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Preparation of Black Phosphorus and the Application in Biomedicine

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Abstract. This work presents an in-depth exploration of black phosphorus (BP) nanosheets, highlighting their transformative potential in advancing cancer treatment. As cancer continues to be a leading cause of death worldwide, current therapies often fall short of delivering targeted and effective treatment with minimal side effects. In response to this need, BP nanosheets are considered to be a kind of promising multifunctional materials for cancer therapy. The work begins with an overview of the pressing challenges and the limitations of current targeted therapies, including issues like drug resistance and systemic toxicity. It then delves into the various methods of BP nanosheet preparation, including top-down and bottom-up approaches, which are critical in enhancing their properties for biomedical applications. Furthermore, the diverse applications of BP nanosheets are thoroughly examined, particularly their roles in photothermal therapy, photodynamic therapy, and drug delivery. BP nanosheets also offer the capability to regulate the tumour microenvironment and enable combined treatment modalities. Their multifunctionality and potential to integrate multiple therapeutic approaches provide a compelling solution to overcome the drawbacks of existing cancer treatments, thus paving the way for safer and more effective therapies.

Keywords: Black Phosphorus; Preparation; Drug Carriers.

1. Introduction

Cancer threatens global health with millions of new cases and deaths reported annually. Despite advancements in early detection and conventional treatments like surgery, chemotherapy, and radiation, the mortality rate remains high, largely due to the disease's aggressive nature and the limitations of existing therapies. One of the critical challenges in current cancer treatment is the need for targeted therapies [1]. This necessity has encouraged the development of various targeted cancer therapies, including monoclonal antibodies, small molecule inhibitors, and nanotechnology-based drug delivery systems. However, these approaches often face limitations such as off-target effects, drug resistance, and systemic toxicity.

In recent years, black phosphorus (BP) nanosheets are used in cancer-targeted therapies. BP nanosheets exhibit tuneable bandgap and good biocompatibility, which make them suitable for drug delivery and phototherapy applications [2]. Unlike traditional drug carriers, BP nanosheets can simultaneously serve as a drug carrier and a therapeutic agent, providing a multifunctional platform for combined therapies. Their ability to load large quantities of chemotherapeutic drugs and release them in a controlled manner under specific conditions, such as pH and light, enhances the effectiveness of the treatment while minimising systemic toxicity. Additionally, BP nanosheets exhibit strong photothermal and photodynamic properties, allowing them to convert light into heat and generate reactive oxygen species, respectively, making them highly effective in combined photothermal, photodynamic, and chemotherapy approaches. These multifunctional capabilities position BP nanosheets as an effective tool in the ongoing explorations to develop more effective and targeted treatments [3].

This review will delve into several key aspects of BP nanosheets in the context of cancer treatment. It will begin with an introduction to BP, followed by a detailed exploration of the various methods used to prepare BP nanosheets. It also highlights the performances that make them suitable for biomedical applications. The review will then focus on the applications of BP nanosheets as drug carriers in cancer therapy, discussing their roles in photothermal therapy, photodynamic therapy, drug delivery, microenvironment regulation, and their integration into microfluidic systems. Finally, the review will examine the potential of BP nanosheets in combined therapies, showcasing their ability to enhance the efficacy of cancer treatments through multi-modal approaches.

2. Black Phosphorus

Black phosphorus is one of the three allotropes of phosphorus. Current research investigated two types of black phosphorus materials, including zero-dimensional quantum dots, and two-dimensional nanosheets. In this review, black phosphorus nanosheet is mainly discussed for its applications as drug carriers.

Black phosphorus nanosheet has a 2D monolayer structure, similar to graphene, and has been employed in several areas such as energy storage, selective sensors and catalysts. The material has a high strength, good optical properties, and high thermal conductivity physically. Chemically, it has tuneable electronic properties and higher chemical stability, making this material suitable for electrochemical energy conversion and energy storage [4].

2.1. Mechanical Exfoliation

Similar to 2D structure materials like graphene, layers of black phosphorus nanosheets are connected into bulk crystals by weak van der waals forces. They are easy to break and can be cleaved to layers of single-layered structures by applying forces to the material. Black phosphorus nanosheets obtained by mechanical exfoliation are high in purity and have little problems with quality. However, this method has a low yield and an uncontrollable product size, shape and thickness. Therefore, it is not applicable for large-scale synthesis and it is not used in mass production [4, 5].

2.2. Sonication Liquid-Phase Exfoliation

As an alternative method, the liquid phase exfoliation method uses several solvents to assist the production of black phosphorus nanosheets. Bulk materials were first immersed in a solvent, and then sonication provided energy to exfoliate the material and obtain thin layers of nanosheets by centrifugation. This method is widely used in the preparation of nanosheets, and a certain number of research has been conducted to investigate different solvents used in exfoliation.

