



(REVIEW ARTICLE)



Black phosphorus nanosheet-based new drug delivery system for the anticancer agents: A review

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Abstract

Cancer has been one among the main threats to the lives of citizenry for hundreds of years. Traditional drug therapy has certain defects such as poor targeting, easy degradation, high side effects, etc. Therefore, to enhance the treatment efficiency of anticancer agents, there is need of developing new drug delivery systems. Black phosphorus is a member of the 2D family, and it possess the potential to construct drug delivery system by virtue of its photothermal therapy, photodynamic therapy, and biodegradable properties. Due to their special structure BP are considered to be the best platform for drug delivery. They have shown large potential as near-infrared photothermal therapy agents and drug delivery systems for cancer therapy. The present review covered advances in BP- based drug delivery system along with its advantages and applications in cancer therapy.

Keywords: Black phosphorus; Photothermal therapy; Photodynamic therapy; Nanomaterials.

1. Introduction

Cancer is one of the world's deadliest diseases. Up till now, huge amounts of, financial and human resources are invested for tumor diagnosis. Various medical imaging technologies, like medical resonance imaging (MRI), ultrasound, and computerized tomography are successfully applied in clinical practice, for various discoveries, and diagnosis of tumors [1-5]. However, due to the variability and complexity of tumor cells, treatment especially of malignant tumors, still faces multiple significant challenges. Current clinical therapies which combat cancer primarily involve surgery, chemotherapy, and radiotherapy (RT). But surgery has the disadvantage of incomplete clearance of tumor cells, and therefore the low efficiency of chemotherapy and side effects of radiotherapy limit their applications.

Recent tumor treatments include photo thermal therapy (PTT), photodynamic therapy (PDT), and gene therapy (GT), but these are still within the experimental stages [6]. Recently, 2D materials like graphene oxide (GO), black phosphorus (BP), molybdenum disulfide are being extensively studied to be used in cancer therapy [7-10]. BP especially is an emerging member within the 2D mono-elemental family, and in recent years, its high mobility, adjustable bandgap, and powerful optical absorption have attracted attention and led to studies in numerous fields, like optical sensing, photodetectors, photocatalysts cancer therapy etc [11-13].

It is biodegradable in nature and thus it is inappropriate to be used as biomaterial. Indeed, these are certain advantages of BP over other 2D materials in developing drug delivery system for cancer therapy [14-16]. Phosphorus may be a vital element for living organisms and constitutes $\approx 1\%$ of the human body's total weight. BP degrades into harmless phosphate in physiological environments, giving it high biocompatibility and low cytotoxicity compared with other 2D materials [17]. BP's degradability in physiological environments prevents it from accumulating *in vivo*, making it a

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highly biocompatible material. With its broad spectrum of absorption and excellent photothermal conversion efficiency, BP nanomaterials have tremendous potential as applications within the biomedical field [18].

BP is proven to be an efficient PTT agent due to its high near-infrared (NIR) photothermal conversion efficiency [19]. Within the same year, exfoliated BP was shown to be an efficient photosensitizer (PS) for the generation of singlet oxygen (SO), with a high quantum yield of about 0.91, making it attractive to be used in PDT [20]. Given BP's good biocompatibility and excellent PTT and PDT capabilities, BP nanomaterials have attracted enormous attention in biomedical applications, and the developments have multiplied in recent years [21–24]. Additionally, the massive area of BP and its fold structure end in large numbers of anchor points for guest therapeutic agents like anticancer drugs, pointing to its eligibility to be used in drug delivery systems. BP offers high drug loading capacity for drugs or other agents due to its high specific area [25].

BP nanosheets (BPNs) loaded with doxorubicin (DOX) were the primary BP-based DDS for synergistic PDT/PTT/chemotherapy to treat cancer, reported in 2017 [26]. Some nanoparticles (NPs) and upconversion nanoparticles (UCNP) have also been successfully constructed for BP-based DDSs [27–31]. Such rapid development of novel therapies should cause the enrichment of monomodal cancer therapies like PDT, PTT, and GT, or to improvements in multimodal therapies [32–37]. Multifunctional DDSs which will be used with surface-enhanced Raman scattering (SERS), MRI, or polyethyleneimine (PEI) imaging also represents the further progress in drug delivery targeting and tracking [38].

