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BORON NANOPARTICLES. CHARACTERIZATION, PROPERTIES, UTILITY AND TOXICITY

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ABSTRACT
This review purpose is to describe boron nanoparticles, their effect on some organisms, including bacteria and fungi, but also the utility and toxicity. In the last decades, various boron containing compounds were developed. Boron nitride is a stable material with physico-chemical properties analogous to graphene with a hexagonal shape. Moreover, this type of products is used in a boron neutron therapy (NBCT), which is a process based on nuclear fission and capture of the boron atom ^{10}B. In addition, nanotoxicology of boron is discussed, due to the fact that has effects on aquatic environments.
KEY WORDS: *BNP, antimicrobial activity, boron, boron delivery agent*

Elemental boron is as a dark brown up to black amorphous powder or an extremely hard, usually silver gray to jet-black, lustrous, brittle, metal-like crystalline solid (α, β-rhombohedral and β-tetragonal and forms of crystalline boron). Boron nanoparticles are considered as a solid fuel for rockets and as a gun propellant due to their desirable combustion heat and fast energy release rate (Kuo *et al.*, 2003; Risha *et al.*, 2003; Kaste & Rice, 2004).

It is generally considered that boron nitride based nanomaterials are not naturally formed, but the cubic crystalline boron nitrides are found in some rare mineral sites of China and Tibet, which suggests their natural occurrence (Du Frane *et al.,* 2016).

Balmain first demonstrated the synthesis of boron nitrides in 1842 by using the reaction between molten H_3BO_3 and potassium cyanide. Since then, an enormous amount of studies has been carried out on the preparation of various boron nitrides nanostructures including nanosheets (Cai *et al*., 2016), nanotubes (Wu & Yin, 2011), nanofibers (Qiu *et al*., 2009), nanoparticles (Tang *et al*., 2008), nanoflowers (Lian *et al*., 2011), etc. Vandenbulcke and Vuillard (1976) studied the influence of substrate material, temperature and supersaturation, on morphology and phase composition of boron deposited on various flat substrates in a forced convective CVD system. They observed that physical aspect of the surface temperature and supersaturation controlled the morphologies as well as the phase composition of the boron deposits (Vandenbulcke & Vuillard, 1977). They also observed that amorphous boron was produced at high deposition rates and at low

temperatures (<1473K). Moreover, it has been demonstrated that field-scale heterogeneity of subsurface plays an important role during the transport and distribution of engineered nanomaterials in the subsurface. The study realized by Cullen *et al.* (2010) studied the impact of field-scale heterogeneities on the mobility of nC60 and multi-walled carbon nanotubes (MWCNT), and observed that the distribution of nanoparticles in the heterogeneous field is much less uniform in the heterogeneous field than in the homogeneous field site, with preferable pathways in more permeable zones. In a study with the purpose to evaluate the biocompatibility of hexagonal boron nitrides, some authors reported that the concentrations of 2D-Boron Nitride Nanomaterials up to 100μg/mL with lateral size dimensions of 30–60 nm did not significantly affect the viability of HEK-293T and Chinese hamster ovary (CHO) cell lines (Lu *et al*., 2016). Pure boron nanoparticles should constitute superior boron delivery agents with even higher boron density (ca. 107 boron atoms per 50 nm particle), but characteristics of hydrophilic boron nanoparticles with well-defined surface properties have not been reported. Recently, a practical surfactant-assisted ball milling method to produce air-stable boron nanoparticles on a large scale has been reported (van Devender *et al*. 2009 a, b).

Over the past 40 years, a variety of boron containing agents have been designed and synthesized, including boron amino acids (Kabalka & Yao, 2003), polyhedral boranes (Diaz *et al.*, 2002), boron porphyrins (Ceberg et al., 1995; Isaac & Khal, 2003), a boronated anti-epidermal growth factor receptor (Yang *et al.*, 2008), DNA binding agents (Woodhouse & Rendina, 2001; Tietze *et al.*, 2002) and monoclonal antibodies (Nakamura *et al.*, 2004).

