Acta Biomaterialia 7 (2011) 16–30

Contents lists available at ScienceDirect

Acta Biomaterialia

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

Review

A review of the mechanical behavior of CaP and CaP/polymer composites for applications in bone replacement and repair

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ARTICLE INFO

Article history:
Received 28 April 2010
Received in revised form 9 July 2010
Accepted 12 July 2010
Available online 21 July 2010

Keywords:
Mechanical properties
Scaffolds
Porosity
Calcium phosphate
Composites

ABSTRACT

Repair of load-bearing defects resulting from disease or trauma remains a critical barrier for bone tissue engineering. Calcium phosphate (CaP) scaffolds are among the most extensively studied for this application. However, CaPs are reportedly too weak for use in such defects and, therefore, have been limited to non-load-bearing applications. This paper reviews the compression, flexural and tensile properties of CaPs and CaP/polymer composites for applications in bone replacement and repair. This review reveals interesting trends that have not, to our knowledge, previously been reported. Data are classified as bulk, scaffolds, and composites, then organized in order of decreasing strength. This allows for general comparisons of magnitudes of strength both within and across classifications. Bulk and scaffold strength and porosity overlap significantly and scaffold data are comparable to bone both in strength and porosity. Further, for compression, all composite data fall below those of the bulk and most of the scaffold. Another interesting trend revealed is that strength decreases with increasing β-tricalcium phosphate (β-TCP) content for CaP scaffolds and with increasing CaP content for CaP/polymer composites. The real limitation for CaPs appears not to be strength necessarily, but toughness and reliability, which are rarely characterized. We propose that research should focus on novel ways of toughening CaPs and discuss several potential strategies.

1. Introduction

1.1. Background

The field of tissue engineering has expanded rapidly since being defined by Vacanti in 1997 as the application of "the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function" [1,2]. Although a range of tissues have been studied, the translation of engineered tissues to clinical applications has been limited. Bone tissue engineering has the potential to reach millions annually through the repair of bone defects caused by disease, trauma or congenital defects. In 2003 the potential market for tissue engineered products for musculoskeletal applications totaled $23.8 billion in the USA and is expected to increase to $39 billion by the year 2013 [3]. In 2004 alone there were 1.5 million bone graft procedures [4]. A substantial portion of these were for the elderly, the number of which is expected to double in the USA in the next 25 years.

Autografts (from the patient) are considered the gold standard for bone defect repair and allografts (from a donor) are also commonly used. While multiple complications and risks are associated with the use of both types of grafts [5–7], these remain appropriate options for some simple and non-load-bearing defects that do not require a significant amount of graft material (i.e. non-critical size defects). However, for many defects the use of allogenic and autologous bone is not an option.

Researchers in bone tissue engineering are working to develop alternatives to allogenic and autogolous bone grafts in order to address the growing needs of the population, and much of the research is scaffold based. A scaffold alone can be used to guide bone regeneration and repair defects or be combined with cells and/or biologics, which are added to further enhance bone regeneration. However, the optimal scaffold "recipe", including target mechanical properties, is still very much under debate.

There are several characteristics that are considered to be essential for bone scaffolds, such as biocompatibility, osteoconductivity and interconnected porosity. Other considerations in bone scaffold design and optimization include biodegradability, permeability and mechanical integrity. Appendix A briefly defines these and other relevant characteristics. Most of these characteristics are coupled, making scaffold design, characterization and translation to clinical applications a challenging prospect.

1.2. CaP bioceramics for bone replacement and repair

Bioceramics are one of the most widely used and/or studied class of materials that interface with bone. Of these, calcium

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1742-7061/$ - see front matter
doi:10.1016/j.actbio.2010.07.012

phosphates (CaPs) have perhaps been studied most extensively. They were first considered for clinical application as a filler for bone defects in the 1920s and first incorporated in dentistry and orthopedics in the 1980s [8]. CaPs and CaP/polymer composites are the materials on which this review will focus.

The interest in CaP-based ceramics for bone replacement and repair is well-deserved, given that they have the requisite characteristics and many other attributes that make them excellent candidates for such applications. CaPs are biocompatible, have a composition and structure similar to the mineral phase of bone [9], are osteoconductive [10–13], have been reported to be intrinsically osteoinductive in some cases [10,14,15], and are bioactive. These bioceramics also have a high affinity for proteins, such as some adhesion proteins and growth factors such as BMP-2 [16], the latter of which stimulates proliferation and differentiation of osteoprogenitor cells. Therefore, CaPs are also appropriate carriers for growth factors and stem cells without the chemical surface modification that is sometimes required for polymers [15]. The degradation products of CaPs are conducive to bone formation and strongly linked to bioactivity; the dissolution process is followed by reprecipitation of a carbonated apatite, which has a composition and chemical structure that is more similar to the mineral phase in bone [17–19]. Finally, the degradation rate for CaPs is typically slow compared to that of many polymers [21] and compared with bone growth [20]. This is advantageous because it removes concerns about balancing degradation and bone in-growth.