Liquid phase exfoliated black phosphorus was first successfully obtained using an N-methyl-2-pyrrolidone (NMP) solution by Brent et al [6]. Since then, black phosphorus nanosheets have been prepared in several different solvents.

This preparation method can be an effective and scalable method of producing black phosphorus nanosheets with relatively high stability, but the sonication could be time-consuming and not cost-effective [7].

2.3. Electrochemical Exfoliation

Compared to other preparation methods, electrochemical exfoliation is environmental-friendly and effective. This method usually conducted at room temperature. This method can be divided into anode exfoliation and cathode exfoliation.

The method of anode exfoliation, also known as anodic oxidation, was performed by using bulk black phosphorus crystal as the anode, and a platinum foil or wire as the cathode in electrolyte (salt with sulphate ion). By increasing voltage, free radicals attack the edges of bulk black phosphorus. At the same time, sulphate ions enter in-between layers of black phosphorus and expand the spaces between layers and exfoliate the crystal. Thin and high-quality nanosheets appear at the bottom of the electrolyte and can be collected by ultrasonication. However, oxidation is unavoidably introduced to products collected this way.

As for the cathode exfoliation, which is named as cationic interaction, black phosphorus powder with a platinum plate inserted is used as the cathode, and other platinum plates are the anode. Both electrodes were immersed in electrolyte, after which voltage was applied. Unlike anode exfoliation, as-prepared black phosphorus nanosheets decrease in thickness and reduce the degree of oxidation [8].

2.4. Chemical Vapour Deposition (CVD)

CVD is a process that involves the conversion of precursors to black phosphorus nanosheets. Precursors react, decompose or volatilise at high temperatures, and then 2D materials will grow on the substrate surface and produce nanosheets. In particular, red phosphorus is used to grow 2D black phosphorus on the silicon substrate [9].

2.5. Pulsed Laser Deposition (PLD)

Pulsed laser deposition achieves thin film synthesis through the bombardment of a solid-phase target via a high-energy laser beam, followed by the subsequent deposition of the molten products onto an alternative substrate. This method is considered to be a clean and controllable technique for preparing nanosheets by treating solid precursors in liquid [9].

3. Applications in the Medical Field

3.1. Photothermal Therapy and Photodynamic Therapy

BPs have demonstrated significant potential in photothermal therapy (PTT) and photodynamic therapy (PDT). A recent study by Liu et al. introduced a novel application of BP nanoparticles (NPs) that are functionalized with PEGylated hyaluronic acid (HA). It is designed to serve as both a tumour-targeting agent and a macrophage converter. This dual functionality is crucial for enhancing the efficacy of cancer treatments by integrating photothermal and photodynamic effects with immune modulation.

The HA-BP nanoparticles exhibit excellent biocompatibility and stability. The study showed that these nanoparticles induce significant photothermal effects under near-infrared (NIR) laser irradiation, leading to localized heating that can effectively kill cancer cells. Additionally, the HA-BP nanoparticles generate reactive oxygen species (ROS) under light activation, facilitating photodynamic therapy. The combination of PTT and PDT not only directly damages cancer cells but also triggers immune responses by reshaping tumour-associated macrophages (TAMs). Specifically, the HA-BP NPs were able to shift TAMs from a pro-tumour M2 phenotype to an anti-tumour M1 phenotype, which further enhances the immune-mediated clearance of cancer cells.

The dual-mode therapy provided by these BP nanoparticles has shown significant inhibition of tumour growth in both in vitro and in vivo models, highlighting their potential as a multi-functional platform for cancer treatment. The integration of PTT, PDT, and immunotherapy into a single nanoparticle system represents a promising approach to overcoming the limitations of conventional cancer therapies and improving patient outcomes [10].

3.2. Drug Delivery

Black phosphorus (BP) nanosheets have garnered significant attention as drug delivery platforms in cancer therapy. BP nanosheets provide an excellent substrate for drug delivery systems (DDS) that enhance the efficacy and targeting of cancer therapeutics. The most common approach involves loading traditional anticancer drugs like doxorubicin (DOX) onto BP nanosheets through electrostatic interactions, which has significantly increased drug loading capacity and improved delivery efficiency. For example, Chen et al. reported a BP-based DDS with a DOX loading capacity of 950 wt%, which significantly improved drug transport and tumour inhibition efficiency in vivo.

Moreover, BP nanosheets have been modified to overcome limitations such as instability and low drug-loading efficiency. Modifications with polyethene glycol (PEG) and other polymers enhance the stability and biocompatibility of BP nanosheets, making them more effective for drug delivery.

PEG-modified BP nanosheets not only improve physiological stability but also allow for the conjugation of various functional agents, enabling targeted and controlled drug release. In a study by Gao et al., PEGylated BP nanosheets were shown to significantly improve the release of DOX in acidic environments, which is particularly beneficial in the acidic microenvironment of tumours.