2. Construction of BP based DDS

BP holds significant promise to be used in DDSs due to its high specific surface-to-volume ratio, photosensitivity, broad light absorption, excellent biocompatibility, and high biodegradability. The main categories of BP platforms are classified in four types: bare BPNs, modified BPNs, BPQDs, and BPHs, etc (**Figure 1**). Using BP as an efficient carrier, many varieties of DDSs are developed by loading drugs that include common clinical anticancer drugs (such as, DOX, PTX, and BTZ), small interfering RNA (siRNA), inorganic components (e.g., Au, Fe₃O₄, Pt, and UCNP), and others. These BP-based DDSs fight cancer in different ways, with some showing a single anticancer effect, while others combine multiple features, such as imaging and biodetection [39].

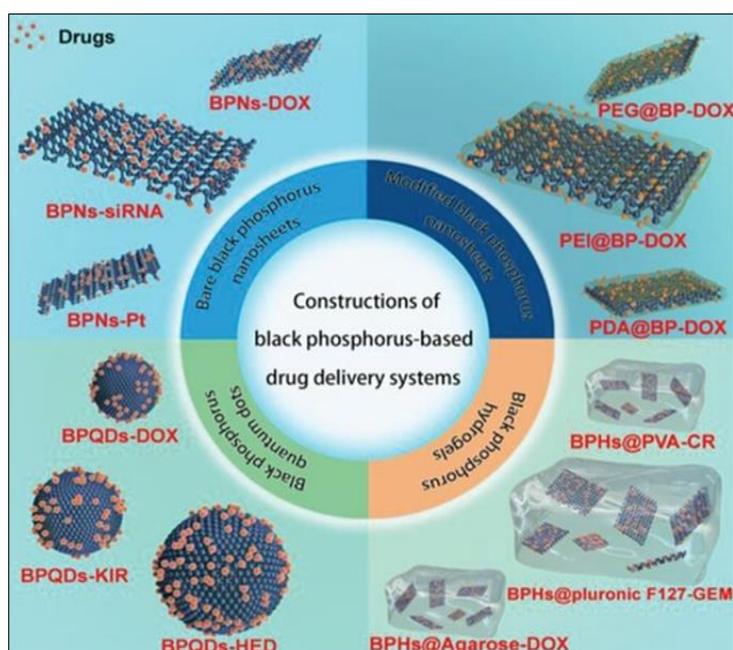


Figure 1 Construction of BP-Based DDS [1].

3. Preparation of black phosphorus nanosheets

The BPNs were prepared by using a simple liquid exfoliation technique (**Figure 2**). Particularly, 20mg of the BP powder was dispersed in 50mL of saturated caustic soda solution of N-methyl-2-pyrrolidone (NMP). Then the mixture solution was sonicated in ice bath for 6 hr. The resulting brown suspension was centrifuged at 4000 rpm for 8 min to

remove the residual unexfoliated particles and therefore the supernatant was collected for further use. Before use, the BPNSs were spun down at 10000 rpm for five min to get rid of NMP [40]. Characteristics of Black phosphorus nanosheets and modified Black phosphorus nanosheets is given in **Table 1**.

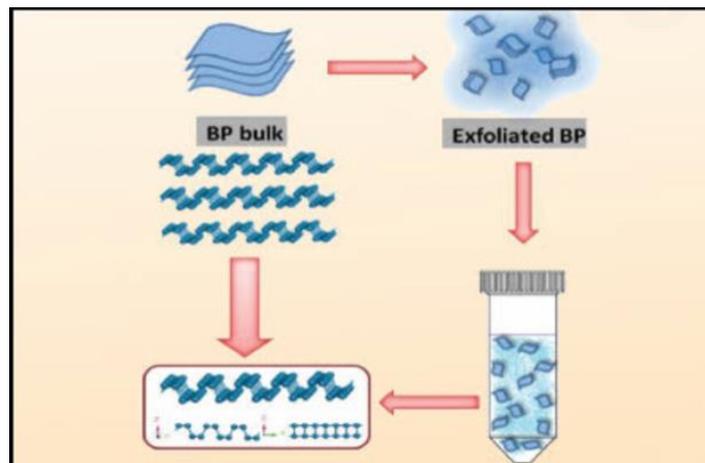


Figure 2 Construction of Black Phosphorus Nanosheets [40].

Table 1 Characteristics of Black Phosphorus Nanosheets [41-42].

SN	Platform	Coating	Bonding Ways	Payloads	Tumour Cells	Remarks
1	Black Phosphorus Nanosheet	None	Electrostatic interaction	Doxorubicin	4T1 tumor cells	It can be loaded with small, positively charged drugs via electrostatic interactions.
2	Modified Black Phosphorus Nanosheet	Polyethylene glycolamine	Electrostatic interaction	Upconversion nanoparticles	Hela cells & U14 cells	It can exhibit good biocompatibility and biodegradability.