The reduction of boron oxide with magnesium was firstly proposed by Moisson in 1892, resulting in about 90% pure boron. In general, reduction of boron compounds with metals is in two steps: first, reduction of B_2O_3 with Al or Mg for obtaining the rawboron; then purification of the raw boron by three-step leaching (HCl→NaOH→HF) (Guo, 1993). The raw boron can be purified to 95–97w/o (Ricceri & Matteazzi, 2003). This manner had being the widely used as a commercial method for producing elemental boron because of its high technical maturity, large-scale production, exothermic reaction, and short reaction time. Nevertheless, boron powders prepared through this complicated method present a large particle size (>1μm), low purity and wide size distribution, which limits their application in the high-tech fields. Therefore, a lot of investigations focused attentions on the improvement of reduction and purification process.

Today, most boron nitride nanomaterials are synthesized into laboratories and are composed of an equal number of B and N atoms that have specific conformations leading to different structure crystallinity (Pakdel *et al.*, 2012). As the most stable form of boron nitrides, the hexagonal boron nitrides have strong

covalent bonds between B-N atoms with a graphene-like structure. The 2D boron nitride layers are held together through van der Waals interactions (Weng *et al.*, 2016).

Some studies have investigated the antimicrobial properties and aquatic toxicity of engineeried nanomaterials, but also their potential effects on human health (Kamat *et al.* 2000; Saiers & Ryan, 2005; Lyon *et al.* 2006).

Furthermore, Horváth *et al.* (2011) examined the in vitro cytotoxicity of boron nitrides nanotubes to four different cell lines (murine embryonic fibroblast cells, murine alveolar macrophage cells, human lung adenocarcinoma epithelial cells, and human embryonic kidney. They found that the boron nitrides nanotubes induced modifications of the metabolic activity as well as of the cell morphology.

ANTIBACTERIAL PROPERTIES OF BORON. Boron nitride (BN) is a stable material with physico-chemical properties analogous to graphene, in its hexagonal shape (Wang et. al, 2017). Graphene is a well known nanomaterial with antibacterial features, due to a set of physico-chemical properties, such as thermal and electrical conductivity, strong mechanical strength and high surface area (Yang *et al.*, 2013). Considering the similar structure to graphene, materials derived from boron nitride should be taken into account when it comes to biomedical applications. To demonstrate the antibacterial activity, Pandit *et al.* (2019) proposed the development of a compound based on boron nitride and low density polypopylene (LDPE). The bacterial strains included for test were: *E. coli, Pseudomonas aeruginosa, Staphylococcus epidermidis* and *Staphylococcus aureus*, grown on suitable media for each type of bacteria. The bactericidal activity of BN-LDPE complexes was demonstrated as being directly proportional to the BN concentration. According to the examination with the scanning electron microscope, the bactericidal activity is manifested through deformation and bacterial lysis, when the microorganisms come in contact with BN. Although the structure and bactericidal activity are common to BN and graphene, at least in the biomedical field, BN is much more recommended, in terms of biocompatibility with human cells and tissues (Merlo *et al.*, 2018). With reference to the action on biofilms, BN exhibit the limiting of bacterial growth, without the appearance of cytotoxicity phenomena when BN is used in concentrations lower than 0.4 $mg \cdot mL^{1}$ (Kivanc *et al.*, 2018).

