Chapter

Functionalized Boron Nitride Applications in Biotechnology

Hélio Ribeiro, Paula von Cardoso Randow, Diego N. Vilela, Milene Adriane Luciano and Lidia Maria de Andrade

Abstract

Due to its interesting chemical, physical, and biological properties, boron nitride has received considerable attention by the scientific and technological communities. However, there is a strong dependency of its structural quality and compatibility in different host systems, regarding its potential applications. The use of these different nanostructures involves several challenges due to their low dispersibility in water and organic solvents; thus, its chemical modification is an important step that gives them specificity. Therefore, the ability to control their surface (physically or chemically) is essential for exploring and building blocks in the nanoengineering of supramolecular structures. In this chapter, we report different boron nitride functionalization processes, as well as their important uses as adjuvants in vaccines, brachytherapy, or drug delivery. Besides some important theoretical studies that have demonstrated the different functionalization possibilities for use in nanomedicine, are also reported.

Keywords: hexagonal boron nitride, boron nitride nanotubes, functionalization, nanomedicine, cancer, drugs

1. Introduction

Boron nitride (BN) is a covalent solid constituted by equal numbers of boron and nitrogen atoms, and its well-known crystalline forms are hexagonal boron nitride (h-BN), diamond-like cubic BN (c-BN), and wurtzite BN (w-BN) [1]. In particular, h-BN is the most stable BN phase under standard conditions that presents two-dimensional (2D) layered structure. The sp^2 hybridization is observed for boron atoms, and bond angle expected between the B-N-B or N-B-N is 120° that forms a perfect hexagonal ring bond network such as graphite, whereas the 2D layers are held together by weak van der Waals forces [1, 2]. Due to its similar structure with graphite, h-BN has common properties with it, like anisotropy along and perpendicular to a basal plane, high mechanical strength and thermal conductivity, and excellent lubrication [1]. Due to its reduced electron delocalization in the π BN bonds, it has a large bandgap making it an electrical insulating nanomaterial; however, h-BN is used as a lubricant (weakly held layers can slide over each other) and can have semiconductor properties. h-BN is also highly thermally and chemically stable and thus is also widely used for durable high-temperature crucibles, antioxidation lubricants, and protective coatings [1] and also has a wide range application in nanomedicine and biotechnology such as cancer therapies [3],

drug delivery [4, 5], biosensing [6–8], adjuvant in vaccines [9], and intracellular delivery [10, 11]. Hexagonal boron nitride also can be incorporated in ceramics, alloys, resins, plastics, and rubbers to give them thermal and chemical stability and mechanical resistance as well [12–15]. BN nanomaterials (**Figures 1** and **2**), such as carbon nanotubes (CNT) and graphene, also are awakened as new perspectives in prophylactic, diagnostic, and therapeutic areas. However, the use of them depends strongly of its chemical and physical modification surfaces that display an important role in their compatibility different host environments.

Its modification surfaces results in homogeneous dispersion medium with minimum restacking or agglomeration which guarantees biocompatibility in different biological or inorganic systems. The nanostructure dispersions in different medium of interest are fundamental to their potential applications [16]. The nanoengineering interfaces between host (organic or inorganic) systems and these nanostructures involve several challenges that need to be overcome. For instance, the restacking or agglomeration process of them does not allow transferring their expected properties to the host system, resulting in an inhomogeneous medium with minimum of compatibility. This undesirable phenomenon of surface can be overcome by physical or chemical modification methodologies, such as covalent or non-covalent functionalization. Thus, our choices will depend on the nanostructure and system desired. There are several types of covalent functionalization, and different functional groups can be chosen, according to their selectivity [16]. In this case, different organic or inorganic functional groups or nanoparticles can be anchored by strong covalent bonds. For instance, it can be introduced on surfaces of oxidized CNTs or graphene oxide (GO), functional groups such as alkoxy (–OR), amino ($–NH_2$), amine (–NHR), alkyl (–R) [17, 18], heteroatom doping, metallic nanoparticles, biomolecules, and biopolymers, among others. These modification

