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Review Article

Bioinert, biodegradable and injectable polymeric matrix composites for hard tissue replacement: state of the art and recent developments

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Abstract

The present review paper examines the use of different types of polymeric matrix composites in hard tissue replacement applications. The review presents the actual state of the art in the fields of bioinert composites for permanent applications, biodegradable matrix composites for temporary applications and the emerging area of injectable composites. In all cases some recent developments are also discussed. The paper starts with an introduction to locate the reader. Bone–analogue composites are then extensively discussed. Several other systems based on an inert polymeric matrix are described, focusing on their proposed applications. A great emphasis is afterwards given to biodegradable matrix systems. The most widely used synthetic bioresorbable systems are analysed and compared with an example of natural origin degradable composites–starch based composites. Finally, composite systems that are non-processable by melt based routes and in many cases injectable are discussed in detail, including several recent developments on this emerging area of research.

Keywords: Biomaterials; A. Polymer matrix composites; B. Mechanical properties; B. Microstructure; E. Injection moulding

Contents

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1. Introduction

The traditional definition of a composite material is a material with at least two phases, a continuous phase and a dispersed phase. The continuous phase is responsible for filling the volume and transfer loads to the dispersed phase. The dispersed phase is usually responsible for enhancing one or more properties of the composite. Most of the composites target an enhancement of mechanical properties such as stiffness and strength, but other properties may be of interest such as transport properties (electrical or thermal) or density.

Matrix materials for composites can be metal, ceramic, polymeric or biologic. Fig. 1 shows the relation between stiffness and strength for a number of materials of interest for biomedical applications. It can be observed that metals and ceramics are always stiffer and can have larger strength than biologic hard tissue. Polymers are mostly more compliant (lower modulus) than hard tissue and can have strengths of the same order of magnitude than hard tissue. Biological tissues show larger spectra of mechanical properties than the other materials. This picture clearly illustrates the great interest of compounding polymers and other materials to obtain composites that attain combinations of mechanical and biological properties similar to those of biological hard tissue.

As in other areas of biomedical research, nature is seen in the area of biocomposites as a guide to design new materials [1]. Mimicking the solutions found in natural materials is one of the most promising ways to reach the target set of properties needed in implant materials.

The development of materials for any replacement application should be based on the understanding of the structure to be substituted. This is true in many fields, but particularly exigent in substitution medicine. The demands upon the material properties largely depend on the site of application and the function it has to restore. Ideally, a replacement material should mimic the living tissue from a mechanical, chemical, biological and functional point of view.

Mineralised tissues such as bones, tooth and shells have attracted considerable interest as natural anisotropic composite structures with adequate mechanical properties. In fact, nature is and will continue to be the best materials scientist ever. Who better than nature can design complex structures and control the intricate phenomena (processing routes) that lead to the final shape and structure (from the macro to the ultrastructural level) of living creatures? Who can combine biological and physico-chemical mechanisms in such a way that can arrive to ideal structure–properties relationships? Who, else than nature, can really design smart structural components that respond, in-situ, to exterior stimulus adapting the microstructure and correspondent properties? In the described line of thinking, mineralized tissues and biomineralization processes are good examples to learn from for the materials scientist of the future. This is especially true for engineers that want to develop composites to replace mineralized tissues.

The main characteristics of the route by which the mineralised hard tissues are formed is that the organic matrix is laid down first and the inorganic reinforcing phase grows within this organic matrix. Oyster shells, coral, ivory, pearls, sea urchin spines, cuttlefish bone, are just a few of the vast variety of biomineralised materials engineered by living creatures. Many of these biological structural materials consist of inorganic minerals combined with organic polymers. The study of these structures has generated a growing awareness that the adaptation of biological processes may lead to significant advances in the controlled fabrication of superior

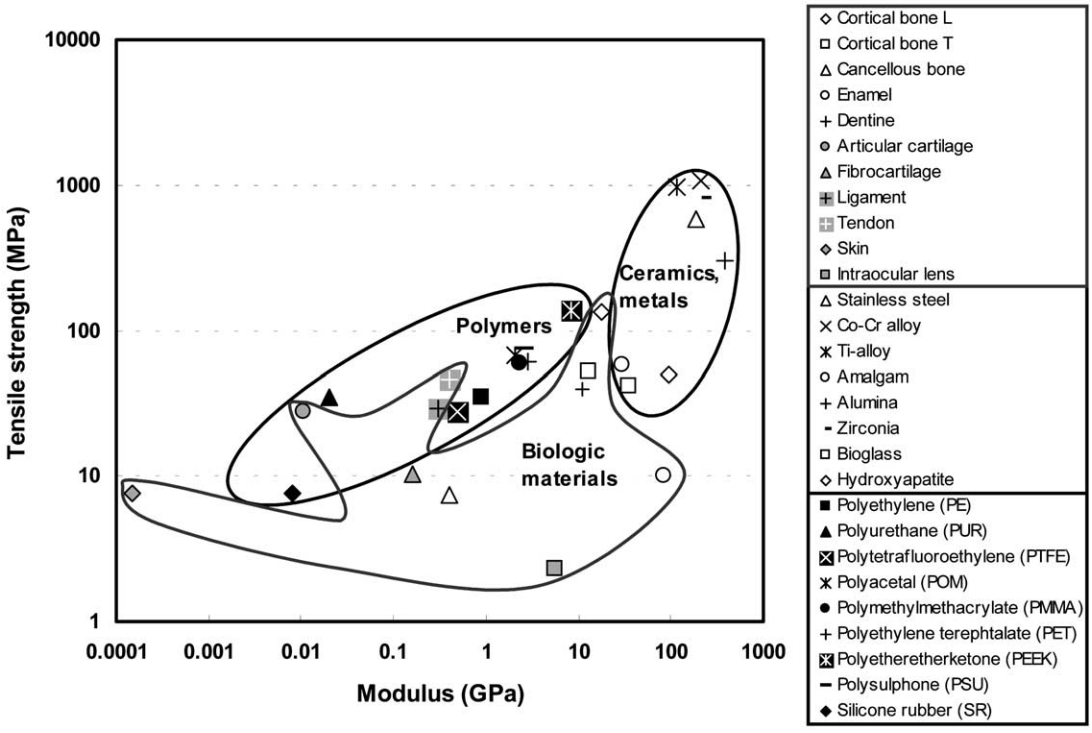

Fig. 1. Tensile strength vs. modulus of materials with relevance for composite design when considering biomedical applications (adapted from reference [7]).

smart-materials. To date, neither the elegance of the biomineral assembly mechanisms nor the intricate composite microarchitectures have been duplicated by non-biological methods.

Bone, for instance, is a composite with variable density ranging from very dense and stiff, the cortical bone, to a soft and foamed structure, the trabecular bone. Normally the outer part of long bones consists of cortical bone, the density decreasing towards the core, where the trabecular bone is found. The trabecular bone is porous and the porosity is filled with osseous medula. Structurally, the bone matrix consists of type I collagen fibres reinforced by hydroxyapatite nano-crystals precipitated along the collagen fibres e.g. [2,3]. The mineral part is responsible for the stiffness whereas the collagen is responsible for its flexibility. A demineralised bone becomes very flexible being easily twisted, whereas a bone without collagen is very brittle [4].

The major component of compact bone is called the osteon. Organised in concentric lamellar matrix, the osteons create cylindrical conduits known as Haversian canals, which provide access for the circulatory and nervous systems. The capillaries within the Haversian canals originate from arteries and veins within the marrow cavity. It is known that the structure of bones is continuously adapted to the stresses applied to it [5]. Thus, any substitution implant material, should be compatible and not disturb significantly the stress environment of the surrounding living tissue [6]. From all the above discussion it becomes evident how difficult it is to design and produce materials that can be used on replacement and fixation of bones or for filling bone defects, especially those that must work under load-bearing conditions. That explains why synthetic materials are only about 10% of the bone grafting market, where autografts and allografts still reign.

The following sections will describe the efforts focused on the development and processing of both bioinert and biodegradable polymeric matrix composites for replacement (long-term or temporary) of hard tissues. Special attention will also be given to injectable systems and to non-melt based processing techniques. The authors believe that both biomimetics and tissue engineering will play an increasing role on the development of novel materials for replacing mineralised tissues, but those topics fall beyond the scope of the present review.

2. Bioinert composites for permanent applications

2.1. Polyethylene-based composites

High-density polyethylenes (HDPE) with very high molecular weight fractions such as ultra high molecular weight polyethylene (UHMWPE) have found application as a load bearing material in joint endoprostheses [8–12]. The advantages offered by UHMWPE include [11] very good sliding properties, good impact strength,

good fatigue resistance and good biocompatibility. In the long term implantation, the behaviour of UHMWPE is compromised by its insufficient wear performance, low stiffness and high creep compliance. The attempts to enhance UHMWPE performance included crosslinking [13–17] and carbon fibre (CF) reinforcement [18,19]. For the latter case, improvements in strength, stiffness, as well as in creep resistance and fatigue strength have been claimed [18,19]. In spite of these results, another study [20] attributed a lower fatigue crack growth resistance and poor wear performance to CF reinforced composites as result of mechanical properties mismatch and lack of adhesion between the two phases. Another approach, based on the self-reinforcement of UHMWPE [21], showed superior tensile properties, creep resistance and impact strength with maintenance of wear properties for the self-reinforced UHMWPE composite material.

