ScienceDirect

Materials Today Chemistry

Volume 25, September 2022, 100987

Remotely controlled electro-responsive on-demand nanotherapy based on amine-modified graphene oxide for synergistic dual drug delivery

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https://doi.org/10.1016/j.mtchem.2022.100987

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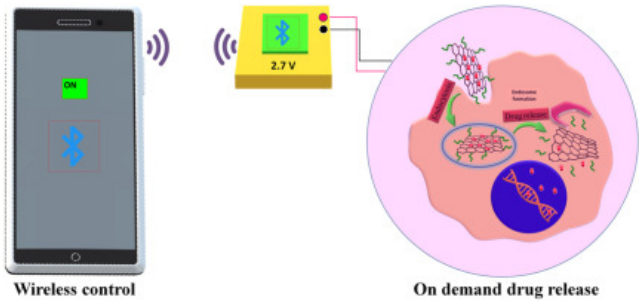
Abstract

This study focuses on the development of a new electric field responsive graphene oxide (GO) nanoparticle system for on-demand drug delivery. Today, GO is an attractive option adopted in various biological applications for its exclusive features such as flexibility, conductiveness, cost-effectiveness, and external stimuli-responsive nature. It is usual to utilize multiple drugs in cancer treatment. This kind of therapy has lesser side-effects, drug resistance, and is more effective than utilizing only one drug. This study aims to determine low-voltage-controlled dual drug (aspirin and doxorubicin) release from GO surface. Here, we have demonstrated how to control the drug release rate remotely with a handy mobile phone, with zero passive release at idle time. In addition, the study focused to estimate the synergism of aspirin with doxorubicin in the release mechanism from GO in the presence of external voltage, using the spectroscopic method. Moreover, we observed aspirin- and doxorubicin-induced synergistic antitumor activity in MDA-MB 231 (breast cancer cell) in*vitro*. Thus, our study presents a noble combination of aspirin and doxorubicin that could be utilized for remotely controlled on-demand drug delivery for triple negative breast cancer treatment, using GO as a carrier.

Graphical abstract



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Introduction

For last few years, stimuli-responsive materials have revolutionized the world of biomedicines and biotechnology. Therapeutic agents can be released from stimuli-responsive drug delivery systems by many endogenous factors such as temperature, pH, biomolecules like enzymes, and so on [[1], [2], [3], [4]]. However, in this process, the main challenge is to locate the drug in a diseased tissue particularly, but not in the healthy tissue, especially when the difference between these tissues is quite negligible; hence raises a possibility of off-target release. In contrast, all these obstacles can be lifted by introducing exogenous factors such as magnetic field, light, heat, voltage are totally separated from the patient's physiology and can deliver the drug in a more controlled and precise way in the targeted region [5,6].

On-demand drug delivery systems that deliver drugs according to the patients need have attracted significant attention as they have reduced the risks and complications involved. Many smart materials are used for on-demand drug delivery by utilizing their responses to various stimulations such as temperature, UV light, magnetic, and electrical stimulation. These materials have fewer side-effects and can trigger the drug release by imposing the abovementioned stimulations.

Reducing the side-effects of anticancer drugs, improving the therapeutic effect, and bioimaging are difficult tasks, and therefore, a constant effort was directed to overcome all these challenges. As a result, numerous new drug carriers have been designed and introduced in recent days. Among these new promising drug carriers, graphene oxide (GO) has been widely used due to its high biocompatibility with a high drug loading capacity. GO is a two dimensional sp^2 hybridized monatomic carbon allotropes with epoxy, hydroxyl, and carboxyl functional groups on its basal plane and edges [7,8]. A large amount of available surface area, a p-conjugated structure, and Van der Waals interactions of GO make it an excellent drug carrier [9,10].

GO is well dispersed in an aqueous solution due to the presence of hydroxyl, carboxyl, and epoxy groups, which significantly enhance the interfacial bonding within the components, and transfer stress efficiently. These advantages make GO an extremely potential nanocomposite material as a drug carrier in the field [11,12]of biomedicine and biotechnology, while being combined with a polymer or inorganic matrix [13,14].

In the present study, our strategy is to develop a graphene oxide (NGO) nanocomposite functionalized with two different drug molecules one is a common anticancer drug for breast cancer, doxorubicin (DOX), and another one is a non-steroidal anti-inflammatory drug, acetylsalicylic acid or aspirin (ASP). It has been observed that patients with cancer on a supplement of ASP have reduced cancer risk and longer overall survival than those who are not [15,16]. ASP is an anti-inflammatory drug most commonly used to treat inflammatory diseases. The association between chronic inflammation and cancer [17,18]suggests that ASP can be effective against cancer. Anticancer effects of ASP have been already established in colorectal cancer [19,20], esophageal cancer [21], gastric cancer [22], liver cancer [23], and pancreatic cancer [24].

We hypothesized that a combination of ASP and DOX (ASDO) could boost the anticancer effect in the treatment of breast cancer. Therefore, this study is designed whether the cytotoxic properties of ASDO are synergistic when used together in MDA-MB 231 (human epithelial triple-negative breast cancer cell line, TNBC) cell line, in*vitro*.

In this work, we have demonstrated that the growth rate of cells is reduced when treated with ASDO compared to cells treated with DOX alone.

Upon application of external stimuli, many materials are able to release drugs. However, most of them need sophisticated instruments except electrical stimulation. Electro-stimulated drug delivery has attracted attention due to the low expense, plainless, and portability of the control equipment, making it manageable for customized applications [6,25]. In this study, we used NGO as an electro-sensitive material to deliver drugs in a controllable manner. In this study, NGO is first modified with an amine group to functionalize it with ASP. This modified ASP-tagged NGO is used for loading anticancerous drug DOX. This drug-loaded NGO then passes through the mobile-controlled external electrical stimulation, which triggers the release of both the drugs (ASP and DOX). Our study estimated the necessary voltage on DOX release from NGO. The release of ASP is another aspect that has been investigated here under the influence of electrical stimulation. The synergic effect of ASP compels the DOX to release more.