BORON NEUTRON CAPTURE THERAPY. Boron neutron capture therapy (BNCT) is a process based on nuclear capture and fission reactions of the boron atom 10B (Nedunchezhian *et al.*, 2016). The physical principle underlying this process is the capture of a epithermal neutron by the nucleus of 10B and the immediate initiation of fission reactions of 11B, whose decay leads to the formation of helium (4He, alpha particle), recoiling lithium nucleus (7Li), high linear energy transfer and low energy gamma ray. These particles have a short

range, comparable to the size of a cell, less than 10 μm (Singh *et al.*, 2019). As is well known, all ionizing radiation has a pronounced biological effect (Donya *et al.*, 2015). Thus, BNCT becomes a tool with a great potential for applicability in medicine. The mechanism by which cell death occurs after exposure to BNCT is unknown. However, it has been postulated that cells enter the state of apoptosis depending on various variables, such as: cell type, phase of the cell cycle in which irradiation takes place and the radiation dose (Galluzzi *et al.*, 2018). BNCT could be useful in treating difficult-to-approach cancers when considering already well-known procedures, such as chemotherapy and surgical procedures can not be used. Mainly, BNCT finds great applicability in the case of brain tumors, especially glioblastoma multiforme, characterized as one of the most aggressive tumors at this level, head and neck tumors and melanomas (Dymova *et al.*, 2020). BNCT consists of two stages, first the boron particles are introduced, most commonly intravenous, into the patient's body and selectively sent to tumor cells, where those accumulates, with the help of delivery agents. Subsequently, the tumor is irradiated with epithermal neutrons, a phase in which the nuclear decay reaction and apoptosis are occurring (Galluzi *et al.*, 2018). Concerning BNCT there are some fundamental issues that arise, such as: neutron source, radiation dosing and the delivery agents (Dymova *et al.*, 2020). As it is absolutely essential that only cancer cells to be destroyed after therapy, the biggest impact in this process lies on the delivery agents. Conjugated boron atoms with phenylalanine in the form of boronphenylalanine (BPA) or borocaptate sodium (BSH) are currently used as delivery agents. They are considered second-generation boron compounds and are not satisfying all the needs related to therapeutic practice. For this reason, the development of much more complex boron compounds that involve certain beneficial features for the whole process, especially bioavailability and accumulation at the tumor level, called third-generation boron compounds is necessary. This type of compounds are in generally boron particles conjugated with different structures, such as: liposomes (Luderer *et al.*, 2019), nanoparticles (Dukenbayev *et al.*, 2019), epidermal growth factors (Yang *et al.*, 2009) and so on. In this regard, Singh *et al.* (2019), propose the development of a delivery agent composed of several structural fractions, overall being an encapsulated liposome based on boron nanoparticles. To increase the bio availability of boron, a fraction of asolectin phospholipid was also conjugated. For better visibility under microscope, a fluorescent dye, Cy5, was also encapsulated. PEG was also added for stability and bioavailability ensuing the conjugation of folic acid to produce a folate-functionalized PEG. The tests and measurements required for toxicity assessments, determination of concentrations and bioavailability were done, and lastly it has been suggested that such a complex may be a potential delivery agent used in BNCT. BNCT efficacy was tested on various standardized cell lines. For

example, Petersen *et al.* (2008), studied the effect of this therapy on the B16-OVA cell line in the murine model. This study deeply emphasizes, by results, the dependence on the use of boron particles and neutron irradiation collectively. Regarding tumor growth, several test variants were applied, either only boron particles were considered, or only neutron irradiation, or both, at different time intervals. Consistent results in decreasing tumor size were observed only when irradiation was corroborated with the use of boron particles and only when the intervention was performed shortly after the injection of tumor cells. The B16 cell line was isolated from a spontaneously grown murine melanoma. It is a cell line frequently used for the study of solid tumors and for the study of metastases (Teicher, 2002).

Also in terms of cancer therapy, in addition to BNCT, boron can also be used as a transport agent for chemotherapeutic drugs. Many patients with tumors are requiring chemotherapy at some point, the big disadvantage of this therapy is the resistance that can be developed. In general, this phenomenon occurs due to overexpression of ATP-binding cassette transporters which causes the rejection of the chemotherapeutic drug and the outflow of the cell (Fletcher *et al.*, 2010). It has been shown that boron nanoparticles can function as drug carriers, taking into account, of course, the reduced cytotoxicity of these compounds (Sukhorukova *et al.*, 2015).