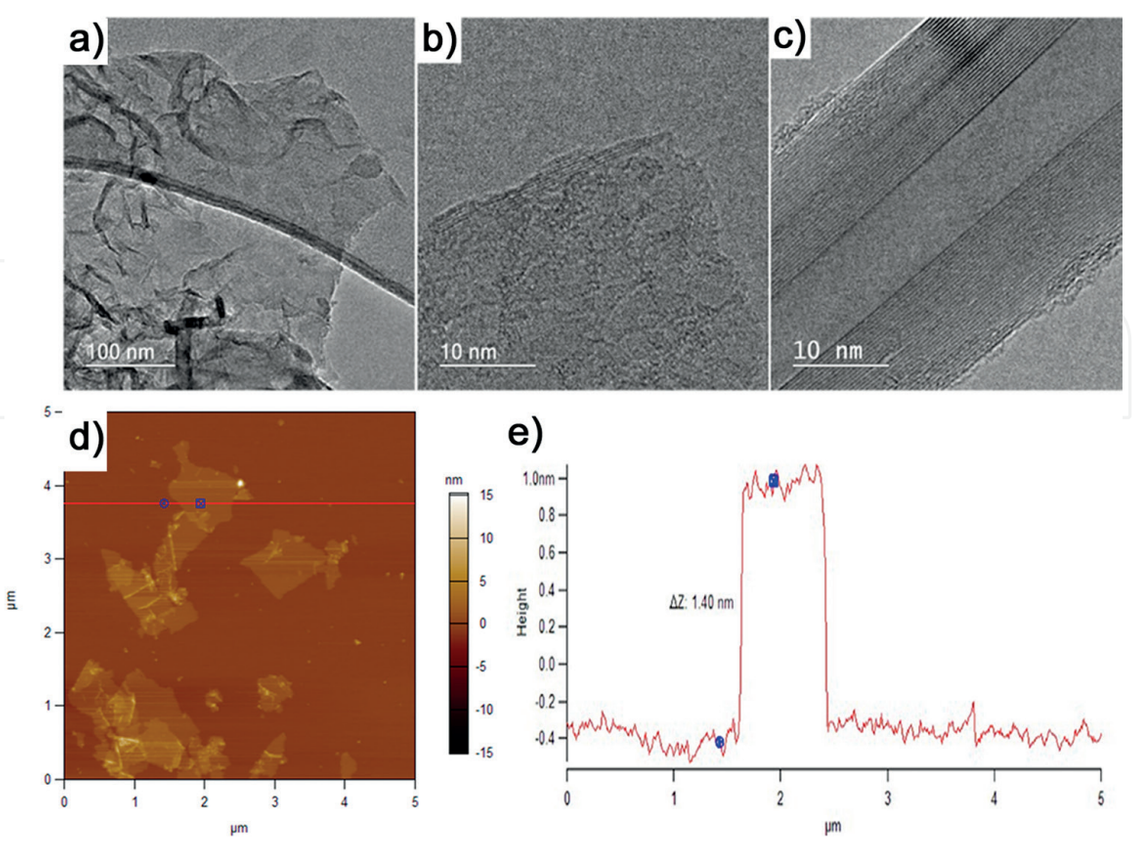

Figure 1.
TEM images of (a, b) h-BN in different magnitudes, (c) multilayered BNTs. (d, e) AFM image and profile of h-BN nanosheets. (Images courtesy of the UFMG Microscopy Center).

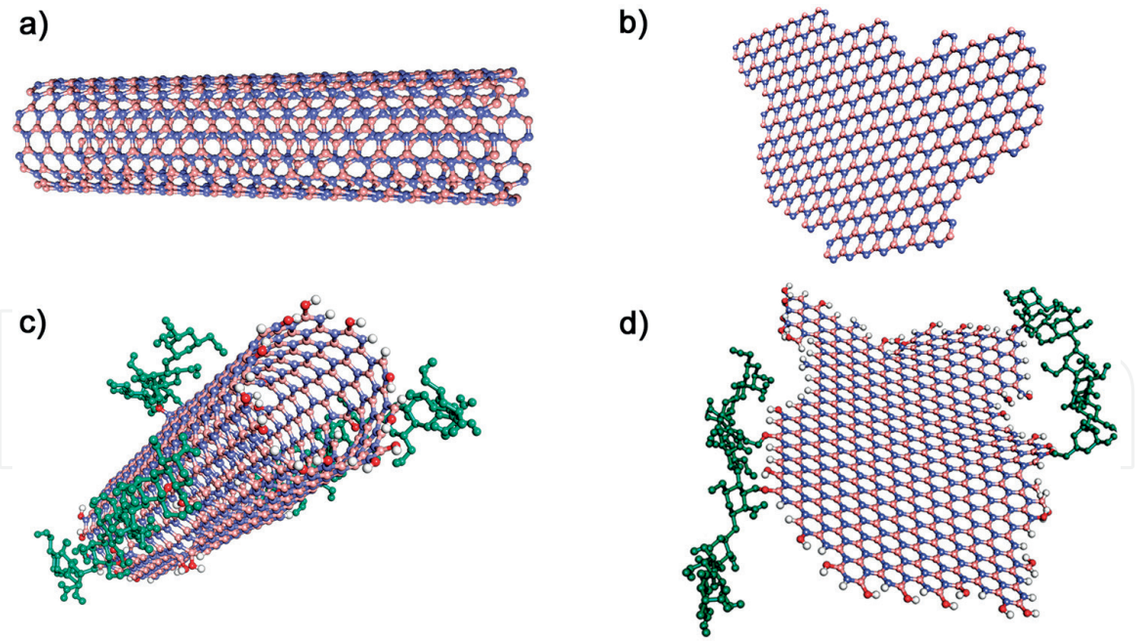

Figure 2.
BNNT and h-BN scheme not functionalized (a, b) and functionalized with different functional groups (c, d).

processes alter significantly their surface interactions, leading them to a large range of solubility in water, copolymers, or organic solvents [16].

On the other hand, non-covalent functionalization of nanoparticles is strongly dependent on their physical interaction with host system through intermolecular forces, such as van der Waals, hydrophilic, hydrophobic, hydrogen bonding, and π-π interactions, among others [19]. Using advantages of these physical interactions of molecules (conjugated, surfactants, etc.), they form homogenously dispersion into different medium with controlled physicochemical properties [20]. The study of different modification surface and their potential applications is very important. Several studies have presented different types of covalent and non-covalent functionalization methodologies in different nanoparticles with several demands, such as in cellulose films or fibers [21, 22], chitosan [23], polyethylenimine-grafted nanoribbon (for recognition of microRNA) [8], vinyl acetate copolymer [20], octadecylamine [1], glucose oxidase biosensing [24], poly (ethylene glycol) [25], DNA [26], and metallic nanoparticles, among others. The most important issue for success and performance of these compounds is the choice of the best tailored functionalization process (bio-nanoengineering) for each type of inorganic or biological system. The physical-chemical modification is an essential step for their relevant applications, leading to nanocomplex chemically stable, well dispersed, and biocompatible with the biological environment of interest. Thus, it is possible to produce smart nano-systems with advanced applications in biotechnology and biomedical areas, such as ecological packaging, bio-robots, and tumor markers for diagnosis and therapy. In this chapter, we propose a brief report about the main methods of functionalization of boron nitride and their advances and potential applications in biotechnology and nanomedicine.