2.1.1. The bone analogue concept

Bonfield et al. [22–48] proposed the use of composites of HDPE with hydroxyapatite (HA), introducing the so-called bone-analogue concept. The research motivation was the development of new biomaterials having adequate biocompatibility and mechanical behaviour that allow for their use on load bearing applications. Historically, bone fixation and total joint replacement have been accomplished with the use of metals that exhibit a much higher stiffness as compared with the typical modulus of bone (between 7 and 25 GPa) [47–49]. Under loading conditions, the differences in stiffness between the bone and the metal originate a stress-shielding effect, making most of the load to be carried by the fixation device. This tends to promote the osteoporosis phenomena [50], compromising tissue healing. The starting point for the development of this bone analogue composite system was the definition of the respective mechanical performance requirements by assessment of the typical bone mechanical behaviour in the light of its intrinsic structure [24]. The attempts to replicate bone mechanical behaviour was based on the reinforcement of a ductile polymeric matrix (PE) with a bone-like ceramic (HA), in which the ceramic assures the mechanical reinforcement of the polymer and both the bioactive character and the biocompatibility of the composite [25–28]. Although not yet used in high load bearing applications, the composites of HDPE/HA are already used to produce middle ear implants, under the trade-name HAPEX® [46]. Alternative bioactive reinforcements have been also investigated for HDPE, namely bioactive glasses [51–53] and glass-ceramic [53–55]. Bioactive glass based composites exhibit lower stiffness as compared to HDPE/HA composites with similar HA content, but elicit a strong bioactive behaviour [51–55], making them specially suitable for soft tissue applications.

2.1.2. Mechanical behaviour dependence on interfacial interaction and HA particle characteristics

The HA particle size and the respective distribution have been recognized [29] as important parameters affecting the mechanical behaviour of HDPE/HA system. Apparently, smaller particle size leads to stiffer composites. Furthermore, the stiffness of HDPE/HA composites is proportional to the HA volume fraction [32]. Nevertheless, although the HA particles increase the material stiffness and enhance the creep behaviour, the higher the HA content, the higher the number of interfaces between the polymer and the ceramic, which has to be taken into account since failure can preferentially occur at the interface when the implant is under mechanical loading [30,31]. Several studies by Bonfield and co-workers [39–43] pointed out the low efficiency of the HA particles as reinforcement agents for HDPE, due to its inherent low aspect ratio and low degree of chemical interaction with the HDPE phase. Attempts [39–43] to enhance the mechanical performance investigated the chemical coupling of HDPE/HA composites by means of silane agents and acrylic acid grafting, allowed for the enhancement of strength and ductility, but did not improve consistently the stiffness [39]. The development of coupling methodologies that increase the adhesion of the HA particles towards the polymeric matrix is believed to be a possible route for the improvement of mechanical performance of these composites [45]. A parallel investigation [56] showed the effectiveness of silane coupling treatments to be dependent on factors such as the particle surface area, the particle size distribution and the chemical reactivity of the HA particles. Another study [57], also conducted by our research group, investigated the use of alternative titanate and zirconate coupling agents and concluded that the positive effect of these agents on stiffness and strength result from their dominant effect as HA dispersion promoters [57]. These coupling agents proved to be [58] clearly non-cytotoxic, which is a great advantage when compared to standard silane coupling agents.

2.1.3. Processing routes for the inducement of anisotropy: Hydrostatic Extrusion vs. Shear Controlled Orientation in Injection Moulding (SCORIM)

Attempts by Bonfield et al. [35–37] to develop bone-matching mechanical performance have relied on the inducement of a strong anisotropic character by means of hydrostatic extrusion. The application of this solid-state processing technique has enabled for the attainment of significant improvements in the composite stiffness. Values of modulus up to 13 GPa could be reported [37]. A complementary approach has relied on the reinforcement of the HDPE/HA composites with high modulus HDPE fibres (HMPE) [31,38]. In this case, the use of very stiff and chemically compatible fibres allowed for further improvements of mechanical

performance. Values of stiffness and strength within the typical range of mechanical performance of human bone have been reported with values of 17 GPa and 113 Mpa respectively [38]. An alternative approach to the mechanical performance enhancement of HDPE/HA composites was followed by Reis and co-workers [57,59] with the use of shear controlled orientation injection moulding (SCORIM). SCORIM operation is based on the application of a macroscopic shear stress field at the melt/solid interface of the polymer during the moulding cycle. This moulding technique proved to be a successful approach for the inducement of an anisotropic character to high density polyethylene [60] and in the respective composites reinforced with HA [57,59]. Values of stiffness between 5 and 7 GPa have been reported [57,59] for HDPE/HA composites. X-ray diffraction patterns and calorimetric studies on SCORIM processed HDPE have revealed respectively signs of C-axis orientation parallel to flow direction and high levels of crystallinity [60]. Several studies [57–59] revealed the existence in SCORIM mouldings of a typical laminated morphology indicating a high level of anisotropy, which was found to be more evident for higher molecular weight PE grades [59]. The higher anisotropy of higher molecular weight materials is confirmed by X-ray diffraction and results from the extensive shish-kebab formation during shear application [60,61]. These studies show the relative importance of the molecular weight characteristics of the HDPE on the attainment of high anisotropic bone-analogue composites. Fig. 2 presents a scanning electron microscopy photograph of a tensile failure surface of a SCORIM processed HDPE, where a concentric laminated morphology is evident. Table 1 summarises the mechanical properties of HDPE/HA composites in terms of their stiffness and strength for conventional injection moulding, SCORIM and also hydrostatic extrusion.

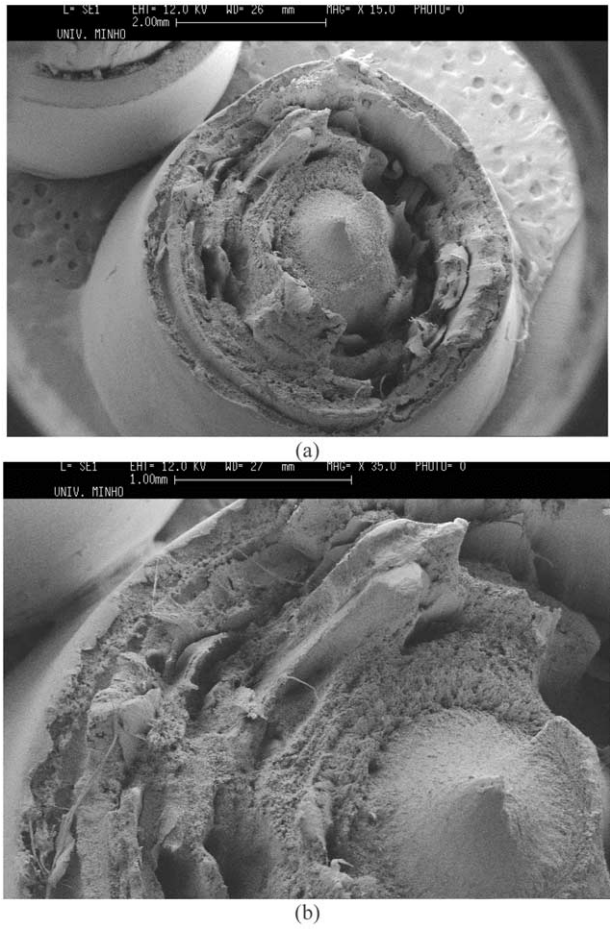

Fig. 2. Scanning electron micrographs of the tensile failure surface of a SCORIM processed HDPE: (a) great view and (b) detail. The concentric laminated morphology exhibits significant anisotropy and develops during the application of a shear stress field to the moving melt-solid interface during cooling.

2.1.4. Hybrid composites based on HDPE/HA composites

In order to overcome the limitations of HA reinforcement of HDPE, Sousa et al. [62,63] investigated the selective replacement of the HA particles in the bulk of moulded parts, where its use is not needed or advantageous, by a very stiff filler, such as short CFs. This would be a possible approach for the development of mechanically strong biocompatible composites. Efforts have been made in order to develop sandwich mouldings comprising a HDPE/HA composite outer layer and a HDPE/C fibres composite core [63]. Upon mechanical testing, the bi-composite sandwich mouldings exhibit two distinct modes of fracture: a relatively brittle fracture associated to the HA filled surface layer and more ductile fracture mode related to CF reinforced moulding core [63]. As a result of the HA loading, these sandwich

Table 1
Reference mechanical properties in terms of the modulus (E), and tensile strength (TS) for HDPE/HA composites[a]

	Conventional injection moulding		SCORIM		Hydrostatic extrusion	
	E (GPa)	*TS* (MPa)	*E* (GPa)	*TS* (MPa)	*E* (GPa)	*TS* (MPa)
HDPE	1.2–1.5	25–100	3.0–7.1	Up to 155	–	–
HDPE/HA	1.6–4.0	35–39	5.9–7.5	Up to 91	13–17	Up to 113

[a] Adapted from References [37,38,57,59,61,64].

bi-composite mouldings exhibit a clear in-vitro bioactive behaviour, which indicates that an in-vivo bone-bonding behaviour can be eventually expected for these materials.

As in typical injection mouldings, the properties of such bi-composite parts vary along the moulding. As an example, rectangular cross-section impact test bars were injection moulded. Ten sample layers, with thickness of ~0.9 mm were obtained by cutting a bar along its length. Each sample was analysed by dynamic mechanical analysis. The storage modulus, E′, at 23 and 37 °C (for a frequency of 1 Hz) is plotted in Fig. 3, as a function of the distance of the centre of the sample relatively to the centre of the original sample bar. The storage modulus corresponds to the real component of the complex modulus, being a measurement of the stiffness of the material. As expected, the stiffness is minimum at the edges of the sample, because one is essentially measuring the HDPE/HA layer. E′ increases as one goes though the centre due to the stiffer HDPE/C material. However, at the mould centre, the corresponding layer exhibit a lower E′, being assigned to the less fibre orientation as compared to the region next to the HDPE/C phase. In fact, the inner HDPE/C phase, possess a skin-core morphology, where higher fibre orientations are achieved at the skin regions.