TOXICITY OF BORON. There has been a significant increase in the use of nanomaterials in recent decades, which leads to a natural concern, namely the effect that these nanoparticles have on organisms. These concerns have paved the way for a new scientific discipline called "nanotoxicology", which deals with the study of the physico-chemical properties of nanomaterials associated with the effect they have on organisms (Donaldson *et al.*, 2004). In general, nanoparticles exert cytotoxicity phenomena on given organisms, given their unique physico-chemical properties, especially relatively high specific surface area (Magrez *et al.*, 2006). Toxicity caused by boron nanoparticles is becoming a fairly common topic, because their applicability in medicine and their environmental implications overall.

Algae are often used in the study of the effects of chemicals on the environment, being considered standard models for the study of toxicity (Schade *et al.*, 2019). To study the potential impact that boron nanoparticles may have on the environment, Daglioglu *et al.* (2017), propose a comparative study, based on boron nanoparticles and boron microparticles, performed on a species of green algae, *Chodatodesmus mucronulatus*, considering the formation of reactive oxygen species, pigmentation and accumulation of particles in cells. In conclusion, the authors pointed out that both microparticles and nanoparticles exhibit cytotoxic phenomena of varying degrees on the studied organism, but with emphasis that

these toxicity effects are more pronounced in the case of nanoparticles. The occurrence of the cytotoxic manifestations of nanoparticles can be associated with a higher biological reactivity of these structures, mainly due to their larger surface area per mass (Oberdörster *et al.*, 2005). Toxicity is very often correlated with the accumulation of reactive oxygen species (Kiura *et al.*, 2005). Thus in the case of boron nanoparticles, the toxicity is also manifested by the formation of reactive oxygen species, an aspect highlighted in a study conducted by Wang *et al.* (2017), when the effects of boron nanoparticles on the nematode *Caenorhabditis elegans* were tested. The results displayed that when used in concentrations above 10 μg·mL-1, the activation of an oxidative-stress response, modulated by MAPK-signaling-related genes, is determined. MAPK (mitogen-activated protein kinases), is a family of enzymes that are generally activated in the event of stressful conditions (Cargnello & Roux, 2011). When comparing the cytotoxicity results of several nanoparticle types on *Daphnia magna* and *Vibrio fischeri*, boron nanoparticles posed the greatest threat regarding cytotoxicity, followed by aluminium nanoparticles and titanium dioxide nanoparticles (Strigul *et al.*, 2009). With reference to medical applications, boron cytotoxicity was tested on several standardized cell lines. In the case of the HUVECs line, a chitosan glycol coated compound containing boron nanoparticles, was tested and it was shown that there are no cytotoxicity effects on this cell line (Del Turco *et al.*, 2013). HUVECs (Human Umbilical Vein Endothelial Cells) is an immortalized cell line used mainly to study the pathology of angiogenesis (Park *et al.*, 2007). Regarding the SH-SY5Y cell line, which is a neuroblastoma cell line, originally derived from a metastatic bone tumor biopsy, used mainly in neurobiological studies (Kovalevich & Langford, 2013), a compound based on boron nanoparticles, conjugated with plyethyleneneiminie, was tested, and the results showed that nanoparticles are not interfering with cellular metabolism or cell viability (Cioffani *et al.*, 2008). When tested on the 3T3 cell line, a murine fibroblast cell line, immortalized spontaneously (Leibiger *et al.*, 2013), the results highlighted the lack of cytotoxicity exerted by boron nanoparticles (Cioffani *et al.*, 2013).

CONCLUSIONS

This review main scope was to describe boron nanoparticles but also their effect and utilities in various sciences. Boron has antibacterial characteristics, tests being done on *E. coli, Staphylococcus aureus, S. epidermidis, and Pseudomonas aeruginosa*. Moreover, this element is used in a boron neutron therapy (NBCT), which is a process based on nuclear capture and fission reactions of the boron atom ^{10}B. In addition, nanotoxicology of boron was discussed.

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