Acta Biomaterialia 42 (2016) 18–32

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review article

Bioactive glass-based materials with hierarchical porosity for medical applications: Review of recent advances

Francesco Baino *, Sonia Fiorilli, Chiara Vitale-Brovarone

Department of Applied Science and Technology, Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Torino, Italy

ARTICLE INFO

Article history:
Received 22 April 2016
Received in revised form 11 June 2016
Accepted 28 June 2016
Available online 28 June 2016

Keywords:
Scaffold
Mesoporous
Drug release
Ion release
Bioglass
Tissue engineering

ABSTRACT

Bioactive glasses have been traditionally used in the clinical practice to fill and restore osseous defects due to their unique ability to bond to host bone and stimulate new bone growth. In the last decade, a new set of bioactive glasses characterized by a highly ordered mesoporous texture has been developed and studied as a smart platform for the controlled release of biomolecules, *in situ* therapy and regenerative applications. This review points out the great potential carried by hierarchical bioactive glass scaffolds that exhibit pore scales from the meso- to the macro-range, and their impact in the broad field of tissue engineering, including the emerging applications in contact with soft tissues and diagnostics. Recent advances in the preparation methods of these multiscale constructs (e.g. mono- or multi-phase scaffolds, fibrous meshes, coated systems, porous nanospheres, and composites) are examined, along with their strengths and weaknesses. A bright future is expected for hierarchical systems based on biocompatible mesoporous materials as they can provide a unique set of functionalities, including enhanced bioactivity, local release of ions and drugs to elicit specific therapeutic effects (improved osteogenesis and angiogenesis, antibacterial properties), and implant/drug tracking, which were unthinkable when research on bioactive glasses began.

Statement of Significance

The advent of mesoporous bioactive glasses led to the birth of a new class of multifunctional biomaterials that have been proposed as smart platforms for local drug release and bone regeneration. Furthermore, mesoporous materials have been recently employed in the development of hierarchical macro-mesoporous scaffolds, composites and implantable systems. This reviews summarizes the latest applications of these multiscale biomaterials in tissue engineering, including the emerging applications in contact with soft tissues and diagnostics. The preparation methods, current uses and potential of these constructs and systems are examined and critically discussed to provide a useful, up-to-date contribution to the scientists working in the field.

Contents

* Corresponding author.
E-mail address: francesco.baino@polito.it (F. Baino).

http://dx.doi.org/10.1016/j.actbio.2016.06.033
1742-7061/

1. Introduction

Bioactive glasses are a special subset of oxide-based biocompatible ceramics that can bond to hard and soft tissues and stimulate new tissue growth while dissolving over time, making them highly attractive materials for healthcare and regenerative medicine [1,2]. The first bioactive glass, belonging to the $45SiO_2$–$24.5Na_2O$–$24.5CaO$–$6P_2O_5$ (wt. %) system (45S5 Bioglass®), was developed by Prof. Larry Hench et al. in the late 1960s [3] and is in clinical use for orthopaedic and dental applications since 1985. Over the years, many other silicate, borate, and phosphate glasses have been proposed for biomedical applications, as comprehensively reviewed elsewhere [4]. Bioactive glasses are commonly produced by melting or sol-gel route. Melt-derived glasses can be poured into moulds to produce components of various sizes and shapes (e.g. prosthetic middle ear ossicles [5]). The melt can also be drawn in fibres [6] or quenched in cold water to obtain a "frit," i.e. irregular pieces of different sizes which can be easily powdered and further processed to fabricate porous scaffolds that act as templates for new tissue growth in three dimensions (3D) [7].

