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Fabrication of a 2D-Surfactant Exfoliated Hexagonal Boron Nitride Nanoparticles as Efficient pH-Sensitive Drug Delivery System for Lung Cancer Therapy

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Abstract: Lung cancer is one of the most prevalent cancers and it is also the primary cause of cancer-related mortality globally. However, due to variations in tobacco use patterns, exposure to environmental risk factors, and genetics, lung cancer incidence and mortality rates vary significantly worldwide. Since smoking is the primary risk factor for lung cancer, developing more effective therapeutic strategies and innovative drug delivery systems may help to raise the disease's survival rates. In this study, a novel pH-sensitive nanocarrier based on a composite of a two-dimensional hexagonal boron nitride (2D-*h*BN) with unique properties was synthesized to deliver Doxorubicin (DOX). Firstly, bulk hBN powder was exfoliated with a sodium cholate salt, sonicated, and centrifuged to obtain the as-prepared 2D-hBN nanocarriers, and finally, DOX was entrapped for targeted drug delivery and tumor therapy. High DOX loading and entrapment efficiency (LE% and EE%, respectively) were obtained. The EE% and LE% for sodium cholate exfoliated 2D-*h*BN obtained were 84.50% and 25.48%, respectively. *In vitro* drug release experiments demonstrated a pH-sensitive non-Fickian release profile with a release percentage of 73.5%. Preliminary *in-vitro* cytotoxicity was done via MTT assay, using the human lung adenocarcinoma cell line (A549), and the 2D-*h*BN@DOX nanocomposites were shown to drastically reduce the viability of the cancer cells compared to 2D-*h*BN, indicating the great efficacy of the former nanocomposites in hindering the proliferation of cancer cells.

Keywords: Boron nitride, Cancer treatment, Doxorubicin, Lung cancer, Sodium cholate

Introduction

Cancer is the second most common cause of disease-related death in humans globally, and it is predicted that 13.1 million people will die from cancer by the year 2030 (Siegel et al., 2024; Lu et al., 2018). Chemotherapy is a common therapeutic option, yet its effectiveness for other cancer types is limited (Fusser et al., 2019). This fundamental cancer treatment has serious side effects and damages normal, non-cancerous cells (Liao et al., 2014; Su et al., 2011). Drug delivery systems (DDS) are designed to reduce unwanted side effects (Prabhakar et al., 2013; Rapoport 2007; Malekimusav et al., 2019).

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DDSs are developed in attempts to regulate drug release in an effort to reduce cellular toxicity while maintaining therapeutic efficacy (Prabhakar et al., 2013; Rapoport 2007; Malekimusav et al., 2019; Amini-Fazl et al., 2019). The ingenious strategy uses pH differences between healthy and tumorous tissues to deliver the anti-cancer drug to the desired location while minimizing damage to surrounding cells (Amini-Fazl et al., 2019). Enhancing permeability and retention (EPR), which causes an increasing buildup of the anti-cancer medication in malignant tissue, is the foundation of DDS (Fusser et al., 2019; Liao et al., 2014; Su et al., 2011; Prabhakar et al., 2013; Rapoport 2007; Malekimusavi et al., 2019; Amini-Fazl et al., 2019; MacEwan et al., 2010) The EPR effect tacitly confers macromolecules to penetrate the interstitial spaces in cancer tissue, thus enhancing the overall efficacy of chemotherapeutic substances (Shi et al., 2017).

To develop DDSs, nanoscale anti-cancer drug carriers can be synthesized to facilitate regulated and prolonged release of anti-tumor drugs and enhance drug distribution (Shi et al., 2017; Arruebo et al., 2007; Merisko-Liversidge et al., 2011; Zhen et al., 2013; Azizi et al., 2018). Therefore, applying cutting-edge and effective methods to cancer therapy, such as nanoparticles-based DDS, would be advantageous in a number of ways (Sarani et al., 2024). Hexagonal boron nitride is an inorganic layered material with a single atom thin with alternating arrangement of B and N similar to graphene and black phosphorus (BP). Among nanoparticles, two-dimensional hexagonal boron nitride (2D-*h*BN) nanomaterials have several intriguing biological and chemical properties such as biocompatibility, antibacterial properties, chemical inertness, thermal stability, and surface functionalization that make them promising materials for diverse biomedical applications (Gautam et al., 2021; Santos et al., 2021). Because of these advantages, scientists and medical professionals may be interested in using such materials in nano-formulations to deliver therapeutics to malignant tumor sites (Feng et al., 2021).

