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Boron-containing bioactive glasses in bone and soft tissue engineering

Preethi Balasubramanian, Teresa Büttner, Valentina Miguez Pacheco, Aldo R. Boccaccini*

Department of Materials Science and Engineering, Institute of Biomaterials, University of Erlangen-Nuremberg, 91058, Erlangen, Germany

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ABSTRACT

Boron is considered to influence the performance of several metabolic enzymes and boron deficiency is associated with impaired growth and abnormal bone development. As such, boron is a beneficial bioactive element for animals and humans. It is also well known that boron stimulates wound healing and improves bone health. The addition of boron in different proportions to bioactive glasses has significant effects on glass structure, glass processing parameters, biodegradability, biocompatibility, bioactivity and cytotoxicity. Different compositions of bioactive glasses (BGs) containing boron, including boron-doped, borosilicate and borate glasses, are being investigated for bone and soft tissue engineering under the premise that these BGs are suitable carriers of boron, indicating controlled release of B species in the biological environment. This paper reviews up to date research and applications of borate, borosilicate, and boron doped silicate and phosphate BGs focussing on their physical, structural, degradation and biological properties for hard and soft tissue regeneration.

1. Introduction

The demand for developing biomaterials with the ability to substitute and regenerate bone has promoted substantial research on bioactive glasses (BGs) for bone tissue engineering (TE) [1–5]. BGs are highly promising in terms of their ability (1) to deposit hydroxyapatite (HA) when in contact with a physiological fluid [6], which creates a strong bond to bone (and soft tissues), (2) to release biologically active ions which activate osteogenic differentiation of stem cells [7,8], (3) to induce vascular ingrowth during new tissue development [9]. All these factors enhance the possibilities of bone regeneration after a defect/injury in the presence of BG. In addition to their successful application in bone regeneration, BGs are being increasingly investigated for soft tissue repair [10]. The impressive development of the field of BG for TE is based on the discovery of Hench and co-workers in the late 1960s, who showed, with the invention of BGs of composition (45S5 Bioglass®) in wt% (45% SiO_2, 24,5% Na_2O, 24,5% CaO, 6% P_2O_5), that artificial materials could develop a strong bond to bone [6] and could be highly interesting in applications including tissue repair or replacement [11]. The medical success that followed [3] is owed to special properties of the early BG formulation as a biocompatible, bioactive, biodegradable, osteoconductive and osteoinductive material [11–13].

In recent years, efforts have increased to improve the biological activity of BGs and to combine BGs with other biomaterials, e.g. biopolymers, to enhance their mechanical properties, chemical stability or biological reactivity. An improvement of mechanical strength and toughness has been achieved, for example, through the development of different glass or glass-ceramic compositions [5,14], through composite materials, e.g. polymer-bioactive glass composites [15–19] or bioactive glass – metal matrices [20]. An important approach for developing enhanced biological activity of BGs is the incorporation of metallic ions in the glass structure thus altering the dissolution of these materials and their bioreactivity when immersed in biological fluids [21]. Metallic ions are on one hand crucial components of human tissue and on the other hand important in controlling cell metabolism whilst also regulating many biochemical processes in the human body [22]. Elements like Si, Ca and P, which are the main constituents of bioactive silicate glasses like 45S5 Bioglass® show a strong effect on the stimulation of osteogenesis and bone metabolism [23–25]. It has also been shown that Magnesium [26,27], Strontium [28], Zinc [29] and Boron [30,31] have an influence on osteoblast activity and are capable of stimulating angiogenesis. Biologically active ions can be employed as therapeutic agents in bioresorbable scaffolds to positively influence osteogenesis and angiogenesis, which has been reviewed elsewhere [21,32]. Especially the effects of B have been widely reported, showing improvement in bone metabolism [33–36]. Applications of B-containing BGs in wound healing have also been reported [37,38]. However, a dedicated review article focussing only on B-containing BGs as a promising class of BGs is not available, which prompted the preparation of this review paper.

