



Biodegradable Materials For Bone Repair Engineering

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Abstract

This review discusses and summarizes the recent developments and advances in the use of biodegradable materials for bone repair purposes. The choice between using degradable and non-degradable devices for orthopedic and maxillofacial applications must be carefully weighed. Traditional biodegradable devices for osteosynthesis have been successful in low or mild load bearing applications. However, continuing research and recent developments in the field of material science has resulted in development of biomaterials with improved strength and mechanical properties. For this purpose, biodegradable materials, including polymers, ceramics and magnesium alloys have attracted much attention for osteology repair and applications. The next generation of biodegradable materials would benefit from recent knowledge gained regarding cell material interactions, with better control of interfacing between the material and the surrounding bone tissue. The next generations of biodegradable materials for bone repair and regeneration applications require better control of interfacing between the material and the surrounding bone tissue. Also, the mechanical properties and degradation/resorption profiles of these materials require further improvement to broaden their use and achieve better clinical results.

Keywords: biomaterials, biodegradable materials, bone regeneration, bone repair, tissue engineering

INTRODUCTION

Bone is a composite natural living tissue which comprises of an organic phase in which calcium containing inorganic phase crystals are embedded . Bone by weight contains about 30% matrix, 60% mineral and 10% water . The bone matrix is primarily collagen which responsible for the tensile strength. The mineral component of bone is calcium phosphate, which imparts compressive strength to the bone tissue . There are two types of bone tissue, cortical (compact), and cancellous (trabecular). Compact bone has Young's modulus of

elasticity ranging from 17–20 GPa and compressive strength in the range of 131–224 MPa while Young's modulus and compressive strength for trabecular bones are 50–100 MPa and 5–10 MPa respectively.

According to the degradation performance, materials for bone repair can be classified into two groups: bio-inert and biodegradable materials. The bio-inert materials have been used widely for clinical use with success; they do have some problems. For example, they are mostly inert implants that stay in human body forever until removed surgically. A major drive for continued research to develop biodegradable materials is the need for new materials with properties tailored to meet the biochemical and biomechanical requirements of bone tissue engineering. The basic concept is that the substitute biomaterial acts as a scaffold for the surrounding cells/tissue to invade, grow, and thus guide tissue regeneration towards new bone formation. Once bone repair and healing has occurred, scaffold removal via in vivo degradation is desirable both from a clinical and a biomechanical point of view. Therefore, biodegradable materials are sought since they can be used as an implant and do not require a second surgical event for removal. The biodegradable materials must support the bone tissue regeneration and repair process while providing mechanical support and degrading to non-toxic products ultimately being removed by the body. While providing a brief introduction to chemistry and properties of major classes of materials, the main aim of this review is to provide the readers with an update on recent developments in different classes of biodegradable materials for bone repair applications.

BIODEGRADABLE MATERIALS:

There are a variety of biomaterials that have been researched upon and used clinically for bone repair and regeneration applications. The degradation of implant materials is accompanied with an unwanted decrease in mechanical properties. However, if the degradation is controlled and gradual, then the loads will transfer from the implants to bone tissue and soft tissues to avoid the stress shield effect. The development of biodegradable rods, plates, pins, screws and suture anchors has progressed in recent years. Biodegradable polymers, ceramics and metals are the main three kinds of widely studied and clinically used biodegradable materials.

POLYMERS

Polymers are macromolecules that are composed of covalently bonded repeating monomers that can be same or different, i.e., homopolymers and copolymers. These materials can be amorphous and crystalline with chains being linear, branched or cross-linked with other chains. Polymer properties are affected by temperature and it is important to synthesize

biodegradable polymers with the glass transition temperature (T_g) above the body temperature as polymers become very flexible above their defined T_g .

Biodegradable polymers are one of the primary and common biomaterials used for bone repair and tissue engineering. Their biodegradability and controlled degradation rates are highly beneficial for clinical applications. The degradation of polymeric materials can be altered by changing their structural composition and fabrication techniques. The degradation process and rate is affected by various factors such as the molecular composition molecular weight (M_w) and crystallinity. The types of monomers making up the polymeric material affect the sensitivity of hydrolysable bonds. The longer the polymer chains are the more hydrolytic chain scissions are required to obtain biodegradation. Since crystallinity is the measure of organization, interactions and packing in a material affects biodegradation, more crystalline materials possess stronger inter- and intra-molecular bonding therefor degrade slowly when compared to amorphous polymers.

