

reported that  $\text{Cu}^{2+}$ -doped bioactive glass-derived scaffolds are able to improve bone-marrow-derived mesenchymal stem cells (BMSCs) endothelial marker production and the formation of typical tubular structures.  $\text{Cu}^{2+}$  released ions stimulate BMSCs to secrete VEGF indicating a potential angiogenic effect. Zhao et al. (2015) synthesized a Cu-doped borate bioactive glass useful for rapid in situ healing of skin wounds. They showed that the ionic dissolution product of the Cu-doped microfibers stimulated human umbilical vein endothelial cells (HUVEC) migration, tubule formation, VEGF secretion, and the expression of angiogenic-related genes of fibroblasts. Cu-doped samples showed a significantly higher capacity to stimulate angiogenesis than the undoped fibers, the effect being proportional to the amount of Cu ions in microfibers.

The angiogenic effect of Cu on bioactive glass composition was also estimated in vivo by Bi et al. (2013) in a rat calvarial defect model at 12 weeks postimplantation. In this study, a borate glass composition (13-93B3) was doped with copper (0.4 wt%, 13-93B3-Cu). Both glass compositions were used to prepare scaffolds with three different microstructures: trabecular, oriented, and fibrous. The authors have shown that the percentage of new blood vessels was generally higher for 13-93B3-Cu scaffold, in particular for fibrous scaffolds. Similar results were obtained in another in vivo study on SKH1 mice for the same glass compositions (13-93B3 and 13-93B3-Cu) (Watters et al., 2015).

In addition to copper, cobalt is also known to play a role in angiogenesis. Cobalt-containing glasses were studied by Azevedo et al. (2010) in order to produce 'hypoxia-mimicking' biomaterials for bone tissue engineering. As previously mentioned, pro- and antiangiogenic genes can be activated by creating hypoxia conditions and cobalt ions are well known for their ability to mimic hypoxia. Azevedo et al. introduced cobalt ions into a bioactive glass composition (co-doped with Zn and Mg). The authors showed that cobalt ions release is within the biologically active limits, being proportional to the amount of CoO in the glass.

## 2.5 APPLICATIONS IN CONTACT WITH SOFT TISSUES

Until recently, great importance has been given to the ability of bioactive glasses to bond to only 'hard' calcified tissue leading to the definition of 'conventional bioactivity'. Relatively little attention has been given to their property of bonding to soft collagenous tissues. Interestingly, the first evidence that showed collagen bonding to 45S5 Bioglass dates back to the seminal experiments performed by Hench and coworkers in the late 1960s, when agglomerates of submicrometric hydroxyapatite crystals were observed to be bonded to bone collagen fibrils produced at the interface with the implanted glass (Hench et al., 1971). Compositional boundaries to allow bonding of silicate bioactive glasses to bone and/or soft tissues were well established about one decade later by Wilson et al. (1981). This set of data was the basis for the development of a few bioactive glass products that exhibited the combined ability of bonding to