Several reports have been done on the use of GO base dual drug delivery system for cancer treatment due to high bioavailability, low systemic side-effects, and rich surface functional modification sites [26]. Most of the drug can be

released in controlled way that prevents the off-target release and improves the therapy efficiency [27,28]. However, several shortcomings in dual drug delivery system limit their applications: (1) Drug leakage may be easily stimulated during delivery of the drug from the blood stream to tumor organelles; (2) drugs released in the cytoplasm have no target organelles, which may influence the therapy effect. Therefore, to eradicate these problems, the leakage of drug needs to take care in the dual drug delivery system. Nonetheless, our investigation assessed whether there is any passive release or not.

Although several works were done on electro-stimulated drug delivery using graphene as a base material, but electro-stimulated dual drug delivery is rare in drug delivery research field. This is the first time we have used ASP and DOX as a model drug which can be delivered simultaneously by external voltage. We have also demonstrated how hydrophilic (ASP) and hydrophobic drug (DOX) can be delivered by using a single delivery platform. Not only that the use of these dual drug has different advantages. First, we have observed in the presence of ASP the release of DOX increased several times, which is beneficial for cancer treatment. Second, the presence of ASP with DOX increases the activation of enzyme caspase 3, 8, and 9 which are responsible for induction of apoptosis in HepG2 cell.

Thus, our target in this study were (i) to realize the effectiveness of ASP in DOX release from modified GO in presence of external voltage, (ii) to examine our system for on-demand drug delivery for both ASP and DOX, (iii) how the passive release problem from as synthesized dual drug delivery system can be prevented, and (iv) finally, execution of a cell study to verify the efficacy of the drug release in the presence of the external voltage and understand the importance of ASP in drug uptake by the cancer cell. Thus, our work presents an excellent dual drug delivery system in the presence and absence of DC voltage, which can be extremely useful for on-demand-controlled drug delivery in the cancer cell.

Section snippets

Materials

Graphite nanopowder was bought from Sisco research laboratories (SRL, India). Ethylenediamine (EDA), *N*-(3-dimethylaminopropyl-*N′*-ethylcarbodiimide) hydrochloride (EDC-HCl), *N*-hydroxyuccinimide (NHS), and dialysis membrane (MWCO 2000) were bought from Sigma-Aldrich Company. From HiMedia (India), 2-(*N*-morpholino) ethane sulfonic acid (MES buffer) was purchased. Doxorubicin (DOX)and ASP were obtained from Sigma Aldrich. Throughout our study, we have used all the reagents of analytical reagent…

Results and discussion

The structural and physicochemical properties of graphite and NGO determine the color of their dispersion in water. After 0.5 h sonication, black particles were visible in the graphite dispersion. Here, most graphite particles precipitated after 0.5 h. On the other hand, blackish-yellow color is formed for singly oxidized NGO. After 2 h, a good amount of GO particles got precipitated in an idle situation. But for doubly oxidized NGO, we obtained transparent and homogeneous yellow-color…

Anticancer activity

In*vitro* anticancer activity of the prepared nanocomposite was evaluated by performing MTT assay (Fig.9a). In this study, we have evaluated the anticancer activity of the nanomedicine with or without applying electrical stimulation and compared to free DOX. Very interestingly, GO–NH–ASP-DOX with 2.7v electrical field has shown superior anticancer activity, whereas free DOX has shown its conventional toxicity pattern [38], and the GO–NH–ASP-DOX nanocomposite also has shown minimal toxicity…

Conclusion

In conclusion, we have shown here that NGO can be used as a dual drug delivery agent, and the release of drugs can be controlled by an external voltage. To exploit the synergic effect of ASP and DOX, we modified NGO and attached two

drugs to it. Our labmade remote-controlled device efficiently released the anticancer drug. The releasing process can easily be switched on and off with a mobile phone by changing the bias voltage. Here, the release of DOX from NGO under the influence of external…

CRediT author statement

Dibakar Sahoo: Conceptualization, Methodology, Data curation, Visualization, Investigation, Supervision, Writing – Original draft preparation, reviewing, and editing.

Tapas Mitra: Conceptualization, Methodology, Data curation, Visualization, Investigation, Supervision, Writing – reviewing and editing.

Kaushik Chakraborty: Design and implimentation of the electronic device (Hardware & Software).

Priyatosh Sarkar: Methodology, Data curation – cell study, Writing – cell study.…

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.…

Acknowledgments

D.S. is grateful to the University Grants Commission (UGC), New Delhi, India, for his UGC Assistant Professorship and for providing UGC startup grant. D.S. is also thankful to DST Odisha for providing DST Odisha project grant. T.M. acknowledges DST, New Delhi, for financial assistance provided in the form of a SERB-National Post-Doctoral Fellowship (SERB-NPDF). The authors are thankful to Prof. Anjan Kumar Dasgupta for giving permission to measure some experiments in his lab.…

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Citation Excerpt :
...Mostly, graphene and graphene oxide derivatives have commonly been employed as novel carriers for cancer therapies [18]. Graphene oxide, with its various remarkable properties, provides a diverse range of applications in a variety of disciplines as previously mentioned [19,20]. Consequently, graphene, which is a single nuclear layer of graphite, was the initial two-dimensional crystal with a high surface area and hydrophobic/lipophilic characters [21], Additionally, it is considered to be a good candidate for thermal and electrical conductor [22,23]....

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e Both authors have equal contribution.

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