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An overview of chitin or chitosan/nano ceramic composite scaffolds for bone tissue engineering

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ABSTRACT

Chitin and chitosan based nanocomposite scaffolds have been widely used for bone tissue engineering. These chitin and chitosan based scaffolds were reinforced with nanocomponents *viz* Hydroxyapatite (HAp), Bioglass ceramic (BGC), Silicon dioxide (SiO_2), Titanium dioxide (TiO_2) and Zirconium oxide (ZrO_2) to develop nanocomposite scaffolds. Plenty of works have been reported on the applications and characteristics of the nanoceramic composites however, compiling the work done in this field and presenting it in a single article is a thrust area. This review is written with an aim to fill this gap and focus on the preparations and applications of chitin or chitosan/nHAp, chitin or chitosan/nBGC, chitin or chitosan/nSiO_2, chitin or chitosan/nTiO_2 and chitin or chitosan/nZrO_2 in the field of bone tissue engineering in detail. Many reports so far exemplify the importance of ceramics in bone regeneration. The effect of nanoceramics over native ceramics in developing composites, its role in osteogenesis *etc.* are the gist of this review.

1. Introduction

In recent years, surgical re-establishment using artificial materials as implants to treat bone defect repair have set up a new baseline in the field of medicine. Nevertheless, the drawbacks associated with these types of treatments have paved way to the evolution of tissue engineering, exploiting the cell-material interactions through the development of three dimensional scaffolds. Polymers, ceramics and metals have been extensively used as materials in the construction of three-dimensional scaffolds for tissue regeneration [1–10]. The 3D scaffolds act as artificial extracellular matrices and provide the necessary cues, allowing cells to proliferate and maintain their specific functions in the provided niche devoid of any adverse reactions and serve as a template for neo-tissue formation. Owing for a suitable microstructure and mechanical properties, an ideal scaffold for bone regeneration should not only have excellent biocompatibility, biodegradability and non-toxicity, but should also be capable of promoting cell adhesion and retaining the metabolic functions of attached cells [11].

The biocompatible natural polymers chitin and chitosan is currently a subject of interest in tissue engineering (bone, cartilage, skin *etc.*) [2,3,12,13], drug delivery and wound healing [14]. Chitin consists of 2-acetamido-2-deoxy-β-D-glucose through a β (1 → 4) linkage and is extracted from the shells of marine crustaceans, insects or fungi. Chitin derived from porifera (sponges) has unique biological properties that serve it as a suitable candidate for biomimetic approach [15–18]. Chitosan, a linear polysaccharide, is derived from partial deacetylation of chitin. It is a copolymer of (1 → 4)-2-acetamido-2-deoxy-β-D-glucan (*N*-acetyl D-glucosamine) and (1 → 4)-2-amino-2-deoxy-β-D-glucan (D-glucosamine) units randomly or block distributed, based on the specific method of deacetylation, throughout the biopolymer chain [3]. The structural similarity of chitin and chitosan to glycosaminoglycans, the major component of the extracellular matrix of bone, have made it a suitable scaffold material for tissue engineering [2,4]. Chemical modification of chitosan is fairly easy due to the presence of the amino group at the C-2 position of the monomer ring, when compared to chitin [19].

Chitin is white, hard, inelastic, nitrogeneous polysaccharide, hydrophobic and is insoluble in water and most organic solvents

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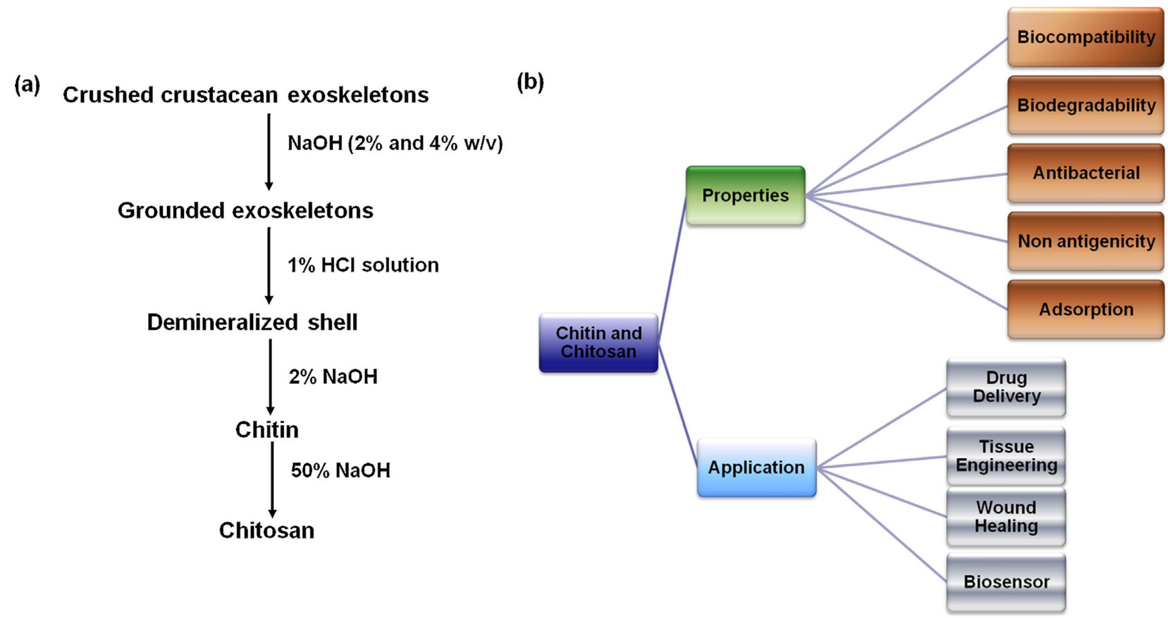