Method

Fabrication of 2D-*h*BN Nanocomposites

Boron nitride powder (CAS 10043-11-5) ~1 μm, 98% was purchased from Sigma Aldrich and cholic acid sodium salt (CAS 206986-87-0) was purchased from Thermo Fisher (Kandel) GmbH, Germany. The 2D-*h*BN utilized herein was fabricated using a liquid exfoliation, sonication, and centrifugation technique based on surfactants, as in (Kurapati et al., 2016) with a few modifications.

Briefly, 0.05 g bulk boron nitride powder and 0.01 g sodium cholate salt were weighed and mixed with 50 mL aqueous solution of deionized (DI) water (pH 7.6) in a glass beaker to induce liquid phase exfoliation. The resulting dispersion was sonicated with a Daihan Scientific Ultrasonic Cleaner (60% Amplitude) for 1 h before centrifugation by Sigma 2-16P centrifuge at 5000 rpm for 90 mins. Subsequently, the dispersion's supernatant liquid was pipetted off and the remaining sediment was reagitated in a fresh aqueous solution of sodium cholate salt and DI water, 0.003 g in 50 mL, respectively. The reagitated sediment was then sonicated at the same previous settings for 5 h more. After the sonication treatment was finished, the solution was divided into aliquots and centrifuged for 90 minutes at 2000 rpm. The sediment that included the unexfoliated hBN was subsequently disposed of, and the leftover supernatant was centrifuged again for 90 minutes at 5000 rpm. Finally, upon removal of the forthcoming supernatant, the nanocomposites utilized herein were found to be surfactant-exfoliated 2D-*h*BN.

Drug Loading

Doxorubicin hydrochloride (DOX) 50 mg (EDA Reg. 24995/2007) was purchased from Hikma Specialized Pharmaceuticals, Badr City, Cairo, Egypt. The DOX loading experiment was done by dispersing 5 mg of the 2D-*h*BN nanosheets in DI water (pH 7.0) and sonicated at 60% Amplitude for 5 mins. Next, the dispersion and 5 mL (0.2 mg/mL) DOX solution in phosphate-buffered saline (PBS (pH 7.4)) were blended in a 1:1 ratio, and the mixture was magnetically agitated for 24 hours at room temperature in a dark cabinet. The obtained solution was dialyzed to remove unbound DOX molecules by centrifuging at 8000 rpm for 30 mins and resuspended in PBS (pH 7.4).

To determine the DOX entrapment efficiency (EE%) and the loading efficiency (LE%), the total amount of unbound DOX was ascertained by measuring the absorbance at 480 nm relative to the DOX standard calibration curve (Fig. 1 (c)) recorded under similar conditions. The EE% and LE% were computed according to the equations (1) and (2) below (Zavareh et al., 2020).

$$EE(\%) = \frac{(\text{Total amount of DOX}) - (\text{Free amount of DOX})}{(\text{Total amount of DOX})} x\ 100 \quad (1)$$

$$LE\ (\%) = \frac{(\text{Total amount of DOX}) - (\text{Free amount of DOX})}{(\text{Total amount of 2D-}h\text{BN})} x\ 100 \quad (2)$$