These findings underscore the potential of BP nanosheets as a versatile and efficient platform for drug delivery in cancer therapy. It is believed to be an effective way of cancer treatments while minimizing side effects [11].

3.3. Microenvironment Regulation

Black phosphorus (BP) nanomaterials have shown significant promise in enhancing microfluidic systems, particularly in tissue engineering applications. A recent study developed a microfluidic 3D printing strategy to create BP-incorporated poly(N-isopropylacrylamide) (PNIPAM) hydrogel scaffolds designed to improve bone regeneration. The inclusion of BP nanosheets within these scaffolds endows them with near-infrared (NIR) responsive properties, allowing for controlled, reversible contraction and expansion of the scaffold channels under NIR irradiation. This dynamic behaviour facilitates the infiltration of cells into the scaffold's channels, promoting vascularisation and subsequent tissue regeneration.

Moreover, the BP nanosheets embedded in the scaffold demonstrate intrinsic bio-mineralisation properties, which accelerate bone regeneration. When exposed to NIR radiation, the BP-PNIPAM scaffolds enhance cell proliferation and osteogenic differentiation, leading to improved outcomes in bone tissue engineering. In vitro experiments showed that the BP-incorporated scaffolds significantly promoted the proliferation and differentiation of rBMSCs (rat bone marrow stromal cells), as well as increased calcium deposition, indicating enhanced bone formation capabilities. The in vivo studies further confirmed that the NIR-responsive BP scaffolds effectively accelerated bone defect healing, highlighting their potential as a robust platform for regenerative medicine.

This research underscores the critical role of BP nanomaterials in advancing microfluidic 3D printing technologies for tissue engineering, particularly by enabling the creation of smart scaffolds that respond dynamically to external stimuli, thereby enhancing the regeneration of complex tissues such as bone [12, 13].

3.4. Combined Treatment

Black phosphorus quantum dots (BPQDs) have demonstrated exceptional potential in combined chemo-photothermal therapies, offering a multifunctional approach to cancer treatment. In a recent study, BPQDs were functionalized with folic acid (FA) to enhance tumour-targeting capabilities, while doxorubicin (DOX) was loaded as the chemotherapeutic agent. This FA-functionalized BPQDs (BPQDs-PEG-FA/DOX) system showed remarkable efficacy in both drug delivery and photothermal therapy (PTT), thanks to its pH-responsive and photo-triggered drug release properties. The BPQDs exhibited high photothermal conversion efficiency, and rapidly increasing temperatures at tumor sites under near-infrared (NIR) laser irradiation, which enhanced DOX release and improved cellular uptake. This combined chemo-photothermal approach demonstrated synergistic effects, significantly suppressing tumour growth compared to standalone therapies.

In vitro and in vivo studies confirmed the efficacy of the BPQDs-PEG-FA/DOX system. In HeLa cells, the system showed superior cytotoxicity, particularly under NIR irradiation, leading to 90% cell death via a synergistic chemo-photothermal mechanism. Tumour-bearing mice treated with BPQDs-PEG-FA/DOX and NIR irradiation exhibited the highest tumour growth inhibition, showcasing the enhanced therapeutic effects of combined treatment. Additionally, the BPQDs demonstrated excellent biocompatibility and low toxicity, making them a promising candidate for clinical applications in cancer therapy. The targeted delivery, high photothermal efficiency, and synergistic effects of BPQDs offer a novel platform for enhancing the efficacy and safety of cancer treatments [14].

4. Conclusion

In conclusion, black phosphorus (BP) nanosheets offer a versatile and powerful platform for targeted therapies. As highlighted in this review, cancer remains a formidable challenge, necessitating the development of therapies that can precisely target tumour cells while theoretically preventing healthy tissue. Despite the progress made in cancer-targeted therapies, many current approaches suffer from limitations such as drug resistance, off-target effects, and systemic toxicity. BP nanosheets, with their unique physicochemical properties, address many of these challenges by serving as multifunctional drug carriers capable of enhancing the efficacy of cancer treatment through PTT, PDT, and targeted drug delivery.

The review has also covered the various methods for preparing BP nanosheets, each contributing to the optimization of their properties for clinical applications. These nanosheets have demonstrated superior capabilities in cancer treatment, including the high ability to modulate the tumour microenvironment. Moreover, BP nanosheets can be integrated into microfluidic systems and combined therapies, further expanding their potential in precision oncology. Overall, the multifunctional nature of BP nanosheets, their ability to integrate multiple therapeutic modalities, and their promise to overcome the limitations of current cancer treatments position them as a transformative tool in the ongoing fight against cancer. Future research and clinical translation of BP nanosheets could lead to more effective, targeted, and less toxic cancer therapies, significantly improving patient outcomes.

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