Fig. 1. (a) Preparative procedure and (b) properties and applications of chitin and chitosan.

unlike hexafluroisopropanol, hexafluroacetone and chloroalcohols [13,19]. Whereas, chitosan, is soluble in dilute organic acids like acetic acid and formic acid. Preparative procedure of chitin and chitosan are shown in Fig. 1(a) Chitin and chitosan are excellent functional materials for biomedical applications because of their high biocompatibility, biodegradability, antibacterial activity, non-antigenicity and high adsorption properties that makes them appropriate for tissue engineering (Fig. 1(b)) [20–24].

The main advantage of chitin and chitosan is the ease with which they can be processed into different forms like beads, gels, microparticles, nanoparticles, nanofibers, scaffolds *etc.* (Fig. 2). Other advantages of chitin and chitosan scaffolds for tissue engineering include the formation of highly porous scaffolds with interconnected pores and to impart osteoconductivity and ability to enhance bone formation both *in vitro* and *in vivo*. Enhanced biomineralization in chitin scaffolds have made it a universal template for the regeneration of mineralized tissues [25].

Chitin and chitosan are good antibacterial and great biocompatible materials that outweighs their limitation of maintaining mechanical integrity making them suitable for tissue engineering [5,12,13] and wound healing [13,14]. Chitin dressings can accelerate wound repair, and regulate secretion of inflammatory mediators such as IL-8, prostaglandin E, IL-1 β, and others [13]. Extensively applied approaches to overcome the constraint of low mechanical property and fast degradation especially in acidic condition or in the presence of lysozyme, are to blend or incorporate other components with chitin/chitosan. The incorporation of nanomaterials basically improves the mechanical strength and biological properties of chitin and chitosan scaffold [7,26–35].

2. Applications of chitin or chitosan/nano ceramic composite scaffolds in bone tissue engineering

In the recent years, significant progresses have been achieved to treat the loss or failure of bone defect healing with cell/scaffold based tissueengineering strategies. Bone replacement or bone defects are treated with autografts, which still remains the gold standard, and allografts. However, the issues of lack of donor site and associated risk of transmissible disease insist in the development of better techniques. While preparing artificial bone, the following criteria must be considered *viz*, morphology, structure, inter-connective porosity, sufficient mechanical strength, biocompatibility and biodegradability. From a clinical viewpoint, the use of artificial scaffolds may be attractive to minimize patient discomfort, avoid transmissible infection, wound formation and reduce the cost of treatment.

Natural bone exhibits a hierarchical structure, consisting of fibrilar collagen, which forms the organic component and HAp, the inorganic component [$Ca_{10}(PO_4)_6(OH)_2$] (Fig. 3). Biodegradable polymers and bioactive ceramics are blended to mimic the native polymer-ceramic composite nature of the extracellular matrix for bone tissue engineering scaffolds [35].

Ceramic materials has found uses increasingly in various fields, *viz* electronics, medicine, optical *etc.* High toughness, temperature withstanding capacity, mouldability etc are their key features. Nano features shows enhanced properties compared to the bulk material. Nanoceramics can be easily synthesized by different methods. In the field of tissue engineering ceramic nanoparticles are increasingly being used in developing bone tissue engineering scaffolds due to its high similarity to inorganic component of bone. This review is divided into different sections that detail the development, *in vitro* and *in vivo* responses of nanoceramic composites of chitin and chitosan. The advantages, drawbacks and applications of chitin or chitosan with bioactive ceramic nanomaterials such as HAp, BGC, SiO_2, TiO_2, ZrO_2 for bone tissue engineering applications are being covered here. This review will also highlight directions for future studies to supplement the application of these scaffold systems in translational studies.

2.1. *Chitin or chitosan/nHAp*

Owing to its coherent nature with that of natural bone composition, biocompatibility and osteoconductivity, nanohydroxyapatite (nHAp) is a widely used biomaterial in bone defect treatment. The properties and applications of nHAp are given in Fig. 4(b). Wei et al. suggested that nHAp particles possess great advantage over micro size HAp, due to their easy dispersion in the polymeric matrix which forms regular pores compared to irregular pores [26].

HAp alone may not be very efficient for the treatment of all kinds of bone defects due to its brittleness. There is need for the