2. Boron nitride functionalization and its implications in nanomedicine

Hexagonal boron nitride is thermal and chemically layered structure more stable than graphitic carbon structures. Due to its excellent chemical stability, a better biological performance is expected [27]. The key for application of h-BN in different

systems is its dispersion by the introduction of specific agents (such as surfactants) or by some covalent attachments [28]. The adequate modification process provides specific surfaces that allow its better solubility or dispersion in different solvents media playing an important role regarding selectivity, for instance, in biological systems [28]. These nanoparticles can be coated with biological molecules to facilitate their interaction with a living system, binding to a specific target, like tumor cells [29]. Regarding the tumor targeting strategies, the enhanced permeability and retention (EPR) effect of nanomaterials is a key mechanism for solid tumor targeting, and it is considered a gold standard for novel radioisotopes design [30]. There are two different types of possible modifications. One is to attach, covalently, a molecule or molecular structure, and the second approach is through physical adsorption onto BN or h-BN surface nanostructure. In addition to improve solubility and dispersion, an important issue that needs to be addressed is the toxicity of boron nitride materials and their behavior in a biological system. The primary objective of toxicology studies is to evaluate the safety of potential drug candidates, using animal models and validated procedures to access genetic toxicology, acute and sub-chronic toxicology, and absorption, distribution, metabolism, and excretion (ADME) studies [31]. The ability to design, format, and run assays that are specific, sensitive, and robust is crucial in biomedical research and plays an important role in launching a drug development project to a successful outcome. One of the most important prerequisites that a new drug must fulfill is nontoxicity. Cell culture can be used to access toxicity and cytocompatibility of BN, detecting several parameters such cytosolic enzyme release, cell growth, and cloning efficiency. Many factors can be defined directly related to chemical kinetics like absorption rates, membrane permeability, intracellular synthetic pathways, biotransformation, oxidative stress, or apoptosis/necrosis induction, distribution, and excretion [32, 33]. The modulation of immune cell response can be evaluated at gene and protein levels, mainly regarding the expression of cytokines and chemokines [33].

A study showed that important cytotoxic effects of pure BNNTs on several cell lines were observed with a concentration of 20 μg/mL. According to this viability test, the levels of toxicity and morphological alterations were cell-type dependent and related to the absence of a biomolecule, causing acute toxicity in cell cultures, due to the increased nanomaterial accumulation [34].

In an interesting study, Ciofani et al. [10] proposed a technique to obtain BNNT stable dispersions for biological applications, dissolving BNNT powder in polyethylenimine (PEI) water solutions via an ultrasonication process. PEI is a cationic polymer for nucleic acid delivery with a high transfection efficiency, enhanced cellular uptake, and endosomal escape. In this in vitro testing performed on human neuroblastoma cell line (SH-SY5Y), PEI-coated BNNTs showed good cell viability in the culture medium. Another study demonstrated that pectin-coated BNNTs (P-BNNTs) are nontoxic for macrophages up to 50 μg/mL after 24 h of incubation. According to this study, cytokine expression was not affected by the administration of the P-BNNT, and its uptake by macrophages did not cause any cell membrane impairment, adverse effects, or inflammation processes in the cell [33]. BN coated with glycol-chitosan (GC) assay was performed to evaluate the BNNT interactions with biological systems and determine their biosafety, using human vein endothelial cells (HUVECs). Various parameters were observed such as cell toxicity, proliferation, cytoskeleton integrity, cell activation, and DNA damage. At the highest concentration, only a small reduction in cell viability and the increase of a vascular adhesion molecule (a marker of cell activation) expression were identified. According to that study, these findings show that GC-BNNTs do not affect endothelial cell biology and can be further investigated for vascular targeting, imaging, and drug delivery [35].

Cytosine-phosphate-guanine (CpG) oligodeoxynucleotides (ODNs) are molecules that present promising therapeutic properties due to their capability of stimulating innate and adaptive immune responses, activating Toll-like receptor 9 (TRL-9), leading to induction of proinflammatory cytokines [36]. The CpG ODNs delivery system was developed by the functionalization of boron nitride nanospheres with PEI. The complex BNNs-PEI showed enhanced dispersity and stability in aqueous solution. Although PEI itself can be used as a drug delivery carrier, the complex BNNs-PEI exhibited much higher efficiency than the PEI alone, increased CpG ODNs' cellular uptake and induced higher expression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF- α) from peripheral blood mononuclear cells. No obvious cytotoxicity was observed with concentrations up to 100 μg/mL [35].