Drug Release

The *in vitro* release experiments were studied in a comparable way to that as in (Espinoza et al., 2022) at the absorbance of the collected buffer solution (PBS) at a wavelength of 480 nm. Briefly, the 2D-*h*BN@DOX pellets from the drug loading experiment dispersed in 5 mL PBS (pH 7.4) were centrifuged at 8000 rpm for 20 mins. Then, the supernatant from the solution was decanted by careful pipetting and a 1 mL sediment of the 2D-*h*BN@DOX was loaded into two different dialysis bags (having a molecular weight cut-off equals to 3.5 kDa) corresponding to the two pH 7.4 and 5.0. And the two bags were dialyzed in a 50 mL PBS buffer solution at 37 °C and agitated gently at 100 rpm in a dark cabinet. At predetermined intervals (0, 1, 2, 4, 6, 12, 24, and 48 h), 6 mL aliquots from each media were extracted from the reservoirs for analysis and replenished with an equal volume of fresh PBS medium, respectively. Equation (3) was utilized to determine the percentage of DOX released.

$$\text{Drug Release}\ (\%) = \frac{\text{DOX in dialysis medium}}{\text{Total DOX in the system}} x\ 100 \quad (3)$$

Cytotoxicity Assay

Using the MTT assay, the capacity of fabricated 2D-hBN nanocomposites, such as 2D-hBN@DOX, to limit the development of lung cancer cells was investigated on A549 cells following treatment with 0 μgmL^{-1}, 65 μgmL^{-1}, 125 μgmL^{-1}, and 250 μgmL^{-1} doses. This rapid quantitative assay measures cellular metabolic activity by evaluating the reduction of MTT to purple formazan crystals primarily by mitochondrial dehydrogenase with the aid of a solubilization solution dimethyl sulfoxide (DMSO), an acidified ethanol solution. This enzyme in living cells is responsible for converting the yellow tetrazole to insoluble purple formazan crystals (Fotouhi et al., 2021). This test was run at 24 and 48 hours after treatment times.

In detail, the fabricated specimens were initially made by dissolving them in a tissue culture media that contained serum. The samples were then sterilized at pH 7.4 with 0.2 mm filtration. Conversely, 5000 cells/100 µL of A549 cells were individually seeded in each well of 96-well plates and allowed to attach to the wells during the course of a 24-hour incubation. Subsequently, the culture media was extracted, 100 µL of four specimen concentrations were added to each well, and the plates were cultured for 24 h and 48 h. Following this procedure, 20 µL of sterile-filtered MTT salt made in PBS pH 7.4 (5 mg/mL) was applied to the wells of the plate, and the plates were incubated for 4 hours after the medium was replaced with 200 µL Roswell Park Memorial Institute (RPMI) with no serum.

The following step involved pipetting off the well suspension liquid, and 100 µL DMSO added to each well, and then the plates were incubated for 20 minutes. The optical density (OD), also known as color intensity, of the wells was then measured at 590 nm (n = 1), and the cell viability values were computed as the difference in OD values between the treated and non-treated cells.

Results and Discussion

The UV-Vis absorption spectra of the fabricated 2D-*h*BN product, investigated by Agilent Carry 60 spectrophotometer (Figure 1.(a)), revealed the characteristic peak of the 2D-*h*BN at 204 nm.

Drug Loading and Release experiments

Drug Loading

The successful loading of DOX onto the 2D-*h*BN was affirmed by also using Agilent Carry 60 spectrophotometer. The 2D-*h*BN@DOX absorption spectra were compared with that of the markers (2D-*h*BN and free DOX). The absorption spectra of the 2D-*h*BN@DOX nanocomposites showed a DOX-related absorbance peak at 481 nm, as shown in Figure 1. (a), which confirmed the successful loading of DOX onto the 2D-*h*BN. Using a DOX Standard Calibration Curve (Figure 1. (c)), the EE% and LE% of the 2D-*h*BN@DOX nanocomposites were calculated. The findings were 84 ± 0.50% and 25 ± 0.48%, respectively.