3.1. Bare BPNSs platform

BPNSs have become the most popular 2D materials and are widely used as a substrate in drug delivery. Due to their negative charge and corrugated surface structure, bare BPNSs can easily be loaded with small, positively charged drugs via electrostatic interaction between the support and the drug with BPNSs as drug carrier, Traditional anticancer drugs achieve higher efficiency in chemotherapy, demonstrating the potential of BPNSs as a drug delivery substrate. As a result, DDSs supported BPNSs have gradually been extended to the sector of GT [43].

Additionally, to drugs with positive charges, ones that are neutral or negatively charged can also be loaded onto BPNSs after the drugs are electrically modified. This versatility makes BPNSs more attractive than other substrates for developing DDSs. Various of the methods that effectively immobilize neutral or negative drugs onto BPNSs, the polymer coating strategy is the best [44]. Chemical bonds like as covalent bonds, coordinate bonds, π -bonding, and then have also been adopted to construct BPNSs-based DDSs. As an example, Zhao et al. prepared NB@BPs employing a method that involved combining Nile blue (NB) dye with BPNSs via diazonium chemistry [45].

3.2. Modified BPNSs platform

Bare BPNSs seem promising for drug delivery, challenges remain such as

- Susceptibility to aggregation and settling in world use.
- Poor physiological stability and easy degradation within the presence of oxygen and water.
- Low drug loading efficiency via electrostatic interaction; and
- Lack of functional groups on their surfaces.

Among the various modifications addressing one or more of those problems, the most BP strategy has electrostatic interaction between BPNSs and modified components and therefore the second approach uses a reaction to conjugate BPNSs. To date, polyethylene glycol (PEG), PEI, Polydopamine (PDA), Poly (2-ethyl-2-oxazoline) (PEOz), and human albumin (HAS) are common BPNSs modification materials (**Figure 3**). PEG–NH₂ has excellent biocompatibility and has been widely utilized in the sector of biomedicine. BPNSs modified with PEG–NH₂ via electrostatic adsorption also exhibited good biocompatibility and physiological stability, with almost no aggregation or degradation, as observed through UV–vis absorption spectra and therefore the Tyndall effect [46-49].

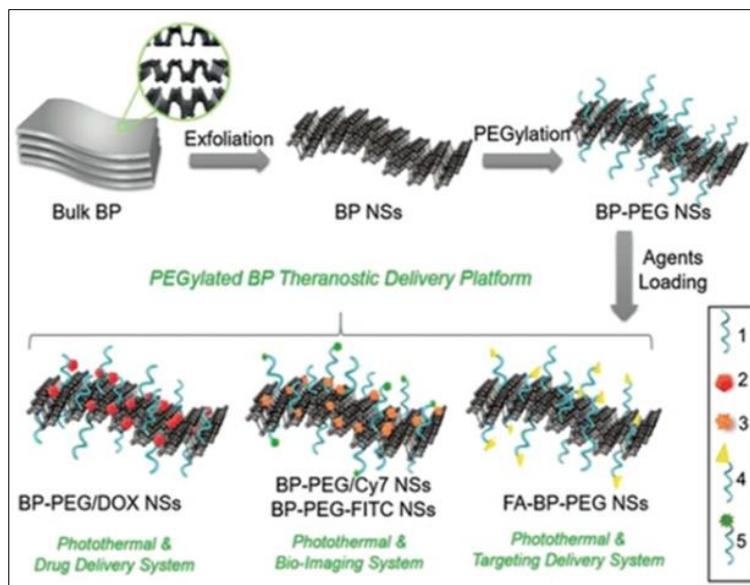


Figure 3 PEGylated BP the ranostic delivery platform [49].

PDA may be a well-known biomimetic polymer with high adhesive capacity that's easily synthesized by the self-polymerization of dopamine in an alkaline environment. In BP-based DDSs, PDA coating also confers enhanced stability and photothermal effects (**Figure 4**) [50].