It was demonstrated that the complex PEI-BNNTs is internalized through an energy-dependent process via endocytosis pathway. PEI coating influences the behavior of BNNTs as it enhances the chemical reactivity of the nanotubes, allowing the interaction with a biological system [37]. In another cell viability assay [36], the MRC-5 culture, a diploid cell line derived from human fetal lung, normally used as a model for early cytotoxicity studies was treated for 48 h with samarium doped boron nitride nanotubes (Sm- BNNTs). This study demonstrated that even at the highest concentration, the cell viability was higher than 70%. This result reassures the findings of previous studies [29, 37, 38], confirming that, in concentrations below 200 μg/mL, BNNTs showed low cytotoxicity, and BNNTs do not appear to inhibit cell growth or induce apoptotic pathways in the cells. It should be noted that the high purity and quality of BNNTs are crucial for their nontoxicity [11, 36]. Many studies were conducted to determine possible toxicity to metabolism and liver morphology, as well as to renal function. A biodistribution study shows a significant elimination of BNNTs by renal excretion and accumulation in the liver, spleen, and intestines [36]. Ciofani et al. results indicate a similar pharmacokinetic behavior in an in vivo investigation of BNNTs in rabbits, with relatively high clearance of GC-BNNTs from the blood, with quick distribution and excretion [39]. The hematological parameters were monitored for up to 7 days. During the observation period, neither unusual behavior including sweating, excitement, trembling, head nodding, or temperature changes was observed. The study showed excellent hematological results without evidence of adverse effect, liver or kidney impairment [18]. A biocompatibility study with planarians indicated that gum Arabic-coated BNNTs do not induce oxidative DNA damage and apoptosis and did not show adverse effects on animal stem cell biology or on tissue regeneration [40].

As the cytotoxicity and biocompatibility of nanomaterials are being elucidated, new approaches overcome this first phase of research, leading to new discoveries and opening doors to novel alternatives. The antimicrobial activity of nanoparticles was investigated on different microorganisms in a study with h-BN. It was demonstrated that the h-BN has a bacteriostatic effect and shows a high antibiofilm activity on preformed biofilm [38]. PEI-BNNTs and other surfactant-coated BNNTs were also examined to elucidate their antibacterial activity. The optical density of bacterial growth curves and the transmission electron microscopy morphology images revealed that PEI-BNNTs exhibit strong microbial activity against *Escherichia coli* and *Staphylococcus aureus* [41]. Because of its low toxicity, high mechanical strength, and chemical stability, BNNTs also are considered to be a promising bioactive material for bone tissue engineering, improving polymers, composites, and scaffold properties [42]. In a study, akermanite (AKM), a bioactive material, was reinforced with boron nitride nanosheets (BNNSs) to ameliorate its mechanical features [43]. Significantly enhancement in compressive strength, fracture toughness, and an overall favorable cytocompatibility characteristics were found. Analysis of osteoblast gene expression and alkaline phosphatase activity measurement suggest that

nanomaterials have a great potential in the orthopedic implant field [28]. Chitosan-based scaffolds are thoroughly studied owing to their biocompatibility and antimicrobial activity. Hydroxylated BNNTs (BNNT-OH) were included into a chitosan scaffold and tested for their mechanical strength. The results of this study indicated that the inclusion of BNNT-OH increased mechanical strength and induced cell proliferation and adhesion decreased the scaffold degradation rate when compared to chitosan-only scaffold and did not cause toxicity to human dermal fibroblast cells [42]. Despite of some different experimental approaches and nanomaterial complexity, most of the studies show very good response of cells and organisms toward boron nitride nanocompounds. Researches about boron nitride applications in biotechnology are at full expansion, and nanomaterial biocompatibility and biosafety require further investigation.

2.1 Functionalized BN as a candidate for imaging and cancer therapy

Nowadays, some challenges regarding the earliest tumor diagnosis and treatment have been discussed considering that time represents a critical point between death and surviving. In this way, nanotechnology appears as promising tool due to its small size and remarkable physical-chemical characteristics as well, opening the as-called nanomedicine era. Traditional imaging resources to identify tumor sites have been applying ionizing radiation equipment. One of the most used is computed tomography followed by scintigraphy such as positron emission tomography coupled with computed tomography images (PET-CT). Likewise, non-ionizing radiation tools are applied such as magnetic resonance image (MRI). However, even though all these strategies possess high-image resolution, they are not completely able to detect smaller precocious tumors a primary indicative of micrometastasis.

There are several efforts to enhance the quality of images especially those taken from MRI. Notwithstanding, technical advances in nanotechnology are creating novel classes of MRI contrast-enhancing agents offering much higher relaxivities than most current clinical contrast agents, which translates into greater MRI contrast enhancement. These nanoscale agents also have the potential to revolutionize in vivo applications of contrast-enhanced MRI since they offer the multiple advantages of low toxicities, extremely high relaxivities, and cell internalization capabilities [44]. One of these nanomaterials presenting good possibilities to enhance MRI contrast is boron nitride nanotubes (BNNTs) containing Fe paramagnetic impurities. One drawback of pristine BNNT is its high hydrophobicity, and to overcome the low solubility of pristine BNNTs in aqueous solution, they can be wrapped with poly-L-lysine creating a PLL-BNNT. This soluble BNNT containing Fe has demonstrated values of transverse relaxivities comparable to commercial superparamagnetic iron oxide nanoparticles suggesting Fe-BNNT as a potential magnetic-enhanced contrast agent for MRI images at a field of 3 T [45]. Much has been investigated to improve the beneficial effects of radiotherapy especially in that case where radioresistant behavior is observed [46]. Radiotherapy is one of the most largely and effective tools to treat cancer using different approaches among then ^{10}B through the boron neutron capture therapy (BNCT). The fundamental concept of boron neutron capture therapy is the production of high-linear energy transfer (LET) particles when one "tags" or "labels" a tumor cell with a compound having a large cross section capable of capturing a neutron. After neutron capture it goes into excited state releasing local energy driving heavy ion products over short distances comparable to the dimensions of cells ~20 μm [47]. The BNCT reaction is presented in **Figure 3**.