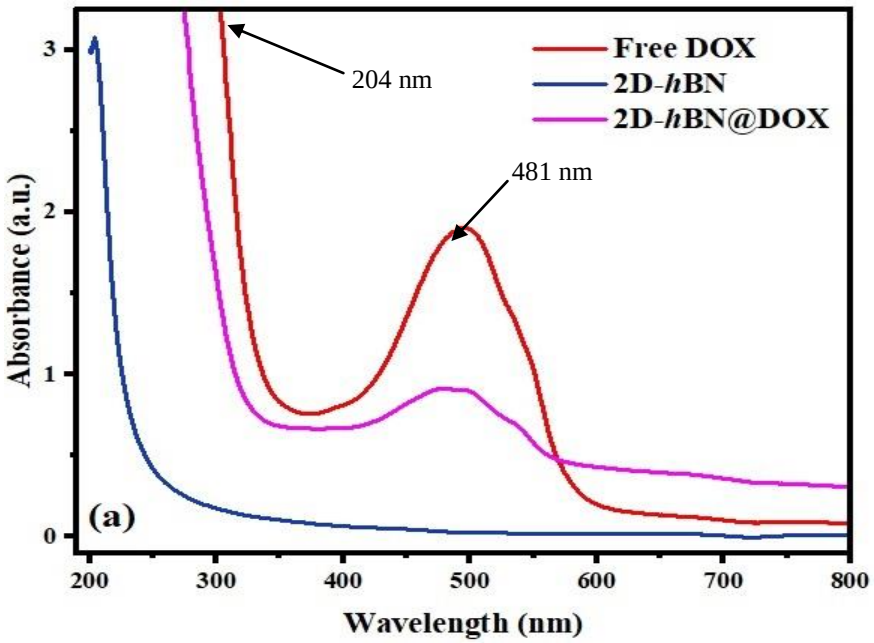

Figure 1. (a) UV-Vis spectra of free DOX, 2D-*h*BN, and 2D-*h*BN@DOX.

Drug Release

The *in vitro* drug release characteristics of the 2D-*h*BN@DOX were studied at physiological pH 7.4 and endosomal pH 5.0 of cancer cells (Figure 2. (b)). The findings demonstrated that in an acidic environment (i.e., pH 5.0), DOX was released more quickly during the first 24 hours and then steadily over the next 72 hours, reaching 73.5%.

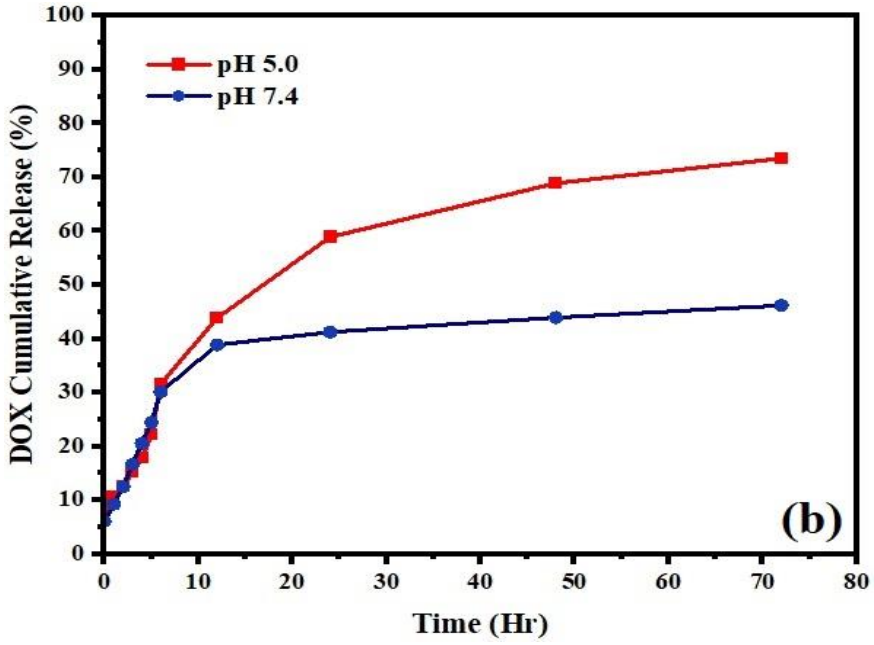

Figure 1. (b) Drug release profile of DOX from 2D-*h*BN@DOX nanocomposites.

