SciMedCentral

Journal of Drug Design and Research

Mini Review

Recent Approaches in Use of Graphene Derivatives in Anticancer Drug Delivery Systems

Zorawar Singh* and Rumina Singh

Department of Zoology, Khalsa College, India

***Corresponding author**

Zorawar Singh, Department of Zoology, Khalsa College, India, Email: zorawarsinghs@rediffmail.com

Submitted: 09 March 2017

Accepted: 27 March 2017

Published: 28 March 2017

ISSN: 2379-089X

Keywords

- Graphene
- Drug delivery systems
- Doxorubicin
- Camptothecin
- Graphene oxide
- Graphene quantum dots

Abstract

Graphene derivatives have emerged as important materials in the development of anticancer drug delivery systems. Graphene, graphene oxide and graphene quantum dots have been used for the successful delivery of different anticancer drugs including Doxorubicin and Camptothecin. The present paper focuses on the recent approaches in the formulations and use of various graphene based nano-composites in drug delivery systems.

ABBREVIATIONS

GO: Graphene Oxide; DOX: Doxorubicin; CMC: Carboxy-Methyl Chitosan; HA: Hyaluronic Acid; FI: Fluorescein Isothiocyanate; NIR: Near-Infrared; Gqds: Graphene Quantum Dots; FA: Folic Acid; Trf: Transferrin; NGO: Nano-Graphene Oxide; PDEA: Poly 2-Diethylamino Ethyl Methacrylate; PEI: Polyethyleneimine; CPT: Camptothecin; HA: Hypocrellin A

INTRODUCTION

Being one of the most common element, more environment and biological friendly than inorganic materials, carbon materials are on the top of the list today in the field of biological sciences [1]. Since its first appearance in 2004, Graphene, a single layer of sp2-hybridized carbon atoms which is arranged in a honeycomb two-dimensional (2-D) crystal lattice, has evoked enormous interest throughout the scientific community [2]. Having planar surface, it shows unparalleled thermal conductivity, remarkable electronic properties and superlative mechanical strength, and thus, have made them attractive in biotechnological applications [3]. Recent advances in nanoscience and technology have enabled synthesis of many new nanomaterials along with development of new devices and nano-analytical methods. Nanoscience has thus opened a number of new doorways in future medicines. However, development of an effective drug delivery system which has the ability to improve the therapeutic profile and efficacy of therapeutic agents is one of the key issues faced by modern medicine [4]. Thus, motivated by the success of carbon nanotubes in a number of biomedical applications, scientists started to work in the field of using graphene in drug delivery systems [5]. Minute size of graphene systems being even smaller than cellular organelles, allows carbon nanoobjects to penetrate basic biological structures, disrupting their abnormal functions and hence making them potential drug delivery carriers. This paper emphasizes the use of graphene and its derivatives as a modular model for being used in drug delivery systems.

Use in anticancer drug delivery systems

Various anti-cancer therapies used today, often pose limitations in cell penetration ability, insolubility, administration, systemic toxicity caused by lack of selective targeting towards cancer cells and inefficient distribution [3]. Graphene nanocomposites have emerged as a promising tool to address these drawbacks. Having high near-infrared absorbance, graphene and its derivatives have been found to be excellent candidates for multimodal imaging guided combined cancer photothermal, chemo- and photo-dynamic therapies [6]. These 'smart' graphene hybrid nanostructures have several functionalities such as stimulus-response mediated delivery into cancer cells, imaging at release sites as well as transfection [3]. In particular, an oxide of graphene, called graphene oxide (GO) when effectively functionalized with anticancer drugs like doxorubicin (DOX) (Figure 1) and porphyrins via both π–π stacking and covalent bonding between their amino and carboxyl groups, shows good solubility and stability in physiological solutions. GO can also uniquely attach to and deliver aromatic, water insoluble drugs [7].

GO when modified with carboxy-methyl chitosan (CMC), followed by conjugation of hyaluronic acid (HA) and fluorescein isothiocyanate (FI) resulted in a GO-CMC-FI-HA conjugate. The release of this functionalized graphene-based material can be

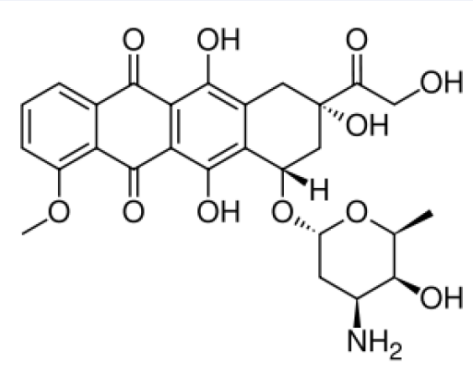

Figure 1 Chemical structure of Doxorubicin (DOX).