In this regard, one of the major ambitions of today's biomaterials science is to obtain porous scaffolds able to effectively drive self-regeneration of tissues. In this regard, it is very important to take into consideration the hierarchical porosity found in Nature. Upon mimicking hierarchically pore-structured natural materials, the resulting 3D scaffolds could perform a similar role. In the design of bioactive glasses, and biomaterials in general, it is therefore necessary to identify the biological environment that they will find and/or replace once implanted, as scaffolds are needed to support cells in tissue engineering applications. Bone, which is often in need of regeneration due to traumas, tumour removal or age-related diseases such as osteoporosis, is a natural composite material mainly made of type I collagen (natural organic polymer) and hydroxycarbonate apatite (inorganic mineral phase) [8]. There are two types of bone, i.e. cortical and cancellous bone. The former, also called compact bone, is a dense structure with high mechanical strength. The latter, also called trabecular or spongy bone, is less dense and weaker compared to cortical bone due to its porous structure close to that of a honeycomb material along the cross-section. It is highly vascularized and frequently contains red bone marrow, where the production of blood cells takes place. The difficulty to provide a suitable vascularization to 3D scaffolds for oxygenation of newly formed tissues is a main drawback for regeneration. The amount of oxygen required for cell survival is limited to a diffusion distance between 150 and 200 μm from the supplying blood vessels [9], thereby the success of 3D constructed tissues strongly depends on angiogenesis.

It is possible to identify at least three major levels of macroporosity that should characterize an ideal scaffold for bone tissue engineering [10]. The first level (below 100 μm) imparts biomimetic features to the biomaterial, as the surface roughness provided by relatively small pores can enhance cell adhesion to the substrate. The second level (100–500 μm) is essential to allow bone in-growth and vascularization and decrease the Young's modulus, thereby reducing stiffness mismatch with the native tissue and the associated risk of stress shielding (although the mechanical strength is reduced, too). Giant macropores above 500 μm can be useful for the passage of suture wires to firmly anchor the implant to the patient's host bone.

As comprehensively reviewed by Miao and Sun [11], calcium orthophosphate bioceramics and related composites with biocompatible polymers have been widely adopted for making pore-graded scaffolds mimicking the hierarchical structure of natural bone at the macroscale. Among melt-derived bioactive glasses, however, at present only 45S5 Bioglass® [12] and the silicate glass CEL2 [13] have been proposed to fabricate glass-ceramic scaffolds with pore gradients at the macro-scale by being processed through a combination of different methods (sponge replication, burning-out of polymeric beads and enamelling).

In the last decade, the advent of ordered mesoporous materials allowed researchers to develop a new set of bioactive glasses combining superior bioactive properties (formation of a surface apatite layer within few hours from contact with biological fluids) and drug uptake/release abilities [14]. In the case of mesoporous bioactive glasses (MBGs), pore dimensions are within the range of 2–50 nm, which are far from those of living bone cells (10–200 μm [8]). This fact makes it impossible to cells to enter the mesopores and, hence, MBGs should be somehow processed to acquire macroporosity in order to allow bone cell penetration, adhesion to the scaffold struts, growth and proliferation that would lead to bone in-growth and post-operative vascularisation [15]. Scaffold processing methods should preserve the original mesoporosity of MBGs, thereby obtaining hierarchical structures that combine macroporosity for bone growth/oxygenation and mesoporosity to allow drug delivery of appropriate therapeutic biomolecules. Table 1 summarizes the correlation between pore size at different scales and pore function in hierarchical macro-/mesoporous scaffolds. In order to avoid any confusion on pore classification depending on the size, the authors strictly refer here to IUPAC notation [16].

In this review, we grouped bioactive glass-based hierarchical materials in three classes, termed "generations" according to their chronological development: (i) sol-gel glass foams, in which nanopores are inherent to the sol-gel process and macropores are obtained by making use of a surfactant as a foaming agent; (ii) porous structures comprising a macroporous scaffold and a pure silica mesoporous coating (a surfactant is used as a mesopore template); and (iii) MBG-based multiscale porous materials (also in this case the ordered arrangement of mesopores is deliberately created by using a surfactant).

2. First-generation hierarchical materials: sol-gel glass foams

Sol-gel glass scaffolds can be considered the precursors of hierarchically structured macro-/mesoporous glass scaffolds [17–19]. However, although sol-gel glass foams exhibit pores at both macro- and nanoscale, their mesoporous texture is arranged randomly instead of being ordered according to a well-defined symmetry since it is inherent to the sol-gel process [20,21].

Bioactive sol-gel glasses were synthesized for the first time in the early 1990s and, compared to melt-derived glasses, can be prepared at relatively lower processing temperatures and exhibit faster resorption properties [22]. Hench and co-workers demonstrated that SiO_2 should be less than 60 mol. % in