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The contribution of rheology for designing hydroxyapatite biomaterials

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ABSTRACT

As a result of aging populations in the industrialized world, the development of biomaterials for bone tissue engineering is becoming increasingly important. Rheology, which is a key parameter in process engineering, plays a decisive role in designing these biomaterials. As a prime example of biomaterials engineering, this review focuses on formulations that are based on hydroxyapatite (HAp). More specifically, we will discuss the contribution of rheology for designing injectable bone replacement materials, composite gel scaffolds, porous scaffolds and scaffolds that can be generated using rapid prototyping or 3D printing techniques.

1. Introduction

One of the greatest features of bone is its inherent capability of regeneration. However, excessive bone loss often necessitates the use of bone grafts. While graft materials are regularly applied that originate from the same individual (autograft), a donor (allograft) or from animal bone (xenograft), artificial graft materials, so-called alloplasts, are on the rise, caused by the vast advances in the field of tissue engineering [1]. Bone is a natural organic–inorganic ceramic composite and contains about 70 wt.% of calcium phosphate, which is dispersed in a matrix of regularly arrayed collagen fibrils. The embedded calcium phosphate in bone has the form of nano-crystalline, needle-like nanoparticles exhibiting a crystal structure that is very similar to hydroxyapatite (HAp) with the chemical formula $Ca_{10}(OH)_2(PO_4)_6$ [2]. Consequently, synthetic HAp has been intensely investigated as a substitute or replacement for bone in biomedical applications [3,4]. A special feature of bone is its hierarchical assembly with open porosity which exhibits high mechanical strength and fracture toughness at the same time [1]. Mimicking this hierarchical organization over several length scales is a major challenge in the field of tissue engineering [5]. Here, special focus lies on replicating the micro- and nanostructuring of bone, along with its chemical composition and mechanical properties [4]. Tissue engineering is an interdisciplinary research field that applies the principles of engineering and life sciences to develop biological substitutes that restore, maintain or improve tissue function [6]. The role of materials science in the tissue engineering field is to develop scaffolds that act as a matrix that fosters cell growth and development of new tissue [7]. Scaffolds for tissue engineering should be biocompatible, able to provide appropriate mechanical support, exhibit favorable surface properties to promote cell adhesion, proliferation and differentiation and eventually provide an environment in which cells be sustained [8,9]. An ideal scaffold for bone tissue should be able to mimic the structure and biological function of healthy osseous tissue in terms of both chemical compositions as well as physical structure and properties [4,10]. One of the most straight-forward utilizations of scaffolds is their direct implantation into the patient. In this case, the surrounding healthy tissue can take care of supplying cells, nutrients, growth factors and anything else that is needed to rebuild the tissue that has to be replaced [1]. For bone replacement materials this means that an osteoconductive and biodegradable material like HAp can be implanted or injected directly into a bone defect or cavity. Governed by the surrounding osseous tissue, the multicellular unit, which is comprised of osteoblasts and osteoclasts, can then rebuild the scaffold material to newly formed bone. This strategy has seen wide clinical use since its inception by Larry Hench in 1969 [11]. There are many different approaches towards the engineering of scaffolds for bone tissue engineering including different materials and multiple processing techniques. For many of these strategies, rheological characterization is critical for the design of concentrated dispersions of ceramic particles (also called slurries), which are usually the precursor to solid ceramics. The rheological properties of these viscoelastic fluids determine in which ways these formulations can be utilized or further processed [12]. However, in the interdisciplinary biomaterials research field,

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the rheology of ceramic formulations is often treated neglectfully and without much thought of the complexities involved.

This review focuses on discussing the rheology of a few exemplary approaches to bone tissue engineering materials based on HAp. These different systems have very distinct rheological properties that could even be used to classify the special applications for these specific types of materials. As will be shown below, mainly standard rheological techniques are used for the rheological characterization of HAp suspensions. These include investigation of the shear rate dependent behavior and oscillatory techniques that determine the viscoelastic moduli G' (the storage modulus) and G'' (the loss modulus). The viscoelastic moduli can be studied as a function of time, frequency, amplitude or temperature [13]. Studies using more advanced techniques like investigation in the non-linear viscoelastic regime are rare due to the complexities of the formulations [14].

In light of the vast numbers of publications in the field of materials' design for bone tissue engineering we want to limit this review to HAp-based formulations as a prime example for a rheologically complex system, while being fully aware of the other morphologies of calcium phosphate (CaP) that are also studied extensively, like e.g. tricalciumphosphate or octacalciumphosphate [8]. We like to present a good overview over the rheology of the portrayed HAp systems that can serve as a basis for further development of HAp materials or CaP systems in general, as well as raising interest in the intricacies and special features of the rheology of ceramic dispersions. More specifically, we will focus on injectable bone replacement materials, composite gel scaffolds, porous scaffolds and scaffolds that can be generated using rapid prototyping or 3D printing techniques (Fig. 1).