An optimal interaction on a cellular and biochemical level is required for a positive outcome to be achieved towards the formation of a functional tissue. There are a few criteria for biodegradable polymers in order to be used successfully for bone repair and tissue engineering applications: (i) the polymer surface should allow for cell adhesion and growth to occur; (ii) post implantation in vivo, there should be no inflammatory or toxic response towards the polymer or its degradation products; (iii) have sufficiently high porosity that is interconnected; (iv) have high surface area and adequate space for extracellular matrix; (v) be completely degradable with controlled resorption timing of the scaffold matrix (degradation rate ideally matching with the regenerating bone tissue); and lastly (vi) the polymeric material should allow reproducible processing into three dimensional (3D) structures.

Based on their origin, polymers can be classified as natural or synthetic. Due to their inherent low strength, natural polymers are mainly used for the repair of small bone fractures that do not impart high loads onto the implant materials. As for the synthetic polymers, by controlling the design and synthesis, polymers with improved mechanical properties can be prepared. Synthetic polymers also have the advantage of having a well-controlled and reproducible molecular structure and are also non-immunogenic.

Natural Biodegradable Polymers: Collagen

Collagen is the most abundant protein present in the human body and is the major component in bone and skin tissues. Collagen is a polymer with repeating sequences having

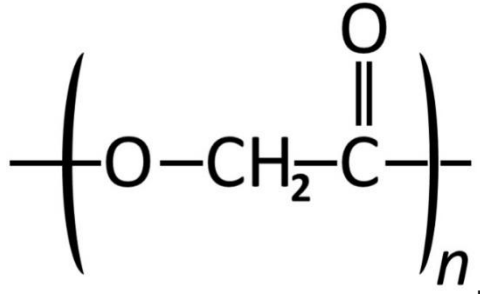
a molecular weight (Mw) of 300,000 and a chain length of 300 nm. The repeating sequences of collagen are responsible for the helical structure and inherent mechanical strength. Due to the fact that collagen undergoes enzymatic degradation in the body, the mechanical and biological properties of collagen have been thoroughly studied for biomedical applications. The collagen rate of degradation can be controlled and altered introducing cross-linking in the polymer chains and also by enzymatic pre-treatments.

Chitosan

Chitosan is a natural biopolymer derived from chitin. It is a linear polysaccharide, composed of glucosamine and N-acetyl glucosamine in a particular ratio. The molecular weight of chitosan may range from 300 to 1000 kDa depending on its source and processing methods. Although chitosan is generally insoluble in aqueous solutions above pH 7, but when placed in diluted acids having pH less than 6, the protonated free amino group of glucosamine facilitates the solubility of the material. Chitosanase, papain and lysozyme are known to degrade chitosan in vitro. The in vivo degradation takes place primarily due to lysozyme and is regulated via hydrolysis of the acetylated residues. The chitosan degradation rate depends on the level of crystallinity and acetylation of the polymer. The chemical alteration of chitosan polymer can affect degradation and solubility rate significantly and the highly deacetylated form demonstrates slow biodegradation occurring over several months in vivo

Synthetic Biodegradable Polymers

The most extensively researched upon synthetic biodegradable polymers are Poly (α -hydroxy acids) also known as polyesters. These synthetic polymers can be synthesized from a wide range of monomeric units via ring opening and condensation polymerization methods. Poly (hydroxyl acid) has an ester bond that is cleaved by hydrolysis which results in a reduction in the molecular weight (Mw) of the polymer. However, this reduction in Mw does not decrease the mass of the implant materials. The rate of degradation of polyesters is dependent on the exposed surface area, crystallinity, initial Mw and the ratio between hydroxyl ions and the monomers (in copolymers)



Poly (Lactic Acid)