BNNTs have been thought as a possible candidate to BNCT due to their considerable high B density. Preliminary in vitro studies have suggested

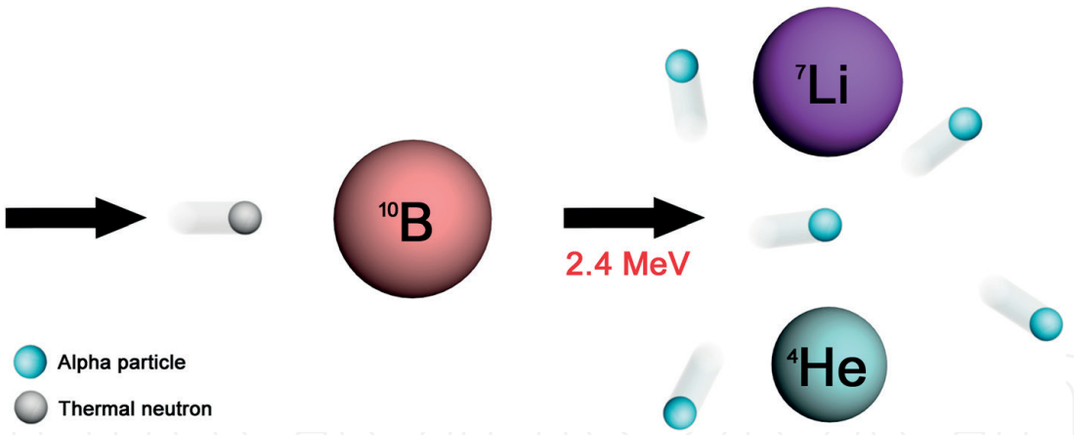

Figure 3.
BNCT reaction scheme. ^{10}B bombarded by thermal neutrons resulting in a nuclear reaction where ^{7}Li nuclei and α particles are released offering a lethal effect localized within a tumor cell.

folate-functionalized BNNTs (FA-BNNT) as a potential boron delivery agent to malignant glioblastoma cells whose results have confirmed a strong and selective uptake of these nanotube vectors by human glioblastoma multiforme T98G cells and for cervix tumor cell line HeLa, but not by normal human fibroblasts [48, 49]. PEGylated BNNT was evaluated as a BNCT strategy in B16 melanoma cell line compared with the conventional B carrier sodium borocaptate (BSH). Although PEGylated BNNT have shown three times higher cellular uptake than BSH, the concentration of ^{10}B delivered wasn't enough to perform BNCT as well as gold nanoparticles functionalized with carboranes as a ^{10}B donator. Even though these nanoparticles have demonstrated high accumulation of B atoms inside cells, they have failure in therapeutic window for BNCT, then requiring improvements in their design as a ^{10}B source [50, 51].

Other applications of BNs in the field of cancer treatment due to their physical properties have been proposed. One of them presents a new boron-containing chlorin derivative as an agent for photodynamic therapy (PDT) and BNCT. Using in vivo xenographic tumor model, the results have shown significant tumor growth inhibition suggesting this nanocompound as a promising agent for PDT and for BNCT as well [52]. Radioisotopes can be used as image resource in nuclear medicine and in some cases as a therapy agent too. BNNT doped with samarium 152, a radioactive isotope from a rare earth metal of the lanthanide group, has shown low toxicity in MRC-5 fibroblasts suggesting this nanomaterial as a potential nanosized β-emission source for nuclear medicine therapy especially for bone metastasis treatment [30].

Another widely used pathway to cancer treatment is chemotherapy. Despite efficient outcomes of chemotherapeutical agents, side effects are usual, and, in some cases, *enhanced permeability and retention (EPR) effect is hampered*. *Doxorubicin (DOX) and* paclitaxel *are a broad-spectrum antitumor drugs widely used for the treatment of several kinds of cancers, including prostate, breast and ovarian*. *As an attempt to improve chemotherapy effects*, different types of nanocarriers are under investigation especially as selectively drug deliver, commonly using liposomes and carbon nanotubes (CNTs). The utility of BNNTs@NaGdF4:Eu composites as a targeted cancer therapeutic for chemotherapy drug delivery, used to load doxorubicin in the absence and presence of a magnetic field, has been demonstrated. By using human prostate cancer LNCaP cell line, the BNNTs@NaGdF4:Eu composite shows a loading efficiency of doxorubicin of about 30% when a magnetic field is applied [53]. Besides, the administration of hollow BN spheres with paclitaxel leads to synergetic effects in the suppression of tumor growth of human prostate cancer as in vitro as in vivo mainly due to apoptosis death [54].

