparative study on the properties of graphene oxide and activated carbon based sustainable wood starch composites. International Journal of biology macromolecules 2018; 115:970-977.
5. Liu Z, Robinson JT, Sun X, Dai H. PEGylated nanographene oxide for delivery of water-insoluble cancer drugs. Journal of American Chemical Society 2008; 130:10876–10877.
6. Lei H, Xie M, Zhao Y, Zhang F, Xu Y, Xie J. Chitosan/sodium alginate modificated graphene oxide-based nanocomposite as a carrier for drug delivery. Ceramics International 2016; 42:17798-17805.
7. Goenka S, Sant V, Sant S. Graphene-based nanomaterials for drug delivery and tissue engineering. Journal Control Release 2014; 173:75-88.
8. Guo Y, Zhang X, Wu FG. A graphene oxide-based switch-on fluorescent probe for glutathione detection and cancer diagnosis. Journal of Colloid and Interface Science 2018; 530:511-520.
9. De Marchi L, Pretti C, Gabriel B, Marques PA, Freitas R, Neto V. An overview of graphene materials: Properties, applications and toxicity on aquatic environments. Science of the Total Environment 2018; 631:1440-1456.
10. Song J, Wang X., Chang, CT. Preparation and characterization of graphene oxide. Journal Nanomaterials 2014. doi:10.1155/2014/276143.
12. Pham VT, Truong VK, Quinn MD, Notley SM, Guo YC, Baulin VA, Ivanova, EP. Graphene induces formation of pores that kill spherical and rod-shaped bacteria. ACS Nano 2015; 9:8458-8467.
13. Bain JM, Lewis LE, Okai B, Quinn J, Gow NA, Erwig LP. Non-lytic expulsion/ exocytosis of Candida albicans from macrophages. Fungal Genetics and Biology 2012; 49:677-678.
14. Luo N, Weber JK, Wang S, Luan B, Yue H, Xi X, alma G. PEGylated graphene oxide elicits strong immunological responses despite surface passivation. Nature Communications 2017; 8:14537.
15. Liu J, Dong J, Zhang T, Peng Q. Graphene-based nanomaterials and their potentials in advanced drug delivery and cancer therapy. Journal of Control Release 2018; 286:64-73.
16. Rourke JP, Pandey PA, Moore JJ, Bates M, Kinloch IA, Young RJ, Wilson NR. The eeal graphene oxide revealed: stripping the oxidative debris from the graphene-like sheets. Angewandte Chemie 2011; 123:3231-3235.
17. Ma D, Dong L, Zhou M, Zhu L. The influence of oxidation debris containing in graphene oxide on the adsorption and electrochemical properties of 1, 10-phenanthroline- 5,6-dione. Analyst 2016; 141:2761-2766.
18. Lee JH, Sahu A, Jang C, Tae G. The effect of ligand density on in vivo tumor targeting of nanographene oxide. Journal of Controlled Release 2015; 209:219-228.
19. Liao KH, Lin YS, Macosko CW, Haynes CL. Cytotoxicity of graphene oxide and graphene in human erythrocytes and skin fibroblasts. ACS Applied Material Interfaces 2011; 3:2607-2615.
20. Hu W, Peng C, Lv M, Li X, Zhang Y, Chen N, Huang Q. Protein coronamediated mitigation of cytotoxicity of graphene oxide. ACS Nano 2011; 5:3693-3700.
21. Chang Y, Yang ST, Liu JH, Dong E, Wang Y, Cao A, Wang H. In vitro toxicity evaluation of graphene oxide on A549 cells. Toxicological Letters 2011; 200:201-210.
22. Aliabadi M, Shagholani H, Yunessnia Lehi A. Synthesis of a novel biocompatible nanocomposite of graphene oxide and magnetic nanoparticles for drug

delivery. International Journal of Biological Macromolecule 2017; 98:287-291.
23. Akhavan O, Ghaderi E, Hashemi E, Akbari E. Dose-dependent effects of nanoscale graphene oxide on reproduction capability of mammals. Carbon 2015; 95:309-317.
24. Sasidharan A, Panchakarla LS, Chandran P, Menon D, Nair S, Rao CNR, Koyakutty, M. Differential nano-bio interactions and toxicity effects of pristine versus functionalized grapheme. Nanoscale 2011; 3:2461:2464.