intelligently controlled and be used as a carrier to encapsulate DOX [8]. Similarly, super paramagnetic manganese ferrite ($MnFe_2O_4$) nanoparticles when deposited on GO by the thermal decomposition of manganese (II) acetylacetonate and iron (III) acetylacetonate precursors in tri-ethylene glycol results in GO/$MnFe_2O_4$ nanohybrids. These nanohybrids poses strong optical absorbance in the near-infrared (NIR) region, can be used as effective T2 contrast agent and their good photothermal stability results in the highly efficient photothermal ablation of cancer cells. When loaded with DOX, they can also be used in chemotherapy, thus suggesting synergistic effect in DOX chemotherapy and photothermal therapy [9].

Graphene quantum dots (GQDs) also serve as fluorescent carriers for DOX, having capacity to be simultaneously tracked and release the drug. Further functionalization of the loaded carriers with arginine-glycine-aspartic acid (RGD) peptides forming DOX-loaded RGD-modified GQDs (DOX-RGD-GQDs), enhanced their uptake by DU-145 and PC-3 human prostate cancer cell lines [10]. Similarly, folic acid (FA)-conjugated GQDs loaded with DOX, can unambiguously discriminate cancer cells from normal cells and efficiently deliver the drug to targeted cells. Thus, stable fluorescence of GQDs enables monitoring of the cellular uptake of these nano-assemblies rapidly as seen in HeLa cells via receptor-mediated endocytosis. It is also seen that consequent release of drugs significantly reduced cytotoxicity to non-target cells [11]. Another quantum-dot-conjugated graphene, formed by functionalizing the surface of hybrid SiO_2-coated quantum dots (HQDs) conjugated graphene with transferrin (Trf) and adsorption of fluorescent antineoplastic anthracycline drug, DOX on the surface of graphene are used as a probe for simultaneous cancer-targeted fluorescent imaging, tracking and monitoring drug delivery [12]. Nano-graphene oxide (NGO) is single-layer graphene oxide sheet down to a few nanometers in lateral width. It shows photoluminescence in the visible and infrared regions that is used for live cell imaging. Loading DOX on NGO functionalized with antibody is used for selective killing of cancer cells in vitro. Having a very small size, intrinsic optical properties, large specific surface area, low cost and useful non-covalent interactions with aromatic drug molecules, NGO is becoming a promising material in biological and medical applications [13]. pH-sensitive poly 2-diethylamino ethyl methacrylate (PDEA) bonds covalently with GO by surface-initiated in-situ atom transfer radical polymerization. Possessing good solubility and stability in physiological solutions, the grafted PDEA-GO can be used to load camptothecin (CPT), a widely used water-insoluble cancer drug (Figure 2) by simple physical adsorption. The GO-PDEA-CPT complex might turn out to be a promising material for site-specific anticancer drug delivery as loaded with CPT normally in a tumor environment and it exhibited high potency in killing N2a cancer cells *in vitro* [14].

Graphene oxide reduced by using riboflavin-5'-phosphate sodium salt dihydrate resulted in a fabricated nano-rGO which showed negligible hemolytic activity demonstrating its safety in drug delivery system. Compared with common carriers, the obtained DOX-loaded nano-rGO nanohybrids exhibited characteristics of high drug loading, good stability, pH-sensitive and sustainable release of drugs. It also exhibited effective cytotoxicity to MCF-7 and A549 cells by non-specific endocytosis mechanism making it an ideal nano-carrier for drug delivery [15]. The above studies suggest that these functionalized graphene-based materials have potential applications for targeted delivery and controlled release of anticancer drugs. On a controversial note though, it was seen that when a photosensitive anticancer drug, Hypocrellin A (HA) was loaded on GO, anticancer activity of HA was decreased. But when a chemotherapy drug, 7-ethyl-10-hydroxycamptothecin (SN-38), was co-loaded on the HA loaded GO forming HA-SN-38-GO composite, the combination therapy exhibited a synergistic anti-proliferative effect compared with photodynamic therapy or chemotherapy alone [16]. A previous paper by the author also emphasized the use of graphene based nanomaterials in different drug delivery systems [17]. (Table 1) shows the use of graphene and its derivatives as drug delivery systems for various anticancer drug molecules.