Despite BNNTs possess extraordinary physical-chemical properties highlighting the potential applications of these nanomaterials in nanomedicine, they have been poorly exploited [55, 56]. The safety and cytobiocompatibility of boron nitride compounds have been reported in vitro using glioblastoma multiforme T98G cells [48], human MRC-5 fibroblast cells [48], human cervix tumor cell line HeLa [49], melanoma B16 cells [50], rat-derived osteosarcoma cell line UMR-106 [51], human neuroblastoma cells SH-SY5Y [37, 57], and human embryonic kidney cell line HEK 293 [11]. However, based on the fact that nanotubes present some similarities with asbestos lung cancer, human lung cancer cells (A549), alveolar macrophages (RAW264.7), fibroblast cells (3T3-L1), and human embryonic kidney cells (HEK293) were also exposed to BNNTs to verify cytotoxicity regarding BN compounds. In fact, the results indicate that BNNTs are cytotoxic in vitro even at low concentration in a time and dose-dependent manner promoting morphological alterations and decreased cellular viability [34].

Nanomaterials applied in medicine are a controversial issue requiring further investigations, especially due to a potential toxicity and environmental consequences regarding B compound disposal, and their biological responses need to be examined like extensively related CNT cytotoxicity reports. Recent progress in the field of nanomedicine research has offered good alternatives on this matter, especially those targeting tumor cells with metal nanoparticles [58]. For a while, the insipient results highlight a promising future for nanomedicine leading to new therapeutic approaches. For instance, graphene oxide may be an effective nontoxic therapeutic strategy for the eradication of cancer stem cells, via differentiation-based nanotherapy [59]. As described above, boron nitride represents one of the most promising nanomaterials in nanomedicine since some drawbacks can be overcome such as improvement of solubility in aqueous solution, high ^{10}B concentrations releasing, allowing their use for BNCT and reducing of cytotoxicity. Moreover, further preclinical investigations will provide the safety and efficacy of BN for image and therapy leading to a more deeply knowledge about biodistribution, clearance, and side effects regarding dose, time, and administration pathways.

3. Computational simulation perspectives of boron nitride nanotubes using as drug carriers for cancer treatment

The advances in nanotechnology have stimulated a large production and storage of information coming from different sources, such as high-processing DNA sequencers, nuclear magnetic resonance, X-ray crystallography, electron microscopy images, and spectroscopic data, among others [60]. This large number of information about different systems needs to be quickly processed and understood in terms of structure, morphology function, and properties being solved by computational simulation (CS) with efficiency and high degree of accuracy [60]. CS has been widely used in studies of aggregation, folding, functionality, and nanoengineering platforms for several proteins, tertiary structures of RNA, and nanostructures surfaces and arises in the development of new techniques and diagnosis and therapy [61]. Thermodynamic properties such as enthalpy, entropy, and free energy of protein conformations also have been used to predict different protein and DNA structures [62], with atomic details applied in complex organisms [63]. By molecular dynamic simulation (MDS), several researchers have investigated the behavior of different nanoparticles, clusters, biomolecules, polymers, ceramics, metal alloys, composites, and fuel systems in relative short-time operation, compared to other non-computational methods. Numerical simulations based on preestablished mathematical models that involve quantum mechanics, molecular mechanics, Monte-Carlo, or a hybrid thereof have been used as well [64].

Quantum mechanics provides the accurate description of the energy about system electronic distribution. However, this description may have some restrictions, such as the size of the system (< 500 atoms) and requires high computational power, due to the large correlation in many electron interactions [65]. This limitation can be overcome by the density functional theory (DFT), to solve many body systems, for example, ionization energy calculations and band theory analysis. In this approach is considered an ab initio method because it does not require initial parameterizations, making this technique faster when used electronic density approximations are used, such as Car-Parrinello and Born-Oppenheimer methods [66]. In the case of molecular mechanics, the potential energy is described in geometric terms by force fields inherent to the molecules, in their internal and external interactions [64]. This approach acts empirically on the integration of potential energies resulted from the intramolecular interactions and intermolecular where the energy of each components or entity must be explicitly parameterized according to the specific equilibrium between atoms and their geometry imposed by their structures [65]. The Monte-Carlo method provides spatial conformation based on the atoms' distribution probabilities predicted by the Boltzmann equilibrium in each random Cartesian coordinate. The selected conformation positions within a tridimensional space, regarding to its rotation, torsion, or twist which needs to be lower than its initial conformation in study [65]. About the computational methods used in nanotechnology, we can highlight several studies in different nanostructures, such as h-BN and BNNTs, explored in several technology areas such as DNA sequencing [66–70], water treatment [71–74], piezoelectric properties [75, 76], and drug delivery [77–79], among others. For instance, the cisplatin (CP) is a well-known agent chemotherapeutic that acts directly on DNA causing defects in the cell repair mechanism and leading to apoptosis. This drug is widely used in treatment of several types of cancer, such as lymphomas, sarcomas, and carcinomas, as well as in the treatment of other types of cancer that are affecting the head and neck, bladder, lung, ovaries, and testicles [80]. However, its cellular uptake sometime is accompanied by large side effects and development of resistance, causing allergic reactions, low immunity to infections, hemorrhages, kidney problems, and gastrointestinal disorders among other effects [80]. Similarly, the doxorubicin is a type of anthracycline that acts in the DNA structure preventing its replication, with important role in relation to other chemotherapeutics that present restrictions, such as cytotoxicity, accumulating irreversibly and compromising muscular tissues, mainly cardiac [81]. The expectation about the use of nanocarriers is related to the possibility whether they eliminate or reduce the harm effects in relation to conventional drugs [82]. From here, we will explore some interesting works about MDS applications considering the potential drug carrier as vector in cancer treatments.