2.2. Other inert polymer composite systems in hard tissue substitution

2.2.1. Polymer composite systems

Generally, tissues are grouped into soft and hard tissues. Bone and tooth are examples of hard tissue whereas skin, blood vessels and cartilage are examples of soft tissue. Accordingly, hard tissues are intended to support loads, being stiffer (higher elastic modulus) and stronger (higher tensile strength) than soft tissues. The need for mechanical compatibility with hard tissue makes metals and ceramics to be many times considered more suitable than polymers for those type of applications. However, this is not true in many cases, basically because metals are much stiffer than human hard tissues and ceramics are not only more brittle but also stiffer than natural mineralised tissues. On the other hand unreinforced polymers are typically more ductile but not stiff enough to be used to replace hard tissues in load-bearing applications. Nevertheless, polymer based composites can be designed to meet stiffness and strength requirements for hard tissue substitution. Several examples of different systems will be discussed in this review.

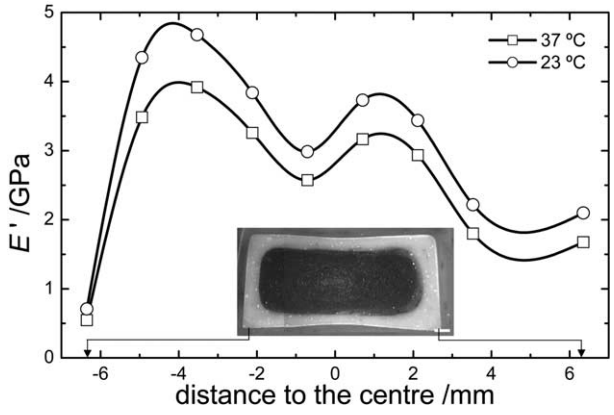

Fig. 3. Micrograph showing the cross-section of a bi-composite bar (cross-section dimensions: 6×12.7 mm^2). The dark region correspond to the CF reinforced moulding core whereas the HA filled surface layer appear as the clear region. Graphics–Storage modulus of samples obtained from cutting an original bi-composite bar though vertical lines over the cross-section, as a function of the distance to the mould centre of the initial bar. The tests were performed using a DMA7e Perkin-Elmer equipment, in a three point bending mode.

The discontinuous phase of polymer composites can be of the same nature or, more commonly, of a different type of material. Polymer matrix composites are being increasingly studied for different applications ranging from coatings, load-bearing implants or biosensors [65]. Examples of polymers proposed as matrices in biomedical composites include poly(methylmethacrylate) (PMMA), polysulfone (PSU), poly(etheretherketone) PEEK or Epoxy resins. The requirements for a polymer material to be used in those applications include fatigue resistance, resistance to ageing in saline aqueous media, biocompatibility, dimensional stability, absence of migrating harmful additives and being sterilisable by standard methods without loss of properties. The biocompatibility requirement includes that the material and its additives are accepted by the surrounding tissue without toxic, inflammatory or allergic reaction [66].

The most common reinforcements for polymer matrix composites are glass and CFs. Other synthetic reinforcements are also available such as aramid fibres (Kevlar) as well as natural fibres such as bamboo [67]. The most interesting reinforcement materials for bone related implants or tissue substitutes are bioactive fillers. Examples of those bioactive fillers are HA and bioactive glasses. Bioactive glass is a special type of glass which has affinity with mineral bone, enabling to obtain both mechanical reinforcement and bioactivity in polymer matrix composites (e.g. [68,69]). Those reinforcements have been subjected to extensive research effort in recent years.

The greatest advantage of composite materials is that they offer the possibility of tailoring its properties by playing with the volume fraction of the discontinuous phase, dimension of the particles (particularly when in fibre form), and its orientation [70]. This way it would be possible to avoid the mismatch stiffness between the properties of metal implants and bone, leading to the stress shielding effect [71,72]. One of the key parameters in controlling the successful design of polymer matrix composites is the efficient control of the interface between the continuous phase (polymer) and the discontinuous phase (reinforcement).

The most promising polymer composites as alternatives to metal based implants such as plates, pins or nails are carbon or glass fibre reinforced PEEK, PSU or Epoxy. Other systems with potential for those applications include the same polymer matrix materials but reinforced with HA and bioactive glasses. Those systems and its properties will be discussed in the following sections of this review.

2.2.1.1. Polysulfone (PSU) composite systems. Medical grades of polysulfone are commercially presenting as combining high strength, being biologically inert, displaying unique long-life under sterilization procedures and being resistant to most common hospital chemicals [73].

Latour and Black [74] studied the effect of simulated in vivo environments such as saline and exudates on the fibre/matrix interfacial bond for PSU composites reinforced with carbon and polyaramid (Kevlar 49) fibres. They observed significant degradation of the interface properties under fatigue stresses and attributed the degradation to the effect of water and salt ions. The CF/PSF interface experienced fatigue failure at approximately 10^5 load cycles at a maximum applied load level of only 15% of its ultimate dry bond strength without indication of an endurance limit being reached. Those results raise some important questions regarding the durability of CF/PSU composite in load bearing orthopaedic applications.

In a study aiming at using polysulfone for the cultivation of osteogenic cells (preosteoblast-like MN7 cells and primary bone marrow fragments) it was observed that the material did not interfere with the proliferation in early stages of bone-forming cells [75]. However the polymer prevented the final steps of matrix formation as measured by collagen synthesis and matrix mineralization. The data reported argues against polysulphone as a material for orthopedic implants.

Marcolongo et al. [76] examined the bone tissue response to a bioactive glass fibre/PSU composite implant. Bone tissue exhibited direct contact with the glass fibres and adjacent polymer matrix and displayed a mechanical bond between the composite and bone tissue after 6 weeks. The fibres resorbed to different degrees and were replaced by calcified tissue resulting in interfacial bond strengths which were significantly higher than all polymer controls after the 6 weeks implantation.

2.2.1.2. Carbon fibre reinforced polyetheretherketone (CF/PEEK) systems. PEEK compounds are high performance engineering polymers and offer good biocompatibility and tolerance by in vivo tissue [77–81]. Zhang et al. [82] studied the long-term compressive properties under physiologic saline conditions of AS4/APC-2 PEEK-61% in volume continuous CF unidirectional composites. It was shown that the material has high stability and applicability for structural permanent orthopaedic implants. Brown et al. [83] reported similar behaviour in the case of short CF reinforced PEEK showing that it does not undergoes degradation of the interface and mechanical property loss under saline environments. However it should be noted that short CFs do not allow to obtain so high stiffness and strength as with continuous fibre composites.

Recently, Abu Bakar et al. [84] proposed the use of HA/PEEK composites for orthopaedic implants for bone substitution. This work highlighted the mechanical properties achieved by reinforcing PEEK with thermal sprayed HA particles. The materials were firstly compounded and then injection moulded. The mechanical properties were shown to increase monotonically with the reinforcement concentration, with a maximum value in the study of 40% volume fraction of HA particles. The range of stiffness reported of 2.8–16.0 GPa and of strength 45.5–69 MPa crossing the lower bound of the properties of human bone (7–30 GPa, 50–150 MPa, respectively).

Wear between bone and CF/PEEK composites is an active area of research (e.g. [85,86]). Fretting and sliding abrasive wear tests resulted in the composite material exhibiting a lower wear rate than titanium-alloys. Currently, studies are underway to develop PEEK reinforced with braided CF structures [87].

2.2.1.3. Carbon fibre reinforced epoxy systems. CF reinforced epoxy is radiolucent, heat-resistant, extremely strong and light (its density is 20% that of steel), has a modulus of elasticity close to that of bone, and an established biocompatibility [88]. The biocompatibility of CF reinforced epoxy composites has also been reported in a number of works [89–91]. Fujihara [92] has reported that composites made of braided carbon fibres and epoxy resins have better mechanical properties than composites made of short or laminated unidirectional fibres. He has also demonstrated that braided fabric reinforced composites made of carbon fibre and epoxy resin could be used to produce bone plates.

The use of a semi-rigid carbon fibre reinforced epoxy plate was tested over a mean follow-up period of 3.3 years for cranioplasty. Five patients, all of whom were elderly women with severe osteoporosis and highly restricted mobility showed no adverse reactions to the plate. It was concluded that prefabricated CF/Epoxy medical grade implants can be considered as an alternative to conventionally clinically utilised materials [93].

2.2.2. Internal fixation of bone fractures

The study of polymer composites for hard tissue applications has been mostly directed to joint prosthesis, bone plates and nails. Of those, the most important

and demanding applications are the hip and knee prosthesis. Key requirements for the materials in those applications besides the biocompatibility and stress protection during healing include the fatigue fracture resistance and wear resistance. We will review some of the implants in use and the attempts to use fibre reinforced polymer composites in those highly demanding applications.

Internal fixation requires the use of implants to keep bone fragments together and include the use of pins, nails, screws or plates. Non-resorbable materials are temporary implants that may be removed after successful healing of the bone fracture. Plate and screw fixation is the most popular method of rigid internal fixation of bone fracture. They are mostly made of stainless steel, Cr–Co or Ti alloys [94,95]. This fixation is intended to provide resistance to dynamic stresses allowing the bone to heal and avoiding the formation of callus at the fracture site. The rigid fixation however, may be responsible for bone atrophy caused by the stress shielding effect previously mentioned [69]. In fact, studies have shown that the magnitude of bone atrophy in Ti alloy (110 GPa) plates is smaller than the one observed in stainless steel plates (210 GPa) [69,96]. This observation suggests that plates with closer stiffness to the one of bone would minimise the stress-shielding effect. Furthermore some concerns subsist about the immuno-inflammatory response of soft tissue around stainless steel and Ti implants [97–99].