Recently, a study reported the use of graphene oxide as a nanocarrier for controlled release and targeted delivery of chlorogenic acid, an anticancer active agent [18]. The successful conjugation of chlorogenic acid onto graphene oxide through hydrogen bonding and pi-pi interaction was confirmed. The loading of chlorogenic acid in the nanohybrid was estimated to be around 13.1%. Pan et al., used Lactobionic acid and carboxymethyl chitosan functionalized graphene oxide nanocomposites as targeted anticancer drug delivery systems. This study reported a targeted drug delivery system built by functionalizing graphene oxide (GO) with carboxymethyl chitosan, fluorescein isothiocyanate and lactobionic acid. The release behavior from both the LA-functionalized and the LA-

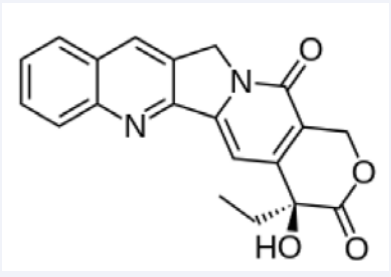

Figure 2 Chemical structure of Camptothecin (CPT).

Table 1: Use of different graphene based nanosystems for the delivery of various anticancer agents.

Sr. No.	Author	Year of publication	Graphene derivative used	Drug/Compound
	Barahuie et al.[18],	2017	GO	Chlorogenic acid
	Jiang et al. [19],	2015	Cellular protease (furin) - mediated graphene-based nanosystem	Cytokine (tumor-necrosis-factor-related apoptosis-inducing ligand, TRAIL) and DOX
	Miao et al. [20],	2013	PegylatedGO nanosheets	Photosensitizer chlorin e6 (Ce6) and DOX
	Mo et al. [21],	2015	ATP-responsive DNA-graphene hybrid nanoaggregates	DOX
	Pan et al. [22],	2016	Lactobionic acid and carboxymethyl chitosan functionalized GO nanocomposites	DOX
	Shim et al. [23],	2014	Reduced graphene oxide nanosheets coated with an anti-angiogenic anticancer low-molecular-weight heparin derivative	DOX
	Song et al. [24],	2014	Hyaluronic acid-decorated GO nanohybrids	DOX
	Tian et al. [25],	2016	Pegylatedfolate and peptide-decorated GO	Anticancer drugs and fluorescein-labeled peptide
	Wang et al. [26],	2014	Chlorotoxin-conjugated GO	DOX

GO, Graphene oxide, PEI, Polyethyleneimine; DOX, Doxorubicin; TRAIL, Tumor-necrosis-factor-related apoptosis-inducing ligand

free material was found to be pH sensitive. Similarly, an another study revealed the possibility of using Furin-mediated sequential delivery of anticancer cytokine and small-molecule drug shuttled by graphene [19].

CONCLUSION

Bringing changes in size and thickness of the GO nanosheets by means of ultrasonication treatment prior to deposition into the nanocomposite, alters the film morphology, drug load, and release profile. This process gives an opportunity to fine-tune the properties of the drug delivery system to meet a variety of therapeutic needs. As discussed in the paper, DOX and CPT have successfully being delivered using graphene based nanomaterials. Although there are many other demonstrations regarding the delivery of anticancer drugs using these nanomaterials, their long-term toxicological and metabolic behavior still merit significantly before bringing them to clinical use.