1.1. Slurry rheology

Before we take a closer look at the specific scaffold materials, we will discuss the general rheological behavior of concentrated HAp dispersions that are used for ceramic formulations. While we largely adhere to publications from 2010 onward for the examples of applied HAp systems, in this chapter, we will revert to fundamental papers mainly from the last decade.

Hydroxyapatite powders that are used for ceramics consist of characteristic needle-like HAp nanocrystals (Fig. 2a). The length of the needles is around 25–50 nm, while the thickness is only around 5 nm. The actual size of the crystallites is highly dependent on the mineralization route, as well as various pre-treatment methods [15–18]. Generally, as well as in the case of HAp ceramics, the rheological behavior of highly concentrated, aqueous nanoparticle suspensions like ceramic slurries is mainly governed by the content of solid particles (Fig. 2c), particle size and shape and the degree of particle agglomeration (see reference [17] for a discussion of non-aqueous dispersions) [12]. At very low shear, the ceramic nanoparticles agglomerate into a 3D-network that percolates throughout the suspension volume. This network causes the often-observed yield stress of slurry and at the same time it is responsible for elastic properties of the suspension [19]. With an increasing shear rate, the network breaks down into smaller agglomerates whose sizes continuously decrease. Characteristically, the viscosity is constant at high shear rates. Here, the agglomerated dispersion is broken up into primary aggregates, i.e. nanoparticle aggregates that cannot be destroyed using merely shear forces. If, as in the case of HAp needles, the particles or their aggregates are anisotropic, they can align in the shear field which further reduces the viscosity (see also Fig. 2b) [18]. Hence, HAp suspensions typically show pronounced shear thinning behavior [19,20]. Some ceramic suspensions also show dilatant behavior, the increase of the viscosity at high shear rates [21]. Because agglomeration and break-up kinetics are not instantaneous, the rheological properties are highly time-dependent, which causes thixotropic behavior [19,22,23]. Thixotropy, i.e. the decrease of viscosity during constant shear followed by a recovery of the viscosity during a period of rest, is a rheological behavior that is often overlooked. For some applications, e.g. rapid prototyping [24], it is a critical property as it allows the fast solidification of the extruded suspensions. Thixotropic behavior can

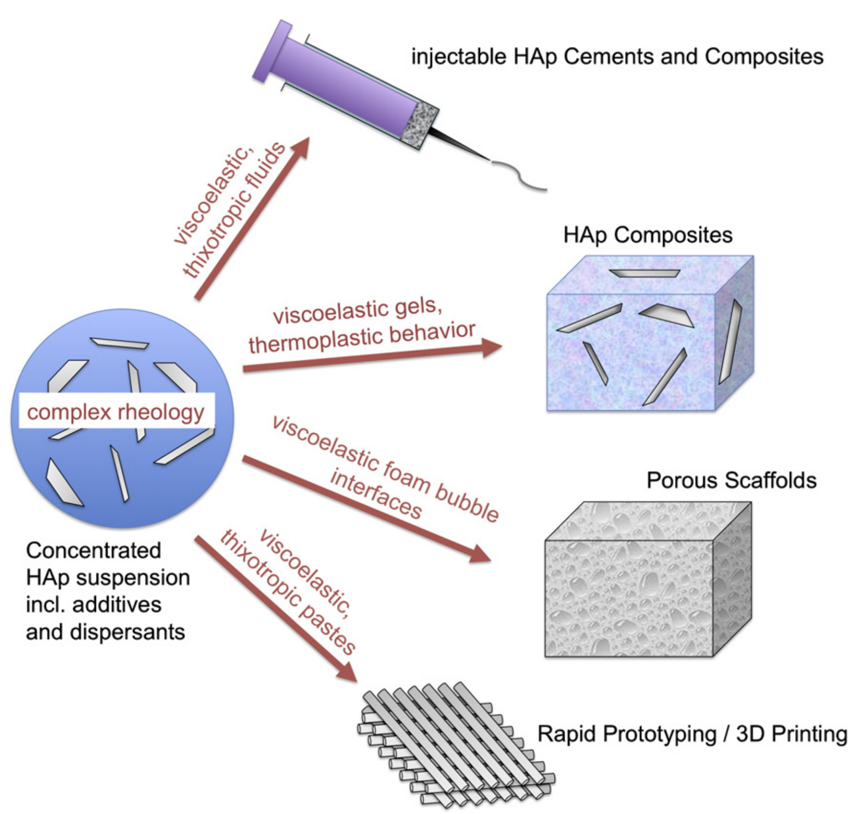

Fig. 1. Overview over the different approaches for the fabrication of HAp scaffolds, classified by their rheological properties.