While a range of CaP compositions have been considered, hydroxyapatite (HA), with the chemical composition $Ca_5(PO_4)_3OH$ and a calcium to phosphate ratio of 1.67 [22], β-tricalcium phosphate (β-TCP), with the chemical composition $Ca_3(PO_4)_2$ and a calcium to phosphate ratio of 1.5 [22], and biphasic calcium phosphate (BCP), which refers to composites of HA and β-TCP with no specific ratio, have received most attention [23]. Among these, HA is most commonly used in clinical applications and has been used in bone cements for the repair of craniofacial defects [24,25], for maxillary sinus floor augmentation [26] and in coatings for hip replacements [27,28]. β-TCP ceramics have been commercialized as bioresorbable synthetic bone substitutes and are used in orthopedic and dental applications [29], including augmentation of the alveolar ridge [30], sinus reconstruction [31] and general bone reconstruction following injury or disease [32]. Perhaps the most emphasized difference between the properties of HA and β-TCP is their relative degradation rates; HA is considered relatively non-degrading while TCPs purportedly degrade readily [33,34]. Thus, the use of BCP with different HA to β-TCP ratios allows manipulation of the degradation rate and other properties by extension.

1.3. Target mechanical properties for bone scaffolds

The need for scaffolds that can be used to repair load-bearing bone defects, which are often also large defects, is apparent. However, the specific mechanical requirements of the scaffolds being studied for the repair of such defects, beginning from implantation through complete healing, are yet to be established. By extension, the most appropriate materials and their corresponding mechanical properties are still under debate.

The target properties such as strength and elastic modulus, that have been explicitly stated or implied in the literature, span several orders of magnitude and several different approaches have been taken with regard to the design for mechanical properties. For example, many papers have stated that bone scaffold properties should match those of natural bone [18,35–38]. Table 1 summarizes the compressive, flexural and tensile strengths, elastic moduli and porosities for both cortical and cancellous bone for reference. Another study took a different approach and optimized scaffold pore architecture such that the scaffold stiffness matched the stiffness of native bone initially and the stiffness of the regenerated bone matched that of native bone at the end point [37]. In a different paper the authors stated simply that "the mechanical properties of the scaffold must be sufficient and not collapse during handling and during the patient's normal activities" [21]. In contrast to these studies, another argued that scaffold strength should be greater than the bone it will replace [39]. The same authors indicated a need for fixation devices to shield scaffolds from loading. These examples from the literature demonstrate the diversity of target mechanical properties for bone scaffolds and that there is no agreement in the literature.

Table 1
Summary of the mechanical properties and porosity of human bone.

	Compressive strength (MPa)	Flexural strength (MPa)	Tensile strength (MPa)	Modulus (GPa)	Porosity (%)
Cortical bone [104–107]	130–180	135–193	50–151	12–18	5–13
Cancellous bone [108–111]	4–12	NA	1–5	0.1–0.5	30–90

NA indicates data not available.

A final strategy is to design scaffolds such that the mechanical properties of the composite of bone and scaffold are within some percentage of the mechanical properties of the host bone. For this, the initial mechanical properties of the scaffold should account for both the change in properties with degradation and the change with the expected bone in-growth, a tall order for some systems whose degradation rates are sensitive to processing parameters and the in vivo environment or simply are not well characterized. For polymers this is an important issue; degradation rates can vary from of the order of days to months [40]. On the other hand, degradation for CaPs can be of the order of months to years, depending on porosity, crystallinity and grain size, for example [41]. The slow degradation of CaPs relative to many polymers implies that stability should be maintained during the period of bone regeneration and that degradation is unlikely to be as important a variable on this time scale.

The properties of CaPs that make them excellent candidates for use in bone replacement and repair have been described previously (see Section 1.1 and Appendix A). Researchers have reported that one of the limiting factors for the use of CaPs in load-bearing applications is strength [21,42,43]. However, a range of porosities and architectures have been characterized for CaPs and, as will also be shown here (see Sections 2.2 and 2.3), CaPs can have strengths and stiffnesses that are similar to those of cortical and cancellous bone (Table 1) in some forms [9,21,36]. On the other hand, few porous polymers or CaP/polymer composites have strengths in the range of cancellous bone [44] (see Sections 2.2 and 2.3). The real limiting factor for CaPs in load-bearing applications may be in the inherent brittleness of this class of materials. Unfortunately, few studies in the literature report properties such as fracture toughness, reliability (i.e. Weibull modulus), or energy to failure for CaP, polymer or composite scaffolds.

To summarize this discussion of mechanical requirements, the issue of defining and achieving the appropriate mechanical properties of scaffolds for load-bearing defects remains a challenge not only for CaPs, but also for porous polymers and for porous CaP/polymer composites. With polymers, tailoring degradation to the balance mechanical properties during growth is a significant challenge, especially considering that most polymer scaffolds have strengths less than bone prior to implantation and degrade relatively quickly [21]. CaPs, in contrast, degrade much more slowly and in a more controlled manner. Thus, the stiffness and strength