Boron is an 'ultratrace element' known to be present in plants since 1857 and in 1923, it was accepted as an essential nutrient in plants to complete their life cycle [39]. Boron plays a structural role in plant cell walls [40] and is also used as a preservative in the form of sodium

* Corresponding author.
E-mail address: aldo.boccaccini@ww.uni-erlangen.de (A.R. Boccaccini).

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borate and boric acid [41]. In animals, boron deprivation has been shown to exacerbate bone abnormalities [42], causing the distortion of marrow sprouts [43] and the decrease of the density of chondrocytes in the zone of proliferation of the growth plate of chicks [44]. Boron deficiency in rats has been shown to decrease bone volume fraction, trabecular thickness and to impair alveolar bone repair [45,46]. Apart from its role in bone functioning, boron deprivation has led to changes in rat behaviour and brain mineral composition [47] and it was also shown that B affects the response to injury or infection [41]. Other biological functions of boron include stimulation of wound healing *in vivo*, release of growth factors and cytokines, increase in the synthesis of RNA and increase of extracellular matrix turnover [33]. Although the exact mechanism for the role of boron has not been clearly defined in all mentioned situations yet, research results suggest that boron has a significant effect in maintaining the structural integrity and/or function of cell membranes [48,49]. The chemistry behind this is explained by Nielsen et al. [41]. Recent results have confirmed that the release of boron from boron nitride nanotubes enhances the osteogenic differentiation of mesenchymal stem cells, testifying the potential of boron in orthopaedic applications [50]. In another study, boron-doped diamond was implanted in the back muscle of a guinea pig for a period of 4–15 weeks showing lower thickness of fibrotic tissue and lower levels of acute, chronic inflammatory and foreign body responses compared to the silicone control [51].

The total content of boron in the human body ranges from 3 to 20 mg, with the highest concentrations found in bone, nails and hair [52]. The presence of boron has an influence on a variety of metabolic actions and boron interacts with calcium, vitamin D and magnesium which are all significant for the bone metabolism process [53]. For example, researchers have observed that there is a difference in the concentration of boron in arthritic bones (3 ppm) and in healthy bones (56 ppm) [54]. Optimal levels of boron are necessary for calcium metabolism and boron deprivation was found to be detrimental for processes associated with bone formation and maintenance. Boron is also needed to prevent excessive bone loss which often occurs in post-menopausal women and in older men [35]. Results from studies in humans have shown that dietary boron may be useful in preventing osteoporosis [55].

BGs, including BGs synthesized by sol-gel methods [56], represent alternative, highly promising carriers for the delivery of boron species in the human body for regeneration purposes. An early study involving the incorporation of boron in the 45S5 Bioglass® network was reported in 1994 [57]. Although the development in the field was initially slow, the increment in published studies in the field is notable, as identified by a simple search in the database Web of Science® using combinations of keywords “boron; bioactive glasses; borosilicate; borate; tissue engineering”. Several patents citing the use of boron-containing BGs for tissue regeneration [58,59] and wound healing [60,61] have been filed. Indeed BGs containing boron, starting from silicate BG with as low as 0.2 wt% B_2O_3 [62] up to 53 wt% B_2O_3 (borate glasses) [63], have been developed and investigated in the past decade. Table 1 shows an overview of investigated compositions, properties and applications of several B-containing BGs produced. This review covers the field of boron containing BGs; including the state of the art of B-doped; borosilicate and borate glasses; also discussing their biological characteristics *in vitro* and *in vivo* and focusing on applications in both bone and soft tissue repair. While the authors have attempted to comprehensively cover the field, the challenge of covering every single paper published is not minor given the notably extensive research being continuously published and some studies may have not been assessed.