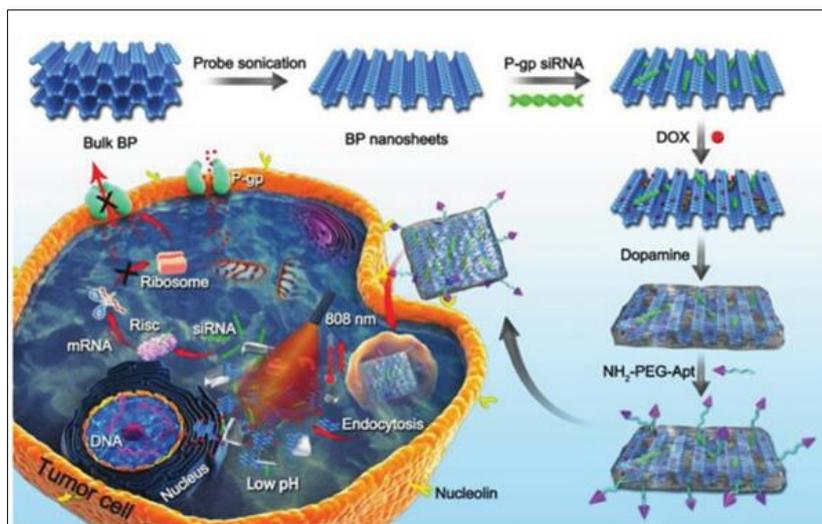


Figure 4 Fabrication nanostructures and combined chemo/gene/photothermal targeted therapy of tumor cells [50].

4. Black phosphorus-based drug delivery system as cancer therapy application

Due to advances in of the molecular, cellular, and physiological mechanisms involved within the initiation and progression of cancer, it remains one of the leading causes of mortality across all age groups. To date, tremendous effort

has been poured into developing therapeutic approaches to beat tumor invasion and metastasis. Current cancer therapies – chemotherapy, PTT, PDT, RT, immunotherapy. Potential of BPNSs based drug delivery system for therapeutic application in Cancer including the subsequent approaches.

4.1. Photothermal therapy

Among various anticancer treatments, NIR PTT mediated by BP-based DDSs has received increased attention due to its noninvasiveness, biocompatibility, and precision targeting of tumors via the utilization of external laser irradiation with adjustable intensity, to attenuate both damage to the encompassing healthy tissues and systemic cytotoxicity [51-57]. As water and blood cells minimally absorb NIR, it can penetrate more deeply into cancer cells than UV/visible light. Photothermal conversion agents harvest the energy from light and transform it into local heat to extend the temperature of the encompassing environment; this heat is often used for PTT to realize the thermal ablation of tumor cells and trigger necrosis (**Figure 5**) [58-65].

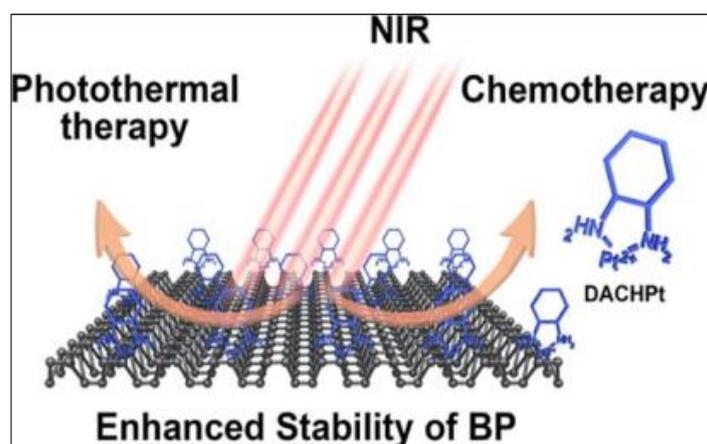


Figure 5 Enhanced stability of black phosphorus [59].

4.2. Photodynamic therapy

Photodynamic Therapy (PDT) has become a promising treatment modality and has been approved for clinical use, including treatment for cancers of the lung, esophagus, and skin. PDT offers significant effectiveness, specific spatiotemporal selectivity, minimal invasiveness, and limited side effects, making it an alternate option for patients who aren't candidates for the radical operations [66-68]. PDT has three major components: light, photosensitizers (PS), and oxygen molecules. A selected light of appropriate wavelength provides energy for activation. A PS administered beforehand and brought up by tumor cells harvests this light and engages in photodynamic reactions with oxygen-containing substrates (e.g., molecular oxygen, water) to supply singlet oxygen (SO) or reactive oxygen species (ROS). This process induces selective damage to tumors by destroying their tissues and therefore the vasculature surrounding them, killing cancer cells [69-77].

Conventional organic PS currently in use exhibit poor water solubility, low stability, and low quantum yield, and other ambiguous security issues [78-80]. consequently, certain semiconductors and photo catalysts are commonly utilized as new PS agents and used in Nano medicine due to its less invasive nature [81-82]. BP may be a metal free semiconductor with a high 102 quantum yield and thus might be a promising therapeutic agent to be used use in PDT [83]. However, its excitation wavelength is within the visible light region, which has limited penetration depth, so tissue interference impedes BP's biomedical application during this capacity. Thus, it's often necessary to load it with molecules which will be activated within the NIR [84].