REFERENCES

1. Snitka V. Graphene Based Materials: Opportunities and Challenges in Nanomedicine. Nanomed Res. 2015; 2: 00035.
2. Geim AK, Novoselov KS. The rise of graphene. Nat Mater. 2007; 6: 183-191.
3. Muthoosamy K, Bai RG, Manickam S. Graphene and graphene oxide as a docking station for modern drug delivery system. Curr Drug Deliv. 2014; 11: 701-718.
4. Liu J, Cui L, Losic D. Graphene and graphene oxide as new nanocarriers for drug delivery applications. Acta Biomater. 2013; 9: 9243-9257.
5. Feng L, Liu Z. Graphene in biomedicine: opportunities and challenges. Nanomedicine (Lond). 2011; 6: 317-324.
6. Yang K, Feng L, Liu Z. The advancing uses of nano-graphene in drug delivery. Expert Opin Drug Deliv. 2015; 12: 601-612.
7. Wang WN, He X. Aerosol Processing of Crumpled Graphene Oxide-based Nanocomposites for Drug Delivery. Curr Pharm Des. 2016; 22: 2491-2500.
8. Yang H, Bremner DH, Tao L, Li H, Hu J, Zhu L. Carboxymethyl chitosan-mediated synthesis of hyaluronic acid-targeted graphene oxide for cancer drug delivery. Carbohydr Polym. 2016; 135: 72-78.
9. Yang Y, Shi H, Wang Y, Shi B, Guo L, Wu D, et al. Graphene oxide/manganese ferrite nanohybrids for magnetic resonance imaging, photothermal therapy and drug delivery. Biomater Appl. 2016; 30: 810-822.
10. Qiu J, Zhang R, Li J, Sang Y, Tang W, Rivera Gil P, et al. Fluorescent graphene quantum dots as traceable, pH-sensitive drug delivery systems. Int J Nanomedicine. 2015; 10: 6709-6724.
11. Wang X, Sun X, Lao J, He H, Cheng T, Wang M, et al. Multifunctional graphene quantum dots for simultaneous targeted cellular imaging and drug delivery. Colloids Surf B Biointerfaces. 2014; 122: 638-644.
12. Chen ML, He YJ, Chen XW, Wang JH. Quantum-dot-conjugated graphene as a probe for simultaneous cancer-targeted fluorescent imaging, tracking, and monitoring drug delivery. Bioconjug Chem. 2013; 24: 387-397.
13. Sun X, Liu Z, Welsher K, Robinson JT, Goodwin A, Zaric S, et al. Nano-Graphene Oxide for Cellular Imaging and Drug Delivery. Nano Res. 2008; 1: 203-212.
14. Kavitha T, Abdi SI, Park SY. pH-sensitive nanocargo based on smart polymer functionalized graphene oxide for site-specific drug delivery. Phys Chem Chem Phys. 2013; 15: 5176-5185.
15. Ma N, Zhang B, Liu J, Zhang P, Li Z, Luan Y. Green fabricated reduced graphene oxide: evaluation of its application as nano-carrier for pH-sensitive drug delivery. Int J Pharm. 2015; 496: 984-992.
16. Zhou L, Zhou L, Wei S, Ge X, Zhou J, Jiang H, et al. Combination of chemotherapy and photodynamic therapy using graphene oxide as drug delivery system. J Photochem Photobiol B. 2014; 135: 7-16.
17. Singh Z. Applications and toxicity of graphene family nanomaterials and their composites. Nanotechnol Sci Appl. 2016; 9: 15-28.
18. Barahuie F, Saifullah B, Dorniani D, Fakurazi S, Karthivashan G, Hussein

MZ, et al. Graphene oxide as a nanocarrier for controlled release and targeted delivery of an anticancer active agent, chlorogenic acid. Mater Sci Eng C Mater Biol Appl. 2017; 74: 177-185.

19. Jiang T, Sun W, Zhu Q, Burns NA, Khan SA, Mo R, et al. Furin-mediated sequential delivery of anticancer cytokine and small-molecule drug shuttled by graphene. Adv Mater. 2015; 27: 1021-1028.

20. Miao W, Shim G, Lee S, Lee S, Choe YS, Oh YK. Safety and tumor tissue accumulation of pegylated graphene oxide nanosheets for co-delivery of anticancer drug and photosensitizer. Biomaterials. 2013; 34: 3402-3410.

21. Mo R, Jiang T, Sun W, Gu Z. ATP-responsive DNA-graphene hybrid nanoaggregates for anticancer drug delivery. Biomaterials. 2015; 50: 67-74.

22. Pan Q, Lv Y, Williams GR, Tao L, Yang H, Li H, et al. Lactobionic acid and carboxymethyl chitosan functionalized graphene oxide nanocomposites as targeted anticancer drug delivery systems. Carbohydr Polym. 2016; 151: 812-820.

23. Shim G, Kim JY, Han J, Chung SW, Lee S, Byun Y, et al. Reduced graphene oxide nanosheets coated with an anti-angiogenic anticancer low-molecular-weight heparin derivative for delivery of anticancer drugs. J Control Release. 2014; 189: 80-89.

24. Song E, Han W, Li C, Cheng D, Li L, Liu L, et al. Hyaluronic acid-decorated graphene oxide nanohybrids as nanocarriers for targeted and pH-responsive anticancer drug delivery. ACS Appl Mater Interfaces. 2014; 6: 11882-11890.

25. Tian J, Luo Y, Huang L, Feng Y, Ju H, Yu BY. Pegylated folate and peptide-decorated graphene oxide nanovehicle for in vivo targeted delivery of anticancer drugs and therapeutic self-monitoring. Biosens Bioelectron. 2016; 80: 519-524.

26. Wang H, Gu W, Xiao N, Ye L, Xu Q. Chlorotoxin-conjugated graphene oxide for targeted delivery of an anticancer drug. Int J Nanomedicine. 2014; 9: 1433-1442.

Cite this article

Singh Z, Singh R (2017) Recent Approaches in Use of Graphene Derivatives in Anticancer Drug Delivery Systems. J Drug Des Res 4(3): 1041.