For instance, Khatti and Hashemianzadeh focused their efforts on the diffusion process of water in loading of drugs inside the BNNT [83]. Their study was about single-walled zigzag BNNT (18,0) sample with length 40 Å and diameter 14 Å to represent the system. They use BNNT containing 18 hydroxyl groups (-OH) at the end and another one with saturated -OH groups at the same position. The model systems were solvated in an aqueous solution with a TIP3P in octagonal box over 12 Å. All systems were solvated with 7544 water molecules in total [83]. The simulations were performed with different combinations that also include the carboplatin (CPt) molecule. The MDS studies were carried out by the AMBER 12 package with SANDER module (at 300 K and 1 atm) using SHAKE algorithm, where each simulation included 5000 steps of solvent/solute running through 10 ns to the step of 2 fs [83]. The diffusion coefficient (D) results can be seen in **Table 1**.

The results showed that the electrostatic interaction -OH groups in BNNT cause different diffusion behaviors in water compared to BNNT nonfunctionalized.

System	D (cm^2 s^{-1} × 10^5)
BNNT/water	0.440
BNNT-OH/water	0.600
BNNT-CPt/water	0.560
BNNT-OH/CPt	1.890

Table 1.
Diffusion coefficient (D) prediction of different BNNT systems in different combinations studied by Khatti and Hashemianzadeh (2016) [83].

Therefore, the drug diffusivity into the nanotube can be related to the diffusive behavior of water molecules inside the tube. The increase of the diffusion rate of water molecules in BNNT-OH is observed according to the diffusion coefficient values. These results showed us that the penetration rate of the drug in BNNT-OH is larger than that nonfunctionalized BNNT, and the electrostatic interactions between carboplatin and hydroxyl groups on the tube edge enhance the permeation rate of the drugs into the nanotube cavity [83]. By MSD study, they observed that hydrogen bonds at the extremities of BNNT produce dipole-dipole interactions between hydrophilic CPt and -OH groups, which allow an efficient condition for the encapsulation of this drug. The hydroxyl groups also maintain the stability of the BNNT and prevent its aggregation into the solutions [83]. An encapsulation scheme of CPt molecules encapsulation into BNNT-OH can be visualized in **Figure 4**.

Nanotube structures are of great interest in nanomedicine as a vector in drug delivery; they can access the cell carrying large amounts of drugs due to their possibility endohedral functionalized surfaces [77]. From this juncture, several works have performed different theoretical methods of BNNT stability by drug encapsulation. For instance, the azomethine (AZ) prevents the carboplatin deactivation process, prematurely before the CPt achieves the cancer cell [77]. Studies have demonstrated that BNNT-OH acts as nanocarriers drugs for CPt complex. **Figure 5** shows a scheme of BNNT endohedrally functionalized with carboplatin, and the DNA linked covalently to the CPt complex.

Duverger et al. used DFT simulations to study the interactions between BNNT-OH in azomethine and an anticancer agent (Pt (IV) complex) linked with an amino-derivative chain. The geometry of the azomethine/Pt/amine system was optimized by different molecular configurations on the inner and outer surfaces of the BNNT. The authors also showed that the molecular chemisorption is possible only when the azomethine is present above two adjacent B and N atoms of a hexagon structure. The attachment of an azomethine and subsequent drug did not perturb the cycloaddition process. These theoretical results showed that the therapeutic Pt (IV) complex was not affected when it was attached onto BNNTs [84]. In another work, Khalifi et al. also demonstrated theoretical results about the use of BNNT particles as carrying drug insertion into to the lipid bilayer [85]. They studied a single-walled BNNT armchair (10,10) with diameter 13.94 Å and length 21.32 Å (also saturated with -OH groups) with its extremities encapsulated with carboplatin (CPt) in ionized solvated ambient to mimic a biological environment. The BNNT-CPt complex can move freely, and a bilipid membrane (BM) is formed by 656 molecules of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine. It was applying DFT method conjugated with classical molecular mechanics [85]. The rapid diffusion of the BNNT-CPt complex toward BM with increased BNNT-CPt hydrophilicity due to surface of BNNT-OH was observed. This diffusion process was energetically favorable to the system due to the contribution of different energy component combinations. According to these results, the possibility of BNNT-OH as a specific ligand for cancer cells allows the more precise encapsulated drug delivery in cell membranes [85].