2.2.2.1. Total hip replacement. Modern total hip arthroplasty has been performed using femoral stems manufactured from stainless steel, cobalt–chrome molybdenum alloy (CoCrMb), titanium aluminium vanadium alloy (TiAlV), and, on a limited basis, polymer matrix composites. Today, only CoCrMb and TiAlV are used in significant numbers [100]. There is ample theoretical, experimental, and clinical evidence to support TiAlV as the material of choice for cementless femoral stems, based on superior mechanical compatibility and biocompatibility. The primary advantage of TiAlV over CoCrMb is a lower modulus of elasticity when compared with stainless steel. This results in decreased stress shielding and subsequent favourable femoral remodelling around the implant. This effect is more significant with the smaller stem sizes used in primary surgery but persists even with larger stem sizes used in revision surgery. The second advantage of TiAlV is its biocompatibility. Titanium–aluminium vanadium alloy is of relatively low–toxicity in concentrations found clinically, and TiAlV is inert in the physiologic environment. With regard to fixation in cementless total hip arthroplasty, TiAlV has been shown to achieve excellent bone ingrowth into porous surfaces. In addition, there is evidence of superior bony ingrowth into TiAlV as compared with CoCrMb. Titanium–aluminium–vanadium alloy is presently the material of choice to be used in conjunction with hydroxyapatite coating. Prosthetic design, stem diameter, and porous-coating applications play significant roles in bony response regardless of metal composition.

Hedia et al. [101] performed a material optimisation study of the femoral component of a hip prosthesis based on the fatigue notch approach. The overall objective of the optimisation was to maximise the stresses supported by the proximal bone whilst at the same time constraining the stress field at all cement interfaces to be no greater than its initial value. The results of the first study suggest that Young's moduli of about 145 and 210 GPa are optimal for the monolithic metal and optimised stems, respectively. A composite prosthesis with a layer of modulus 31 GPa added to the optimised stainless steel stem in the proximal region only, was found to significantly increase the stresses in the proximal bone and reduce the stresses in the cement whilst retaining the advantages of an outer stem profile very similar to that of the original metal prosthesis.

A comparative stress analysis of a polymeric composite hip joint replacement was performed by Akay and Aslan [102]. A prototype short carbon-fibre reinforced PEEK prosthesis was manufactured by injection molding. Finite element analysis was conducted on intact femurs and femurs fitted with the CF/PEEK and the titanium prostheses under various loading conditions. Finite element models were validated by experimental strain gauge measurements by using synthetic femurs. Agreement between the two methods was obtained except in the hoop strain of the femur in the calcar region because of the assumption of the isotropic material properties. The stem stresses were lower for the CF/PEEK prosthesis than for the titanium prosthesis. The maximum stress was in the spigot of the CF/PEEK prosthesis, but in the middle third of the stem of the titanium prosthesis. Stress generated in the cement was almost equal for both prostheses although more load was transferred, via cement, to the femur with the CF/PEEK prosthesis because the load transfer took place over a larger area.

Jacobsson et al. [103] compared two cementless femoral components, a composite stem and the more rigid metal design, in a randomised, prospective study of 56 patients with a mean follow-up of 4 years. Patients were matched in 28 pairs, and one of each pair was treated with each femoral component. The composite stem gave fewer signs of stress shielding radiologically, but showed significantly inferior results at the 2-year and 3-year follow-up in terms of patient pain. The overall failure rates for the femoral components were 43% for the composite and 11% for the metal. These results contrast with those of earlier experimental and clinical studies, in which isoelastic composite/bone properties appeared to be advantageous.

2.2.2.2. Unicompartmental and total knee replacement. There is some evidence for a large unmet need for these surgeries [104], and with the ageing of the population it is likely that demand will increase [105]. There are unsolved problems with these procedures. The knee replacement is not totally safe, having a significant incidence of peri- and post-operative mortality and morbidity. Those operations are expensive, and the relative cost-effectiveness of surgery when compared with more conservative interventions, still needs to be shown. There are a proportion of patients who do not obtain the great benefits in pain and function or in whom the prosthesis fails after a relatively short time [106]. Thus, there is a need to learn how to improve the value of knee replacement surgery, aiming at improving materials, design and surgical methods to maximise patient benefit.

Knee replacement surgery is indicated on the treatment of severe knee arthritis [107]. A variety of recent reviews have been published concerning both unicompartmental and total knee replacements [108–110].

A trial was made to use polyethylene and CF/polyethylene composite materials for knee replacement [111] the result not being promising. Those results hindered further research on the application of composites for total knee replacement.

2.2.2.3. Screws, plates, nails. A composite material of PEEK and short, chopped E-glass fibres was used to produce a segmental bone replacement implant [112]. Composite materials were chosen because their properties can be tailored to match the requirements. Material selection was accomplished with the aid of modeling software, which predicted the composite properties based on its composition and fibre directional parameters. The moulded parts were characterized both destructively and non-destructively. The results of tensile tests performed on moulded parts were comparable to those using commercially supplied samples.

A method of securing CF-reinforced epoxy bone plates with CF polysulfone expanding rivets was investigated [113]. Six CF-reinforced epoxy bone plates were secured to rods with CF polysulphone rivets and six were secured with standard cortical stainless steel screws. These constructions were then subjected to pure torsional load to failure. The CF expandable rivets failed at a greater torsional moment making them attractive for this application.

The suitability of a braided CF-epoxy composite for bone plate application was studied by Veerabagu et al. [93]. They have shown, based in finite element calculations, that the strain and stress supported by those plates is able to overcome the stress shielding problem without leading to fibre/matrix debonding on the composite.

Schandelmaier et al. [114] studied the biomechanics of femoral interlocking nails. They concluded that it is the profile which is decisive for the torsional stiffness of femoral locking nails in the bone implant complex. The presence of a slot in the profile is of special importance. Unslotted nails have a significantly higher torsional stiffness than slotted nails.

Al-Shawi et al. [93] reported the use of carbon fibre reinforced epoxy plates for periprosthetic supracondylar femoral fractures. The plates were made by pressurized heat lamination of carbon fibre sheets preimpregnated with epoxy resin and placed in a mould in a predetermined order and orientation. The advantages are highlighted in fractures involving poor-quality bone and particularly in the treatment of distal femoral fractures in the elderly. In their study the patients were elderly with marked osteoporosis and with poor mobility.

2.2.2.4. Spinal implants. Rivard et al. [115] proposed a new spinal implant system (SIS) without fusion (bone graft). In an FDA recommended in vivo testing (animal model), it was assessed whether the PEEK polymer could be used in a SIS without any harm of wear debris to the nervous tissue (spinal cord and nerve roots). Evaluation took place at 1, 4, and 12 weeks' post-surgery. The macroscopic and semiquantitative histologic analyses of the spinal cords (dura mater) showed normal vascularization and particle adherence to the connective tissue especially at the injection sites. Neither necrosis nor swelling of the dura mater and nerve roots was observed. Those results give good indications about PEEK polymer effect on the spinal cord and thus it seems usable as component in the spinal implant system.

3. Biodegradable composites

3.1. Synthetic bioabsorbable polymers

Much research work has been devoted to the production of bioabsorbable surgical devices that could avoid a surgical operation for their removal, thereby reducing the pain of the patients and the total cost of the treatment when compared, for example, to the use of metallic devices. In this case, the stress-shielding phenomena associated with the use of rigid metallic implants could also be minimised. The continuous degradation of the implant causes a gradual load transfer to the healing tissue, preventing stress-shielding atrophy and stimulates the healing and remodelling of the bone. Some requirements must be fulfilled by ideal prosthetic biodegradable materials, such as biocompatibility, adequate initial strength and stiffness, retention of mechanical properties throughout sufficient time to assure its biofunctionality and non-toxicity of degradation by-products [116,117].

Poly(α-hydroxy esters), such as poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA) or their copolymers,

poly(DL-lactic-co-glycolic acid) (PLGA) are among the few synthetic polymers approved for human clinical uses, including those for small load-bearing applications [118,119]. As seen further in the text, they exhibit biocompatibility, biodegradability and are easily processed by conventional melt based routes. A review of the general properties of lactic acid based polymers can be found elsewhere [120,121]. The different ways of producing such materials, such as polycondensation, ring-opening polymerisation, chain extension and grafting, are also presented in that work. The main features of PGA, and especially its application for devices in trauma and bone surgery, were reviewed by Ashammakhi and Rokkanen [122].

Other materials of relevance includes poly(ortho esters), poly(glycolide-co-trimethylene carbonate), poly(p-dioxanone), poly(anhydrides), poly(ε-caprolactone) (PCL), poly(β-hydroxybutyrate) (PHB) and poly(PHB-hydroxyvaleric acid). A list of references on those materials can be found in ref. [117]. A review of the synthesis of different biodegradable polymers can also be found elsewhere [123].

3.1.1. Degradation of Poly(α-hydroxy esters)

L-Lactic acid occurs in the metabolism of all animals and microorganisms, and thus, it is in theory an absolutely non-toxic degradation product of (co)polylactides. Glycine is ultimately formed during degradation of PGA which can also enter the tricarboxylic acid cycle and be metabolised into water and carbon dioxide. There is a general consensus that degradation of poly(α-hydroxy esters) in the aqueous media proceeds via a random, bulk hydrolysis of the ester bonds in the polymer chain. This process is catalysed by the ends of the carboxylic chains that are produced during the ester hydrolysis [124]. During degradation, the soluble oligomers which are close to the surface of the piece leach out towards the aqueous medium faster than the chains located inside the matrix. This gradient of concentration in acidic groups leads to the formation of a skin composed of less degraded polymer [125–127]. The existence of diffusion of the degraded products explains the delay between the decrease of mechanical properties and decrease of molecular weight. PLA is much more hydrophobic than PGA due to the additional methyl group in the structure of PLA. Therefore PGA degrades much more quickly (a few weeks [128,129]) than PLA, which can remain stable for over 1 year [130], or more depending on its degree of crystallinity. Copolymers of PLA and PGA do not have interpolated properties of the pure components: for example, copolymers containing equal ratios of PGA and PLA degrade faster than pure PGA.

The degradation in semi-crystalline polyesters undergoes preferentially within the amorphous regions because of a higher rate of water uptake than the crystalline regions. The degraded segments could then diffuse and give rise to recrystallization; this increase of crystallinity during hydrolytic degradation can be detected from the whitening of the specimens [131].