2. Boron–based bioactive glasses

2.1. Structure, physical and mechanical properties

The addition of B_2O_3 has significant influence on the characteristic thermal, structural and mechanical properties of glasses [83]. In this section, key effects of B on properties of relevance for biomedical applications are discussed. One of the early papers in this field studied the effect of addition of boron on the crystallization capabilities and bioactive behaviour of gel-derived glasses in the CaO-P_2O_5-SiO_2 system [64]. The base composition (without any additions) was amorphous when it was obtained by melting but it showed a crystalline HA ($Ca_5(PO_4)_3(OH)$) phase when it was derived from sol-gel method. When 5 mol% boron was added to the base gel, a lower degree of crystallization with the presence of crystalline calcium silicate (Ca_2SiO_4) was observed [64]. In a study in which B_2O_3 in the range 0.7 mol% − 3.7 mol% was added to SiO_2-Al_2O_3-Na_2O-P_2O_5-CaO-MgO glass, a slight increase in the glass transition (T_g) and decrease in the working temperature range were found. By replacing Na_2O with B_2O_3, there is a decrease in the number of non-bridging oxygens (NBO) which is known to cause an increase in T_g. Up to a content of 2.7 mol% of B_2O_3, the glass became stronger but with further increase of boron content, the glass became more fragile. It was reported that this effect is due to the structural changes occurring in the glass as [BO_3] structural units are formed, which leads to a more cross-linked and rigid structure, whereas with increase in B_2O_3 content (higher than 2.7 mol%) [BO_4] units are formed which occurs via the transformation of metaborate into pentaborate giving the glass a more floppy and distorted structure causing an increase in the glass fragility. The −B-O-Si- bond with four-coordinated boron in Na_2O-B_2O_3-SiO_2 glasses is easily broken and significant phase separation occurs as the bond energy is weaker than that of the three-coordinated boron [127]. Also, there is a decrease in the liquidus temperature and this means that, for example, the ability to form fibers will increase in glasses with high B_2O_3 [81]. Gharbi et al. [110] reported an increase in thermal stability and a decrease in melting temperature of glasses in the borosilicate system with increase in boron content. Surface crystallization with the formation of large crystals (> 100 μm) and a coarse microstructure was also observed in a SiO_2-CaO-MgO system doped with B_2O_3 (4.52–5.33 wt%), P_2O_5, Na_2O and CaF_2 [112]. A recent study involving the synthesis of silicate and borate glasses (of the system SiO_2-B_2O_3-CaO-$P_2O_5Na_2O$-ZnO) with increasing amounts of TiO_2 revealed that the borate glasses possessed greater processing window over the silicate glasses, making them more suitable for coating metallic implants [104] and potentially useful to fabricate scaffolds.

In borosilicate and borate glasses, three distinct absorption regions can be identified for B_2O_3 in infrared spectra: 1200–1450 cm^{-1} for B-O stretching of BO_3 units, 850–1200 cm^{-1} for B-O stretching of BO_4 units and a region around 700 cm^{-1} for bending of B-O-B linkages of the borate network [111]. The presence of weak peaks at 415 cm^{-1} and 668 cm^{-1} were observed by Pan et al. [74] and Balasubramanian et al. [105] which represents Si-O-B linkages confirming the presence of silicon units in the boron network. These structural and physical changes occurring in the glass network influence also the dissolution and degradation properties of the glass, which is explained in Section 2.2 Melt-derived calcium borophosphate glasses were prepared by adding different concentrations of boron to calcium phosphate [67]. Raman and infrared spectroscopy revealed that the glass network consists of highly charged species of phosphate tetrahedral with 3 (pyro) or 4 (ortho) NBOs and the boron atoms are predominantly present in the form of $B\varnothing_3$ or $B\varnothing_2O^-$ units. A small fraction of $B\varnothing^{4-}$ units was also evident in the glasses with high CaO content [67]. O'Connell et al. [101] synthesized five quaternary borate glasses of the system B_2O_3-SrO-Na_2O-La_2O_3 and studied the role of rare earth elements such as La on the borate glass structure. La was found to cause mixed cation clustering and with increase in the La_2O_3:Na_2O ratio, La removes the NBO from the network in order to form O^{2-} ions, thereby, stabilizing the network. The authors demonstrated that the substitution of La in place of Na in quaternary high B systems yielded a sustained release of strontium ions from the network. This approach gives the opportunity to produce boron-containing glasses for controllable functional implant