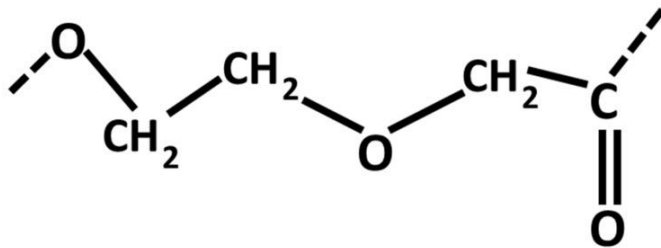
Poly (lactic acid) (PLA) was first used for medical applications as sutures and rods for the treatment of mandibular fractures in dogs, and since has been researched upon extensively. PLA is aliphatic thermoplastic polyester with linear polymeric chains and undergoes in vivo biodegradability via enzymatic and hydrolytic pathways (Figure 2). PLA has excellent mechanical and thermal properties, is biocompatible and biodegradable and has a renewable source which makes it affordable and available for biomedical applications. Lactic acid is a chiral molecule and exists as two stereoisomeric forms which result in distinct polymers based on morphology such as l-PLA, d-PLA, d,l-PLA and meso-PLA. l-PLA and d-PLA are stereoregular, d,l-PLA is a racemic polymer (mixture of l- and d-lactic acid), and meso-PLA is obtained from d,l-lactide. Crystalline l-PLA that is resistant to hydrolysis and amorphous d,l-PLA that is more sensitive to hydrolysis are mostly used for clinical applications. In vivo, the Lactic acid that is released by PLLA degradation is converted into glycogen in the liver or incorporated into the tricarboxylic acid cycle and excreted from the lungs as water and carbon dioxide.

Poly (ε-Caprolactone)

Poly(ε-caprolactone) (PCL) is an aliphatic polyester that is a semi-crystalline polyester and can be processed in various forms due to it being highly soluble in a variety of organic solvent. PCL is a polymer that has a very high thermal stability when compared with other aliphatic polymers. The decomposition temperature (Td) of PCL is 350 °C, while the Td of aliphatic polyesters is usually between 235 °C and 255 °C.

Poly-para-dioxanone

Poly-para-dioxanone (PDS) is a polymer consisting of multiple repeating ether-ester units. PDS is obtained by the ring-opening polymerization of para-dioxanone monomer. PDS is a polyester used in the field of medicine in form of films, laminates, molded products, foams, adhesives and surface coatings. Due to its excellent biocompatibility, biodegradation and flexibility, PDS has been investigated for use in tissue regeneration and fracture repair applications. PDS when used for internal fixation of fractures has been shown to be completely biodegradable within the bone tissues. PDS can be resorbed completely in vivo within 5–7 months via the alteration of its crystallinity, molecular weight M_w and the melting temperature.



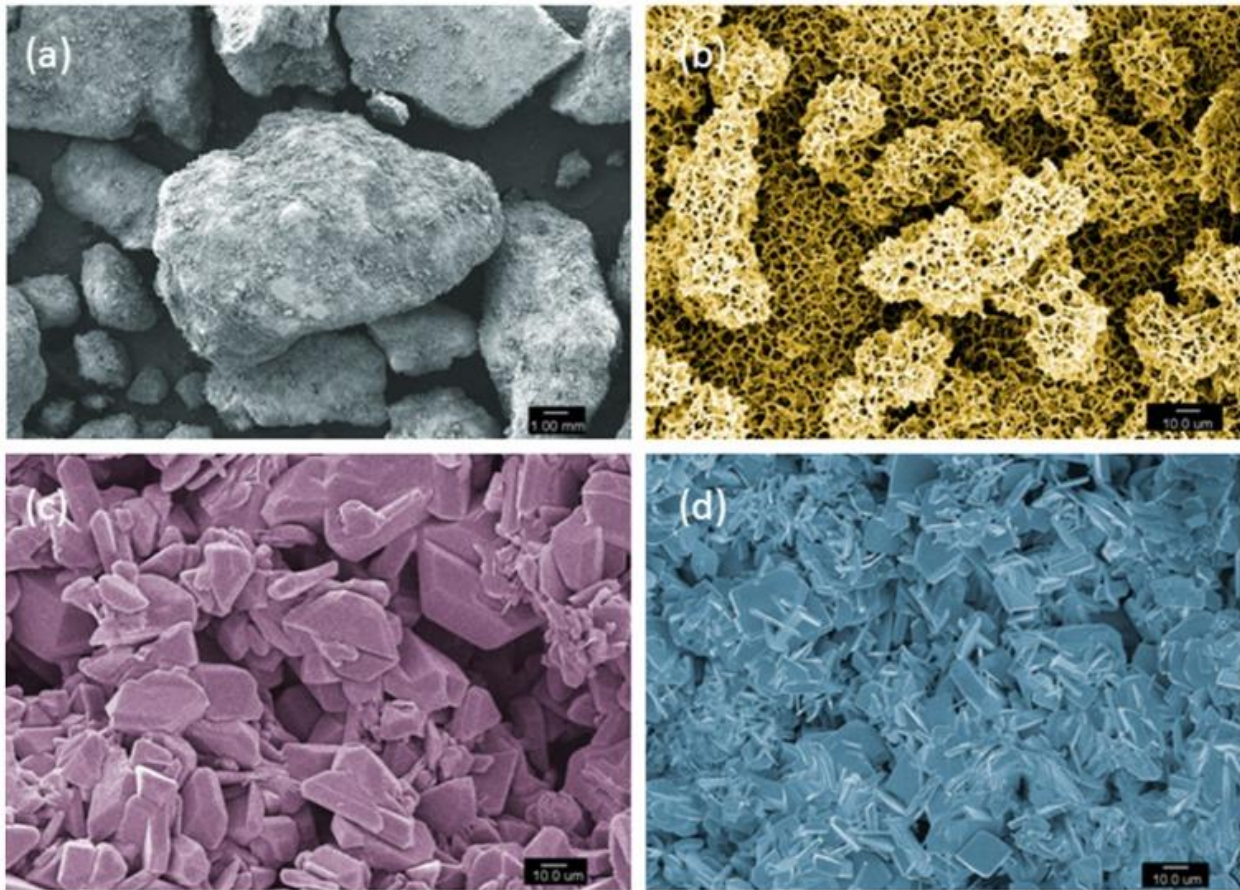
Bioceramics:

Ceramic biomaterials were initially investigated and used in the field of orthopedic surgery as an alternative to metallic biomaterials. Bioceramics are currently used for bone defect filling, fracture repair and stabilization and replacement of diseased bone tissues. Ceramic materials are biocompatible, have corrosion resistance and demonstrate tremendous bioactivity. Disadvantages of bioceramics include poor fracture toughness, brittleness and extremely high stiffness. The strength of degradable bioceramics is significantly lower than that of non-resorbable materials. Solution-driven and cell-mediated processes are considered to be responsible for degradation of bioresorbable ceramics. Lamellar bone replacement occurs after cellular degradation of the ceramic matrix has taken place. The biological behavior of bioceramics is dependent on the physical characteristics and chemical composition.

Tricalcium Phosphate

Tricalcium phosphate (TCP) is a resorbable and bioactive ceramic material (Figure 5a). TCP has two crystalline forms: 1. α -TCP and 2. β -TCP and the crystallinity and chemical

composition resembles closely to that of the mineral phase of bone tissue . TCP demonstrates a higher rate of biodegradation than hydroxyapatite after implantation in vivo which is regulated by a combination of passive dissolution and osteoclast mediated resorption . TCP has been used as synthetic bone defect fillers in dental maxillofacial and orthopedic application . TCP demonstrates osteoconductivity and active resorption due to its interconnected microporosity which plays a vital role in the graft-bone complex remodeling process . Preclinical experiments have shown TCP to almost completely resorb (~95%) after a month and half of implantation in rat tibias with new bone formation and marrow reformation . Similar bone in-growth has been observed for TCP implantation in cancellous bone in canine models . TCP bone replacement grafts have shown to be rapidly infiltrated with bone and slowly resorb by osteoclasts between 6 and 24 months .



Scanning electron microscope micrographs of (a) β -Tricalcium phosphate granules; 50 \times magnification; (b) Hydroxyapatite, 5000 \times magnification; (c) Dicalcium phosphate dihydrate crystals, 5000 \times magnification; (d) Dicalcium phosphate anhydrous crystals, 5000 \times magnification.

Conclusion

The development of biomaterials for bone repair devices and prostheses is a challenge from an engineering and biological perspective. In the field of biomaterials research, degradable materials for bone repair and regeneration are actively sought and generate a lot of interest since their biodegradable nature allows avoiding the second surgery and reduction in the pain and cost for patients. Natural and synthetic polymers and bioceramics are already in clinical use as biodegradable materials and magnesium based metals are a new class of biodegradable materials in development. The mechanical properties, biological behavior and biodegradation mechanism vary for different biomaterials. In comparison with polymers and bioceramics, the tensile strength and stress elongation of magnesium alloys is higher. The highest level brittleness is exhibited by the ceramic materials. From a biological perspective, it has been shown that more new bone is formed around bioceramics and magnesium alloys than around polymers. This can be attributed to It is expected that the next generation of biodegradable materials will demonstrate vast improvements in implant and biological tissue interfacing based on the knowledge gained from recent research. However, extensive work is required in order to obtain the ideal bone repair and regeneration biomaterials in the future.

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