3.1.2. SR-composites from Poly(α-hydroxy esters)

PLLA have intrinsically interesting mechanical properties with an approximate tensile modulus of 3–4 GPa, tensile strength of 50–70 MPa, flexural modulus of 4–5 GPa, flexural strength of 100 MPa and a strain break of about 4% [120,132,133]. The mechanical properties of PLLA may however vary with molecular weight and crystallinity [134]. For PGA, the tensile modulus and strength can reach 6–7 Gpa and 60–100 MPa, respectively, and a strain at break between 1.5 and 20% [132,133,135]. Again, such values are highly dependent on the molecular weight and crystallinity. The mechanical behaviour of such materials is not enough to be used is many orthopaedic applications, such as for the fixation of fractures and osteotomies and as interference screws for ligament repairs.

Alternative processing routes of poly(α-hydroxy esters) have been proposed in order to produce specimens with enhanced mechanical properties. It was shown that PLLA and PGA fibres exhibiting an high orientation structure can be produced by mechanical deformation, using well-known processing methods from the polymer technology, such as oven drawing, zone drawing, zone annealing, die drawing, hydrostatic extrusion or rolling. For example, by melt-spinning, fibres of PLLA can present 390–1800 MPa of tensile strength and 6.5–9.3 GPa of tensile modulus [136–140]. By solution-spinning, PLLA fibres can reach 560–2300 MPa of tensile strength and 9.6–16 GPa of tensile modulus [136,141]. PGA can also be spun into the fibre form, when the molecular weight is 20 000 to 145 000 [142].

The sintering of such fibres at high temperature and pressures allows to produce composite devices (that can be, for example, rods, screws, tacks, plugs, arrows and wires) in which the polymer matrix is reinforced with the same material [143–145]. Such self-reinforced (SR) materials exhibit a significant mechanical improvement over all mechanical properties, relatively to the corresponding isotropic materials. For example, Manninen [146] reported a study from Pohjonen et al. [147], where injection moulding PGA, sintered SR-PGA and hot-drawn PGA rods with 2 mm diameter presented bending modulus of 7, 10 and 13 GPa; bending strengths of 218, 260 and 330 MPa and shear strengths of 95, 192 and 260 MPa, respectively. For SR-PLLA screws, very good initial properties could also be observed, with bending moduli of 7 GPa; bending strength of 200 MPa and shear strength of 110 Mpa [145]. The shear strength decreased to 65 MPa (76 MPa in vitro) and 35 MPa (80 MPa in vitro) after 12 and 24 weeks of degradation in vivo conditions. This clearly demonstrates the more

aggressive effect felt by implants on in vivo conditions. Another study of in vivo and in vitro (static and dynamic) degradation in polylactides were reported by Mainil-Varlet et al. [148], where parameters such as crystallinity, molecular weight, mechanical properties and morphology are followed against degradation time. Data on degradation of PLA, PGA and other polymers where also collected by An et al. [117], being possible to observe that the degradation time of biodegradable pieces in vivo could depend strongly on their geometry and test conditions. Another study by Törmälä et al [149] on SR-PGA rods demonstrated that the strength of some specimens could be retained over 8 weeks.

The degradation time of implants may have implications in the tissue reactions on the degradation products. If the degradation is fast, the degradation products may not have time enough to be absorbed, due to poor vascularization or low metabolic activity. For example, PGA implants have been found to produce fluid-filled sterile sinuses with subsequent drainage, due to increase of osmotic pressure or pH [150,151]. This could happen 8–16 weeks after the operation [152]. As PLLA implants degrade much more slowly (SR-PLLA may take up to 5–6 years to resorb completely) they are more tolerated by the organism. Of course it is quite arguable if something that will remain for such a long time in the organism will ever be resorbed and if it should be considered as a resorbable implant. However, it is clear that the more amorphous PDLLA resorbs over 2–3 years and the liberated crystallites could induce an inflammatory response [117]. This well known inflammatory response, and the typical pH drop associated with PLA and PGA implants is one of its major drawbacks. These materials are still the gold standard in applications of biodegradables in medicine, but this drawback may hinder their increased use in applications such as tissue engineering scaffolding. In addition, it was shown that the surface morphology or the wettability in PLLA films could influence the inflammatory response [153], and typically cells do not attach well to PLA and PGA based materials. A fairly complete revision of the inflammatory reaction in animals and humans upon a number of materials can be found in ref. [117].

SR composites can be used in a variety of applications, such as in bioabsorbable fixation in fracture treatment or in other orthopaedic surgery fixations. They have been used since 1985 and the number of operations with such materials has exceeded 300 000 [152]. One can use such systems in glenoidal rim fractures, fractures of the proximal and medial condyle of the humerus, fractures of the lateral humeral, femoral and tibial condyle, fractures of the olecranon, radial head and distal radius, fractures of the hand, metartarsal bones and phalanges of the toes, fractures of the femoral head and neck, fractures of the patella and displaced ankle fractures [117,152,154]. Other examples of the use of bioabsorbable fixation of bone in osteotomies, arthrodesease and other reconstructive surgeries can be found in the review by Rokkanen et al., which included applications in orthopaedic surgery and traumatology in children [152].

These bioabsorbable implants have the advantage to be able to be combined with drugs or other active substances that facilitate or accelerate tissue healing and they have themselves osteostimulatory effect. They offer thus considerable advantages to be used in arthroscopical and other minimum-invasive surgical techniques [152]. Nevertheless the low water-uptake of this type of polymers does not allow for using swelling as a parameter on the design and tailoring of the release profiles of bioactive agents from these materials.

3.1.3. Poly(ε-caprolactone)

Poly(ε-caprolactone) (PCL) is also a semicrystalline aliphatic polyester, highly compatible with osteoblasts [155]. PCL exhibit high crystallinity and is highly hydrophobic, thus having lower biodegradation in vivo than PLA [156]; therefore PCL is an interesting material for application requiring long degradation times. As for the other mentioned polyesters, the degradation in vivo of PCL also involves random hydrolytic chain scission of the ester linkages. Despite the modest mechanical properties (tensile modulus of 200–440 MPa and tensile strength of 20–42 MPa), PCL has been used in different biomedical application, such as in scaffolds for tissue engineering of bone and cartilage [157]. To improve the mechanical properties, PCL has been blended or copolymerised with other polymers, such as PLA or PLGA [158–160]. Due to the relatively low melting point, PCL may be easily processed by conventional procedures. Therefore, PCL may be easily filled with stiffer materials (particles or fibres) and processed by melting techniques. Again the major drawbacks of these materials are its too slow degradation in-vivo, and the poor cell adhesion and proliferation on their surfaces, which combined limit their biomedical applications.

3.1.4. Polyactive™

Polyactive™ is the trade name of a biocompatible block copolymer composed by a soft, amorphous, hydrophilic, poly(ethylene glycol), PEG, and hard, semicrystalline, hydrophobic poly(butylene terephthalate), PBT [161]. Some years ago it has been claimed [162,163] that if the weigh ratio of PEG/PBT is higher than 55/45, the material has bone bonding ability and is simultaneously biodegradable. Unfortunately, for such ratios the copolymer has poor mechanical properties. However, other authors stated later on that such copolymer is not, in fact, osteoconductive (e.g. [164]). Even the investigators that originally developed such systems stated more recently that a biomimetic coating

of the copolymer with a bone-like apatite layer [165] would be needed for the polymer to disclose an in-vivo bone bonding behaviour.

The inclusion of hydroxyapatite (HA) particles has been shown to be an interesting way to improve stiffness, offering at the same time an enhancement of osteoconductivity. Interfacial bonding between HA and the copolymer may be induced by using polyelectrolydes on the HA particles, such as polyacrylic acid and poly(ethylene-co-maleic acid) [166,167]. The coupling of polyactive™ on the surface of the HA particles could also be improve via hexamethylene diisocyanate [168]. It was found that both tensile strength and Young's modulus could be significantly improved by the introduction of such chemical linkage. Besides Polyactive™, other polyether-polyester block copolymers have been produced. An interesting example is the PEG/PLA copolymer, which have been reported in the literature (see for example ref. [169]).

3.1.5. Bioactive composites

There are several advantages in incorporating bioactive ceramics into biodegradable polymers, in order to produce hybrid materials. As for non-degradable polymeric matrix composites, calcium phosphate particles, such as hydroxyapatite (HA) or tricalcium phosphate (TCP), would improve osteoconductivity and bone bonding properties [170]. Furthermore, the biocompatibility could be enhanced as the ceramic particles that induce an increased initial flash spread of serum proteins compared to the more hydrophobic polymer surfaces [157]. Additionally, foreign body reaction due to the release of acidic degradation products could be also minimised by the buffering effect of the basic resorption products of HA or TCP [171,172]; the ceramic can act as hydrolysis barrier, delaying the degradation of the polymer [173]. The auto-generated increase of local acidity due to degradation, for example, of PLA could enhance solubility of the ceramic that could be used in new bone formation [174].

The most currently studied bioactive degradable composites are obtained by combination of poly(α-hydroxy esters) and HA; combinations with PCL were also proposed [175]. For completely absorbable bioactive implants one should use bioresobable ceramics such has non-sintered HA, tetracalcium, octacalcium phosphate and especially TCP [176–178]. A ceramic used to reinforce polylactides with a three- or fourfold higher in vitro solubility than α-TCP should be mentioned in this context [179,180]. The obtained composites presented suitable degradation characteristics and interesting mechanical properties, in the range of cancellous bone.

It was shown that the spread of attached human osteoblasts onto PLA and PCL films reinforced with sintered and non-sintered HA is higher than for the polymers alone [181]. Also in that work, biochemical assays relating cell activity to DNA content allowed to conclude that cell activity is also more intense for the composite films. Cell culture tests on a composite of TCP and a polylactide were also reported [176]. Also in this case, the composite showed no cytotoxicity and evidenced good cell attachment to its surface.