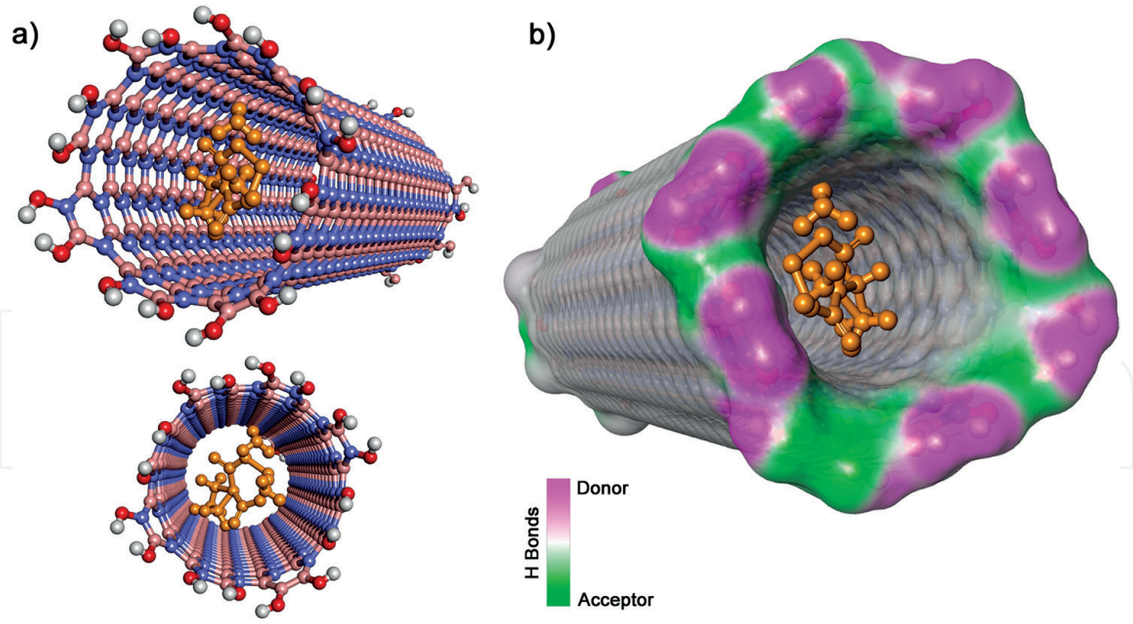

Figure 4.
CPt molecule encapsulated by BNNT-OH (a) and electrostatic force field of BNNT (b).

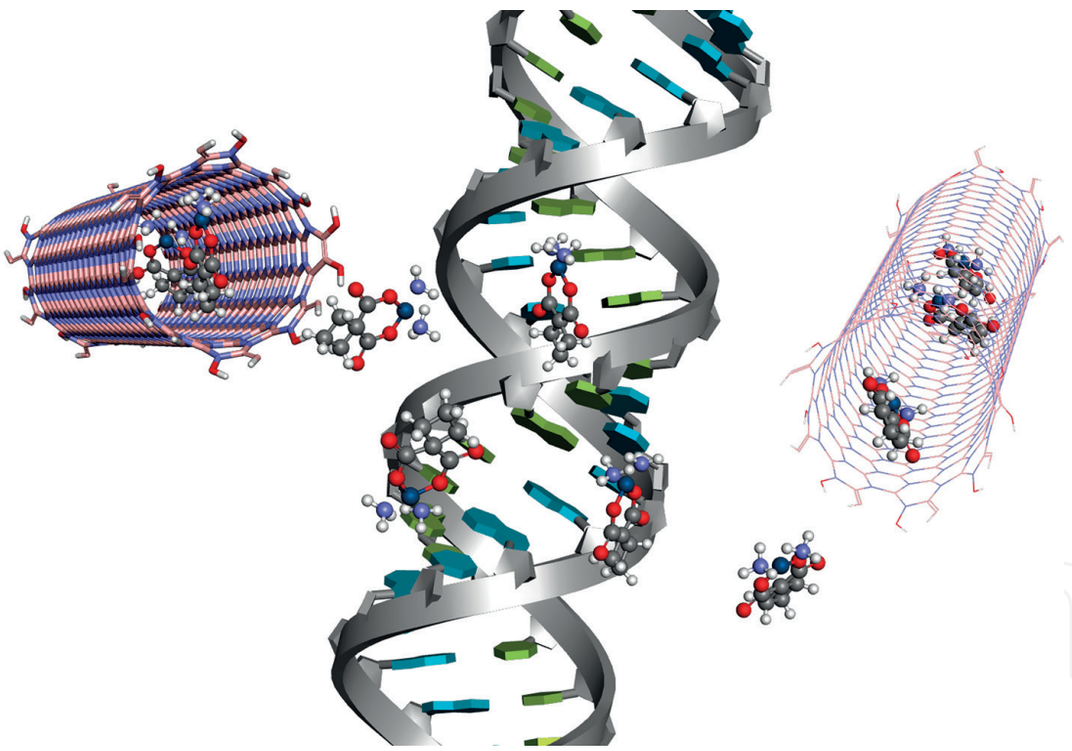

Figure 5.
Theoretical prediction of BNNT (sticks and wires) by delivering CPt molecules directly into DNA, one of the great promises of nanobiotechnology.

4. Conclusion

In this chapter we highlighted some experimental and theoretical works under different BN functionalization structures with potential biomedical applications. However, the most important aspect for success and an optimal performance about these compounds are the choice of the best tailored modification process for each biological system in study. Their physical-chemical modification is an essential step for relevant applications, leading to different systems chemically stable, dispersed,

and compatible with the environment of interest. Thus, it is also possible to produce nano-templates with advanced applications in biotechnology. Clearly, computational simulation is an important support tool in science that contributes to reduce time, costs, and risks. In the case of cancer, several types of drugs already exist; however, their delivery to their specific sites remains a big challenge and leads to undesirable consequences. Thus, the computational methods in conjunction with nanotechnology can optimize parameters and procedures maybe improving diagnosis and treatment, the chances of cure. Based on all what have had proposed and investigated, boron nitride arises as a promising nanomaterial for several application even in nanomedicine and nanobiology.

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Conflict of interest

The authors also declare that there is no conflict of interest in this work.

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