According to reports, medications that are linked to or encased in cell membranes can be influenced by the environment's pH. The cell membrane can progressively lyse, or dissolve, in an acidic environment, allowing the drug to be released more easily. In contrast, after 72 hours, the DOX release rate was 46.2% under neutral conditions (pH = 7.4). Since tumor tissue grows best in an acidic environment, controlling the production of DOX in a way that is pH-responsive may be advantageous for the treatment of cancer. Moreover, DOX's adverse effects might be lessened in physiological settings due to a reduction in its circulatory leakage. The results suggest non-Fickian diffusion drug release mechanism which was noted by the rapid release at first then tailing off over time. This high release percentage proves the enhanced pH-responsiveness and controlled-release behavior of the 2D-*h*BN@DOX.

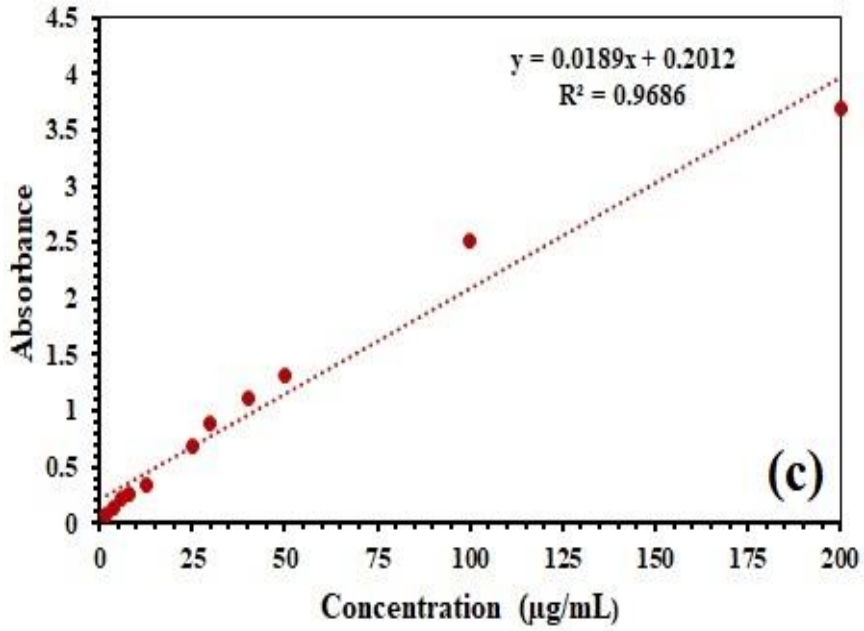

Figure 1. (c) DOX standard calibration curve.

Cytotoxicity Assay

To determine the potential of the fabricated 2D-*h*BN nanocomposites in suppressing the development of lung cancer cells, the MTT assay results showed no significant cytotoxicity on the A549 cell lines after treatment for 24 and 48 h with 2D-*h*BN, as shown in Figure 2. (a) and (b), affirming that the nanocomposites were non-toxic.