The poly(α-hydroxy esters)/HA composites are mainly prepared by incorporating the ceramic into a polymeric solution. The gels suspensions of HA, which may easily exhibit good dispersion of particles, may then be dried under vacuum. The resulting solid composite may be shaped using different processing techniques. One can also obtain the composites by mixing HA particles with L-lactide prior the polymerisation [173]. An interesting list of references assigned to the different ways of preparing such composites may be found in a work of Durucan and Brown [182]. Nevertheless, it should not be forgotten that typically non melt based routes lead to the development of systems with lower mechanical performance and many times require the use of toxic solvents and intensive hand labour.

One of the PLA/HA composites showing highest mechanical properties was developed by Shikinami and Okuno [183]. The initial bending strength of 280 MPa exceeds the bending strength of cortical bone (120–210 MPa); this strength could be maintained above 200 MPa up to 25 weeks in phosphate-buffered saline solution. Moreover, the modulus could reach 12 GPa [183], one of the highest stiffnesses reported in bioactive polymers. Such composites were obtained from precipitation of a PLLA/dichloromethane solution, where small granules of uniformly distributed unsintered HA microparticles (average size of 3 μm) can be obtained [183]. Unfortunately the authors do not give many details on both the extrusion and compression moulding processing of the material. Moreover, it would be also interesting to try to develop such kind of biodegradable materials using melt based processing techniques, that may prevent the use of solvents, with possible toxic effects and will eventually generate systems with a better mechanical performance. It was suggested that PLLA pieces alone requires a period of time to achieve the possibility of hydrolysis into the inner core; however, for the composites, the samples could be filled quickly with water and homogeneous hydrolysis could proceed. More complete tests on the biodegradation of the HA/PLLA composite rods in subcutis and the medullary cavities of rabbits were investigated mechanically and histologically [184]. The degradation was found to be faster for the case of using uncalcinated HA instead of calcinated particles.

The non-inflamatory response of the tissues pointed out for the bioactive behaviour of the implants [184]. In fact, in a more detailed study, it was found new bone formation at 2 weeks after implantation, especially for the formulation with highest HA content [185]. In that

work, direct bone contact with the composites, without intervening fibrous tissue, was detected by SEM. Another work [186] gave further indications for the bone bonding capability of such composites, where the loads required to detach plates fixed on the surface of the bilateral tibial cortices in rabbits were measured at 4, 8 and 25 weeks after implantation. For any implantation time, the bonding strengths in the composites were always greater than for the pure PLLA implants. In this context, the bioactive character of the composites was also verified by the formation of HA onto their surfaces after 7 days of immersion in simulated body fluid [183]. It should also be referred herein that bone-like apatite layers could be deposited on PLA fibres from a biomimetic process [187]. In that case, the fibres should be previously immersed in a simulated body fluid with ion concentrations nearly 1.5 times of those in the human blood plasma.

A good strategy to improve even more the mechanical properties of bioabsorbable materials could be the combination of previously oriented polymeric fibres with the ceramic particles. Materials based on the concept of self-reinforcement, using polylactides, with the addition of TCP or HA were studied using conventional mechanical testing [188] and dynamic mechanical analysis [189]. Typically, the flexural modulus increased from ~6.5 GPa, for the case of pure polymer, to 7–8 GPa for the case of the composites. On the other hand, the flexural yield stress increased from ~65 MPa, for the unfilled material, to 70–80 MPa, for the 70% by weight HA content composite, and 80–100 MPa, for the 70% by weight TCP composite. We can thus conclude that at this point these composites exhibit less mechanical performance than the bioactive composites developed by Shikinami and Okuno [183]. However, the concept of combining self-reinforcement and ceramics seems to have great potential and there are certainly technical aspects related with the composition and the processing that could be improved.

An important aspect that should also be addressed in more detail is the interfacial properties between the ceramic and the matrix phases. It also appears that this issue has been neglected in the context of absorbable composite despite a lot of effort has been done in the enhancement of the interfacial adhesion in conventional polymer matrix composites (e.g. [56,57,190]). A recent study pointed out for the importance of measuring the fibre-PLLA matrix interface adhesion using both microbond and fragmentation methods [191]. Fibres of carbon, absorbable calcium carbonate, PGA and chitin were used. This study included the monitoring of the interface performance during in vitro hydrolysis. The importance of the chemical treatment of the CFs in polylactide composites has been investigated by looking at their mechanical properties, including the study of the influence of the in-vitro degradation [192,193]. Such kind of studies should be, in the authors' opinion, carefully extended to ceramic/polylactides composites.

The discussion up to now has been mainly devoted to the development of compact composites. However, porous bioabsorbable materials have gained increasing interest, especially in the area of tissue engineering [194]. High porous, synthetic, three-dimensional scaffolds can serve as the growth substrate for osteoblasts or osteoprogenitor cells. In fact, polylactides have been studied as scaffold materials for applications in bone tissue engineering [195]. However, there is a need for enhancing the mechanical properties of such systems. Therefore, porous composite materials of polylactide/HA have been proposed to overcome this problem, increasing also the osteoconductivity of the scaffolds [196–198]. These scaffolds could improve, for example, the bulk penetration of osteoblasts into the inner pores, where in pure PLLA scaffolds the osteoblast attached primarily on the outer surface of the foam [197]. Also the number of cells was always higher in the composite scaffolds during 6 weeks of in vitro cultivation [197]. It is clear from these studies that also in the area of bone tissue engineering bioactive composite systems offer in many cases better properties than those of pure polymeric materials.

3.2. Starch based degradable polymers as an example of natural origin systems

Biopolymers are an important source of materials with a high chemical versatility and with high potential to be used in a range of biomedical applications. Many of them are readily available and their properties may be easily changed by different physical and chemical methods. This enables tailoring of important properties such as the water-uptake capability, degradation kinetics or the mechanical properties that will target the desired specifications for a given application. Natural based materials are also usually biocompatible and non-cytotoxic due to their similarity with living tissues.

A great number of different natural based materials have been studied and proposed for different biomedical uses, namely polysaccharides (starch, alginate, chitin/chitosan) or proteins (soy, collagen, fibrin gels) and, as reinforcement, a variety of biofibres such as lignocellulosic natural fibres. Good reviews have described the properties of such systems (e.g. [116,199]), and this would be beyond the scope of this review. In this review we will be discussing only starch based polymers, as an example of natural origin polymeric matrix composites that have been proposed for biomedical applications. Such systems have been emerging recently as candidates for being used in different applications, such as in scaffolding for the tissue engineering of bone and cartilage, materials for bone fixation and replacement as well as for filling bone defects, carriers for the controlled release

of drugs and other bioactive agents, and new hydrogels and partially degradable bone cements.

3.2.1. Starch and starch based materials

Starch designates the major polysaccharide constituent of photosynthetic tissues and of many storage organs in plants. Starch consists of a mixture of amylose, a linear macromolecule consisting of α-(1→4)-glucan, with amylopectin, a highly branched macromolecule that consists of a α-(1 > 6)-glucan with α-(1→6) linkages at the branch points [200–202]. In vegetables, starch is produced in the form of granules that can vary in terms of size and composition [200,201,203]. In plants, starch is found as semicrystalline granules, containing both crystalline and amorphous domains, in three main overall crystalline variants: A (cereal), B (tuber) and C (smooth pea) [202]. The semicrystalline starch can be disrupted by extrusion technology with the appropriate combination of shear, temperature and plasticizers [202], in a process designated as gelatinisation. Gelatinisation is also achieved by low temperature methods based on the use of solvents [204].

Within the plastics technology field, starch or starch based plastics have been studied as biodegradable or partially biodegradable materials for replacing and decreasing the environmental impact of traditional commodity plastic materials [202,205,206]. Several studies [207–215] described the processing and/or the properties of starch materials containing plasticizers, designated as thermoplastic starch (TPS). Although conventional processing routes such as extrusion or injection moulding can be used for these materials, the associated thermo-mechanical environment induces structural modification and eventual degradation of the starch [216–220]. Various works reported the development of mixtures of starch with other polymers such as cellulose acetate (CA) [221], PCL [222,223], ethylene vinyl alcohol copolymer [224–231], ethylene-vinyl acetate copolymer [232–235] and low density polyethylene (LDPE) [236–239]. Several starch based blends are commercially available under the tradenames Mater-Bi and Bioplast, from Novamont (Italy) and Biotec (Germany) respectively [221,240], among many others.

3.2.2. Starch as Biomaterial

Starch-based polymers present an enormous potential to be widely used in the biomedical field, as these natural polymers are totally biodegradable and inexpensive when compared to other biodegradable polymers available [203,207]. Reis et al. [241] proposed the blends of starch with (1) ethylene vinyl alcohol copolymer (designated as SEVA-C), (2) cellulose acetate (SCA), (3) polycrapolactone (SPCL) and (4) poly(lactic acid) (SPLA) as potential alternative biodegradable materials for a wide range of biomedical applications [241–263]. These blends exhibit a bioactive behaviour by means of adequate ceramic loading with fillers such as HA [241–246] and bioactive glasses [248,249], or by means of biomimetic routes [250] coupled with a degradation behaviour when immersed in simulated physiological media [251–253]. These materials exhibit a biocompatible behaviour demonstrated by several in vitro [255–257] and in vivo studies [257]. These characteristics justified their study for a broad range of applications such as bone fixation/replacement applications [242–249], bone cements [258,259], drug delivery devices [260,261] and tissue engineering scaffolds [255,262,263].