The antitumor performance *in vivo* was even stronger, clearly demonstrating the potential applicability of UCNPs–BPNSs as a PDT antitumor agent with a one 808 nm laser. BPNSs based self-supporting oxygen system that catalyzes excess intracellular H_2O_2 to O_2 by well-designed heme oxidation, which may offer enough oxygen for PDT [85]. Few-layer black phosphorus (FLBP) nanosheets show potential application in biomedicine like as PDT, and are therefore commonly utilized in anticancer therapy and nanomedicine due to being relatively less invasive. As an emerging 2D layered semiconductor, FLBP nanosheets have recently been utilized as a completely unique PS in PDT [86].

4.3. PTT combined with Chemotherapy

A multifunctional nanoplatfrom supported BPNS was developed for chemo-photothermally synergistic cancer therapy. The BPNSs were successfully prepared by a liquid exfoliation technique. Doxorubicin (DOX), as a model drug, was loaded into the cavity of poly amidoamine (PAMAM) dendrimers using thin film hydration method. Then, PAMAM@DOX was coated on the surface of BPNS using an electrostatic adsorption method that combined bath sonication with magnetic stirring. Hyaluronic acid (HA) was also modified onto the BPNS-PAMAM@DOX through electrostatic adsorption. PAMAM and HA layer could effectively isolate BPNSs from water and air to reinforce physiological stability.

BPNSs and BPNS-PAMAM@DOX-HA were characterized by particle size, zeta potential, morphology, UV-vis- NIR absorption spectra, stability, photothermal performance and photothermal stability. This nanosystem exhibited an honest Ph and NIR dual-responsive drug release property. Additionally, the obtained BPNS - PAMAM@DOX-HA nanocomposites possessed excellent PTT efficiency both *in vitro* and *in vivo*. The *in vitro* cell experiments suggested that the targeted BP NS-PAMAM@DOX-HA presented greater cytotoxicity and better cellular uptake efficiency [86]. Although chemotherapy has achieved a particular degree of success within the treatment of cancer, monotherapy has deficits that limits future development and application, including poor drug specificity and targeting, low cellular uptake efficiency, and drug resistance caused by future use.

PTT could also be a light physical hyperthermia strategy with some effectiveness but also ineluctable deficiencies. When these two therapies are combined, though, they will address each other's drawbacks. For instance, PTT is during a position completely to eradicate cancer cells, whereas chemotherapy could also be a systemic treatment paradigm for killing both Bimodal synergistic cancer therapy that mixes PTT with chemotherapy is now well documented as an efficient strategy [87].

4.4. PTT combined with PDT

Combined photothermal and photodynamic therapy is implemented for excellent performance in inhibiting tumor growth. An imaging guided mitochondria targeting photothermal/photodynamic nanosystem has been developed for functionalized BPNSs. In the nano system, BPNSs are coated with polydopamine (PDA) then covalently linked with both Chlorin e6 (Ce6) and triphenylphosphonium (TPP) through carbodiimide reaction between the amino and therefore the carboxyl group, forming BP@PDA-Ce6&TPP NSs. Due to the strong absorbance of BP@PDA within the NIR region and therefore the highly efficient ROS generation of Ce6, the as-prepared nanosystem with mitochondria-targeting capacity (TPP moiety) shows remarkably enhanced efficiency in neoplastic cell killing [88].

5. Analysis of BPN-based drug delivery systems

Qualitative and quantitative analysis of various drug delivery systems including herbals drug delivery systems is last and essential part of analysis that ensures the quality and safety of the products. The systems includes tablets, capsules, liposomes, nansuspensions, etc [89-132]. BPN-based drug delivery systems containing drugs are also analyzed by routine quality control techniques. The quality control techniques includes high performance thin layer chromatography, high performance liquid chromatography, gas chromatography, Uv-spectrophotometry, etc [133-157].

6. Future prospective

The fascinating charm of the system with enhanced performance has gained the attention of the researchers throughout the world to focus their eyes on the development of BP-based formulations. Notably, it is likely to be found to exhibit more incredible biological functions with the exploration of more BP-based systems.

7. Conclusion

Taking the advantages of black phosphorous nanosheet-based drug delivery systems over other delivery systems, this could be the best choice of option for the delivery of anticancer agents. This will help the drug to reach at the specific site and shows target oriented effect. Further, it could be used in biomedical fields too.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares no conflict of interest.

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