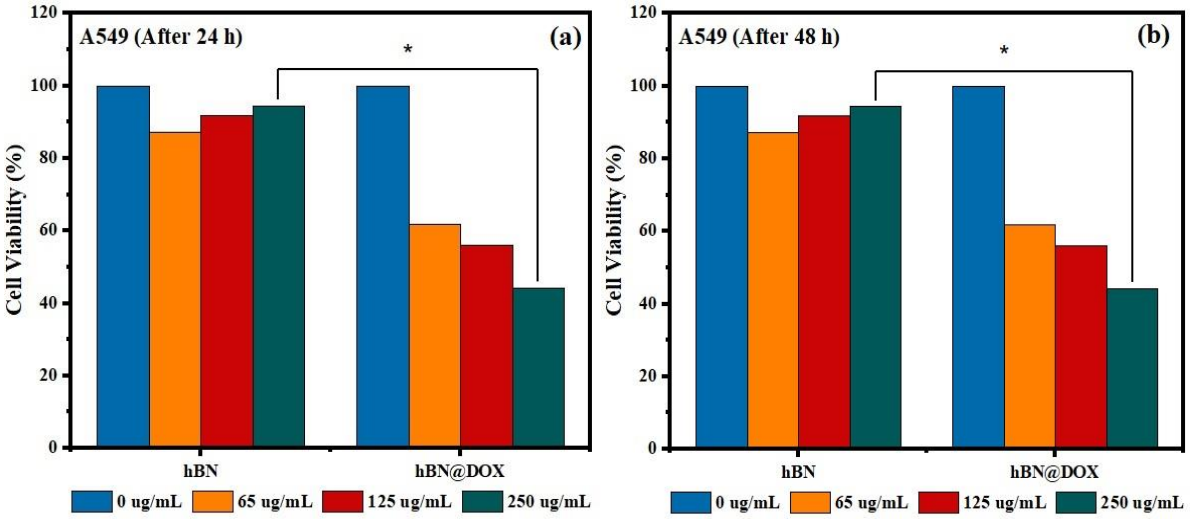

Figure 2. Cell viability results. *$P < 0.05$ is statistically significant.

There was a concentration-dependent cell viability feature for all samples as illustrated in Figure 2. (a) and (b). The cell viability increased as the 2D-*h*BN sample concentration was raised, indicating the nanocarrier's

biocompatibility, vice versa it is true regarding the 2D-*h*BN@DOX sample (Kumar et al., 2018; Khalef et al., 2024). Specifically, following 24 hours of treatment with 65 μgmL^{-1} and 250 μgmL^{-1} concentrations of 2D-*h*BN samples, 87% and 94% of A549 cells' viability were detected. These results indicate the nanocomposites' biocompatibility and further validate their safety for application in cancer drug delivery.

However, following a 24-hour treatment with the 2D-*h*BN@DOX nanocomposites, the viability of the cancer cells decreased to 61% and 44% at concentrations of 65 μgmL^{-1} and 250 μgmL^{-1}, respectively. This indicates that the DOX-loaded 2D-*h*BN possesses cytotoxic properties. The A549 cell line's cell viability results after 48 hours of treatment were comparable to those after 24 hours. There is a high metabolic rate in cancer cells which makes them engulf every biocompatible substance in their surroundings through endocytosis without being cognizant of its cargo (DOX).

Conclusion

In conclusion, a 2D-*h*BN DDS exfoliated from bulk boron nitride powder with a surfactant sodium cholate salt was successfully fabricated in this study. Anti-cancer drug (DOX) was loaded and released from the 2D-*h*BN in a pH-dependent manner. Benefiting from the encapsulation of nanoparticles with DOX, the 2D-*h*BN@DOX exhibited enhanced performance in terms of biocompatibility and drug-loading capability. Furthermore, the high drug release percentage at acidic environment endowed the 2D-*h*BN@DOX with specific targeting capacity at tumor sites. Finally, preliminary MTT assay experiment with A549 cell lines also affirmed a tumor-inhibiting effect of the 2D-*h*BN@DOX nanocomposites.

Recommendations

There is a need to conduct further cellular uptake experiments to evaluate the effectiveness of the 2D-*h*BN nanoparticles loaded with different anti-tumor drug(s) in determining how well nanoparticles are internalized by cancer cells, which is essential for their therapeutic efficacy. Also, apoptosis assay, cell cycle arrest, and *in vivo* tumor therapy is required to help determine whether nanoparticles can induce programmed cell death (apoptosis) in cancer cells, to halt the division of cancer cells, thereby preventing tumor growth and proliferation, to evaluate of the efficacy of 2D-*h*BN@DOX nanocomposites for treating A549 cells-injected mice models, respectively.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS Journal belongs to the authors.

Acknowledgements or Notes

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