3.2.3. Structure development of starch based blends

The consideration of starch based systems as potential biodegradable biomaterials for tissue replacement/fixation, or as tissue engineering scaffolds to be applied in load-bearing sites demands a compatible mechanical performance with human bone, i.e. a bone-matching mechanical performance. The research approach to develop such mechanical behaviour in compact starch based materials relied on two approaches: (1) the combination of the biodegradable system with a bioactive reinforcement and (2) the inducement of a deliberately orientated morphology during the respective processing operation [241–247]. The use of non-conventional processing techniques on SEVA-C and SEVA-C/HA composites was studied by Reis et al [241–244] that reported an enhancement of the mechanical properties following application of shear controlled orientation in injection moulding (SCORIM). The combined use of twin-screw extrusion (TSE) in the compounding stage and of SCORIM in the moulding process allowed for the development of starch based composites with an induced structural orientation and high mechanical performance [241–244]. The improvements in mechanical performance observed with SCORIM application were attributed to the solidification of the polymer under a controlled macroscopic shear field that induces orientation of the molecular structure. This has been observed for starch based materials in a study [247] focussing on the SCORIM processing of SEVA-C, where the solidification of the polymer in an extended state, as imposed by the shear field applied during SCORIM was observed to increase molecular orientation, crystallinity and consequently the stiffness and strength of SEVA-C.

3.2.4. Influence of bioactive fillers

The incorporation of bioactive fillers such as HA [243–246] or bioactive glasses [248,249] in SEVA-C aims to assure the bioactive behaviour of the implant and to provide the necessary stiffness within the typical range of human cortical bone properties. For SEVA-C, the increase in HA content leads to a desirable increase in stiffness [244–246]. Maximum values of stiffness above 7 GPa were reported for a HA weight content of 30% by

weight [244]. However, the reinforcement of SEVA-C with particles such as HA affects the typical rheological behaviour of the blend, which demands for a careful optimisation of the processing parameters during injection moulding [247]. For composites filled with bioactive glass particles, the mechanical performance was also shown to be dependent on bioactive glass contents [248]. Values of 3.5 GPa and 51 MPa were reported respectively for tensile modulus and strength for composites of SEVA-C filled with only 10% by weight Bioglass® particles [249]. Bioactivity tests have shown that the reinforcement with bioactive fillers such as Bioglass® or HA particles is efficient to assure the desired bioactive behaviour of the composite [246,249]. However, the efficiency of the two fillers is considerably different. SEVA-C/Bioglass® composites displays a bioactive behaviour above 10% weight Bioglass® [249], while the same behaviour is only observed, in the case of SEVA-C/HA composites, for 30% weight [246]. In any case the required filler amount is much less than it has been reported for other systems that are not capable of up-taking water.

3.2.5. Degradation behaviour and biocompatibility of starch based blends

The blends of starch with ethylene vinyl alcohol copolymer (SEVA) when immersed in a simulated physiological solution exhibit two modes of degradation behaviours [242]: a weight loss associated to the leaching of plasticizer and other low molecular weight additives and a weight loss associated to the intrinsic chemical degradation of the polymer. These polymers are also enzimatically degraded [242] in the presence of α-amylase that can be found in human saliva, blood or pancreas. For SEVA-C, the degradation behaviour evidences a dependence on the molecular weight of the blend, being more pronounced for lower molecular weight materials [242]. The leaching of plasticizer and other processing additives occurs in two stages, the first stage occurs for times of immersion between 0 and 6 days [253], which causes a steep decrease in sample weight, and a second stage for times of immersion between 6 and 15 days, for which the weight loss levels off. The enzymatic degradation takes place more prominently in a third stage, becoming evident for times of immersion above 15 days [253]. The typical final degradation products are low molecular weight starches, fructose and maltose. These products are clearly biocompatible and do not lead to any inflammatory response. Concerning biocompatibility, SEVA-C and SEVA-C/HA composites exhibit a non-cytotoxic behaviour [256,257], inducing a satisfactory tissue response when implanted as shown by in-vivo studies [257]. Furthermore, the SEVA-C/HA composites induce a positive response on osteoblast-like cells to what concerns cell adhesion and proliferation [256]. Although, SEVA-C appears to be less cytotoxic than SCA, comparative studies indicate a better cell adhesion to compact SCA substrates [256], including porous SCA scaffolds [255]. Cytotoxicity tests have shown that the composites of SCA with HA have a similar response to the one observed for SCA [256].

4. Composite systems non-processable by melt-based techniques

Although in the previous sections we have shown that melt-based, polymer matrix composites are being increasingly accepted as the best alternative for hard tissue replacement, there are several clinical situations on which they cannot be used. As an example, injectable systems may be preferred when the fracture, defect or hole must be fixed and posses mechanical resistance immediately, when it is in a position difficult to reach or has a complex shape or simply because of the ease handling and implantation of these systems. Moreover, some materials are not able to be melt processed, either because their processing temperatures are so high they would degrade before melting (softening) or because they are designed to incorporate substances that do not stand high temperatures (proteins, drugs, etc.); in those cases alternative methods should be used.

Despite this review paper dealing mainly with polymer-matrix composites, injectable systems presenting ceramic matrix and the polymer as the dispersed phase were also chosen to be included in this section for a couple of reasons: they were developed exactly to minimize some of the disadvantages of polymeric based bone cements; the matrix in these systems is the same material used as dispersed phases in some polymer–matrix composites; and they present properties that make them more useful for other kind of applications (different than those of their polymer-based counterparts). Therefore, their inclusion in this review is aimed at giving the reader a more complete picture of the different materials, properties and applications (load bearing, non-load bearing) that can be obtained with injectable composites.

This section then is divided in three parts: (1) injectable composite systems with ceramic matrix,; (2) injectable composite systems with polymeric matrix; and (3) composites processed by other techniques.

4.1. Injectable ceramic-based systems

When polymers are incorporated into a ceramic matrix, the resultant materials combine the flexibility of polymer fabrication and modification with the reinforcing effects and bioactive behaviour of ceramics, being ideal for hard tissue replacement. They become stronger due to the bridging effect exerted by the macromolecular

chains on the ceramic crystals. So far, although these composites present advantages over the monolithic injectable ceramics, there are yet some drawbacks that must be overcome.

Calcium phospate cements (CPC) were developed in the late 1980s [264] and, although being an excellent alternative to conventional acrylic bone cements in terms of osteoconductivity (they set inside the body to form HA) and thermal damage (the setting occurs at or near body temperature), they are whashed-out due to their long setting time and to the penetration of body fluids before setting completely. So, despite the formation of hydroxyapatite (HA) in vivo during setting of CPC being attractive as a hard tissue subsitute (since it occurs at body temperature and pH and without immune response), the material suffers from the same brittleness problems as the pre-shaped products, being useful only for space-filling. To solve these problems, useful alternatives are fast setting CPC (which sets much faster than conventional CPC materials) and the preparation of composite cements by the addition of polymeric viscous gels (which reduce the liquid penetration to the cement paste) into the liquid component of the cements [265,266]. The combination of both approaches is being increasingly studied, as will be shown in the next paragraphs.

TenHuisen and Brown [267] studied the effects of gelatin on the kinetics of HA formation and on the microstructure of HA which is formed. The effect on the rate of formation, on the solution chemistry and in the microstructure of the composite compared to the pure CPC was negligible. The only observed difference was the presence of gelatin interconnecting the HA clusters. However, the composites were produced without mixing of the components, only addition of the gelatin solution on the solids, what is a very different condition when compared to the intense mixing occurring during CPC composite preparation. And of course the preparation method could influence negatively the obtained results.

Sodium alginate (alg) was also proposed as the polymer component [268,269]. While the conventional CPC (c-CPC), after 1 week of implantation, induced a severe inflammatory response and was completely crumbled, the so called anti-washout type fast-setting CPC incorporating sodium alginate (aw-FSCPC(alg)) showed no inflammatory response and did not crumble; one explanation was the fast rate of HA formation in the latter cement [270]. This phenomenom would additionaly result in higher mechanical properties since the initial stages after implantation.

Later the interest moved to chitosan(chi), because it has more pharmacological benefits for bone formation than the alginate [271]. The authors studied the soft tissue response to aw-FSCPC(chi) and tried to understand the origins of the good response to CPC, by using different organic compounds [266]. In spite of the fast transformation to apatite being claimed as the origin of the good tissue response to these cements, they showed, by comparison with composite cements with citric and acrylic acids, that the dominant role was played by the fast setting (that is, high initial mechanical strength). However, this is a necessary, but not sufficient, condition for this behaviour.

When implanted in tibia, the composite was surrounded by thin fibrous tissue, while particles of the c-CPC were scattered and surrounded by foreign body reaction giant cells [265]. These results agreed with previous ones obtained by the same group where severe inflammatory response 1 week after subcutaneous implantation was found only for c-CPC, not for the composite with alginate [272]. However, although aw-FSCPC(chi) showed better soft tissue response, it did not promote bone formation when compared to c-CPC. One possible reason could be the very low amounts of chitosan used (approximately 0.14%), what could not have sufficient pharmacological effect to regenerate bone. Mickiewicz et al. [273] also prepared composites of CPC incorporating different water soluble polymers (polyelectrolytes, proteins and neutral polymers). The polymers that did not promote any improvements in mechanical properties, and did not change the morphology of the cement, only induced a crystal growth relative to the pure cement. On the other hand, those who did increase compressive strength gave rise to nanocrystalline agglomerates, smaller and more interpenetrated than the other composites, which could explain their improved properties. However, the solid/liquid ratio was not kept constant for the different formulations, and this parameter is known to play an important role in the mechanical properties. And, although the compressive strength was found to increase up to six times, the best systems presented setting times 30 to 230% higher than the commercial cement, what is also an important point to consider regarding injectable systems.

Fujishiro et al. [274] also developed a CPC/gelatin gel composite (since this gel possesses good cell affinity and forms a viscous gel with water). Indeed, the addition of the gel confered stability to the composite in simulated fluids, increased the compressive strength (up to 5% of gelatin gel) and promoted a time dependence of compressive strength similar (but with values always higher) to the cement without gel.

Daculsi et al. [275,276] developed a composite injectable bone substitute (IBS) based on biphasic calcium phosphate, BCP (60% HA + 40% β-TCP), and 2% aqueous solution of methylhydroxypropyl cellulose (MHPC) that hardens in situ and was said to be perfectly biocompatible, resorbable and easy to fit bone defects (due to their initial plasticity). They found that the best ratio BCP/solution was 65/35. Regarding cytotoxicity, although direct-contact assays showed no

differences among the composite, its components and the control, the extracts of the composite or BCP showed inhibition of cell proliferation. Anyway, bone ingrowth was observed at the same time resorption of calcium phosphate ceramic occurred.

Later, they studied the interactions between the two phases. After mixing, there was a decrease in the mean diameter of BCP granules, and this influenced the viscosity of the paste [277,278]. They found dissolution of grain boundaries (specially of those without lattice continuity) and of β-TCP crystals during interaction of MHPC and BCP and precipitation of apatitic crystals on HA crystals surface. Both phenomena were responsible for the observed granulometry changes [275].

Although the fabrication of injectable ceramic based composites in most cases improved the mechanical properties of the system and provided the material with resistance to fluids penetration, these achievements were limited by the amount of polymer that can be added to the paste. Mickiewick et al. [273], for instance, reported that after a critical concentration (that depended on the type and molecular weight of the polymer, but was always around 10%), the polymer started forming a thick coating on the crystal clusters, preventing them from interlocking, originating plastic flow and, as a consequence, decreasing mechanical properties. Fujishiro et al. [274] also reported a decrease in mechanical properties with higher amounts of gel, which was attributed to the formation of pores due to leaching of gelatin in solution. Therefore, it seems that mechanical properties, although improved by the addition of polymers, are still a limitation for the application of ceramic-based injectable systems in load-bearing sites.

4.2. Injectable polymer based systems

Although polymers offer several advantages over injectable ceramics, such as easier tailoring of mechanical properties and degradation times [279] and possibility of functionalization to interact specifically with certain cell types (due to the widely varied polymer chemistry) [280], they yet suffer from problems like low (or no) ability to bond to bone and not enough mechanical properties for the desired (hard-tissue replacement) application.

In spite of polymethylmethacrylate (PMMA) based bone cement being currently the most widely used polymer-based injectable, biodegradable materials, as in other biomedical applications, offer several advantages and, for that reason, are being increasingly studied. Poly(propylene fumarate) (PPF) has been proposed as a substitute to PMMA in partially degradable bone cement [281]. PPF is an unsaturated polyester with double bonds that can be crosslinked in vivo by different monomers [281,282]. Gerhart et al. [281] compared an experimental biodegradable bone cement (PPF-MMA) with a commercial one in terms of antibiotic release from the cement and mechanical properties, finding that the experimental one achieved and mantained considerably higher antibiotic levels for a longer duration than the commercial one. However, although the initial mechanical properties of the cements were good, they decreased by a factor of 12 just 4 weeks after implantation. To solve that problem, they developed a composite with TCP and CaCO3 as fillers, which hardens in 24–36 h, had properties much higher than human trabecular bone and workable enough to be packed in defects of complex shape [281]. They found that compressive strength and resistance to degradation increased with increase in MMA concentration. The calcium dissolved from the composite, although not directly proportional to degradation time, helped to keep the pH at higher values (as compared to the control). Thus, the composite seemed to be compatible with bone remodeling [283].

Later on, He et al. [284] studied the effect of double bond ratio and β-TCP content on crosslinking and mechanical characteristics of PPF-based injectable composites. The increase in double-bond ratio and/or the addition of β-TCP resulted in an increase of mechanical properties. An important advantage of this system over other polymer-based injectables is the very low temperature of reaction (crosslinking) which was always lower than 40 °C. However, even with the filler, the mechanical properties were still too low to be suitable for bone replacement or cements.

In vitro studies in formulations including also a porogen agent showed that increase in PPF molecular weight or incorporation of β-TCP increased the mechanical properties and that the formulations maintained the minimum requirement for replacement of human trabecular bone during 7 weeks [285]. There are, however, a threshold molecular weight above which the number of crosslinked double bonds per PPF chain is independent of the chain length, therefore the molecular weight does not affect the compressive properties, but does affect the heat released during crosslinking and the gel point [286]. Due to continued crosslinking during immersion in phosphate buffered saline (PBS), these materials presented an increase in mechanical properties during the first weeks of implantation, being claimed as the first biodegradable materials with these properties [287]. After in vivo implantation no sample were mechanically intact beyond 3 weeks [288]. The β-TCP concentration altered greatly the mechanical properties; in fact, without the ceramic the formulations remained stable for only 1 day. Histological evaluation showed an initial inflamatory response followed by a formation of thin fibrous capsule encasing the samples. However, although the material is claimed to be injectable, it was crosslinked (18 h), UV-sterilized (1 h) and aged (2 h) at room temperature prior to implantation (as a pre-shaped cylinder) [288].

Partially degradable polymer–polymer composites were also produced by the incorporation of up to 23% by weight of poly(caprolactone) (PCL) in the solid phase of acrylic-based bone cement formulations [289], aiming at producing injectable systems for drug delivery in non- or small-load bearing applications. The vancomycin release was much improved (comparing with a pure PMMA control) and the lower polymerization temperature was better for the incorporation of the drug, but the mechanical properties were negatively affected by the PCL.

Another partially degradable innovative bone cement was developed by Reis et al. [259], who used a totally new approach. They used a natural-origin polymer (a polymeric blend containing corn starch) as the solid phase and an hydrogel forming monomer (acrylic acid—AA) in the liquid phase, together with the MMA monomer. Due to the ductility of the system, up to 30% by weight of HA could be added to the solid phase without deleterious effects on the mechanical properties. Indeed, significant improvements were found in both tensile and compressive modulus, and, by playing with the solid/liquid ratio, the tensile and compressive strengths could also be improved. Moreover, an apatite layer was formed as early as 7 days of immersion in simulated body fluid, and this layer thickened with longer immersion times. The authors concluded that 20% by weight of HA was the optimized amount for this system. This type of system presents also other advantages. It is partially degradable, allowing for bone ingrowth into the degradable phase original location facilitating the fixation of the prosthesis due to an interlocking effect. Also the water-uptake capability of these bone cements facilitates the release of antibiotics or other bioactive agents incorporated on the bone cement, being simultaneously less aggressive to the surrounding tissues. Finally nothing is changed on the concept and application of the cement, which helps on introducing it into clinical practice.

As the several alternatives (partially or fully degradable polymers, injectable ceramics) did not yet present properties that make them suitable for being used as bone cements, the inert acrylic-based systems continue to be the best formulation. But, due to their lack of fatigue resistance and bioactivity, the incorporation of fillers (specially bioactive fillers) seemed to be an appealing approach to improve their behaviour. Several authors [290,291] incorporated bioactive particles in bone cement, but the results were not satisfactory due to deterioration of mechanical properties after adding a large amount of the particles or lack of bioactivity when the amount was low. Sogal and Hulbert [290] added HA to two commercial bone cements and found that the ultimate tensile strength decreased even for small filler loadings (10%).

A group from University of Kyoto has been deeply involved in studying novel formulations with bioactive particles. They incorporated apatite–wollastonite (AW) glasses (AWG) and glass–ceramics (AWGC), glass beads (GB) and HA on bisphenol-α-glycidyl methacrylate-based resin (Bis-GMA), and explained the bioactivity of their systems in the following way [292]: there is a formation of an uncured surface layer (due to inhibition of polimerization by oxygen) that results in uncovering naked bioactive powders on the surface; these incompletely polimerized oligomers are leached from the surface and the exposed bioactive filler allows the formation of a dense and uniform apatite layer, due to its high bioactivity.

The interfacial failure load (on the cement–bone interface) was found to be in the order abraded > uncured > > cured surfaces [293]. At both abraded and uncured surfaces the bioactive particles are exposed to the bone, but in the second case the interface is weaker, proably due to leaching of unpolimerized monomer.

Because of this mechanically weak interface, they developed a novel formulation consisting of bioactive fillers (AWGC, GB, HA), PMMA powder and MMA resin [294]. This PMMA-based cement is advantageous over the bis-GMA one because it raises less concerns regarding the compatibility issue and has less residual monomer after polymerization. The materials containing GB had better mechanical properties than the others (because of the smaller spherical shape and the glassy phase that resulted in good silane treatment) and higher bioactivity. Besides, they decreased the maximum temperature of polymerization (T_{max}) and the residual monomer content.

Shinzato et al. [295] showed that the compressive strength, the bending modulus and the affinity index (a measure of the length of bone in direct contact with cement) increased with increase in the glass beads up to 70% by weight. This high loading did not cause deleterious effects on the handling properties of the cement.

After soaking in water at 75 °C for 5 days, bone cements with less than 0.2% of silane coupling agent had better mechanical properties; the same behaviour was observed in the affinity index of implanted specimens. This was attributed to the fact that a monolayer of the silane coupling agent formed around the glass beads when its concentratin was 0.2%; with thicker layers (higher concentrations of the agent) the ion transport (necessary for bone formation) was disfavored, leading to lower osteoconductivities [296].

The particle size of GB was also studied [297]. As the smaller ones have a larger surface area, this may help expose more bioactive surface on the surface of the cement, creating more contact with the bone. The mechanical properties also increased with decreasing particle size due to improvement of filling effect. However, as small particles may cause strong foreign body reaction, care should be taken to avoid their separation

from the bone cement surface. As they found degradation of glass beads due to increased filler loading, the use of small beads also could be advantageous since it is possible to reduce the load while keeping the mechanical properties and osteoconductivity.

When implanted in sites exposed to mechanical stress, the cement still bonded to bone, but the affinity index was lower than for the cement in non-load bearing conditions, probably due to micromotion between cement and bone at the interface [298].

Mousa et al. [299] added AWGC to several commercial bone cements and also prepared a novel formulation. The commercial bone cements with the ceramic had improved mechanical properties over the conventional ones, but the best formulation was the one with intermediate molecular weight of the PMMA powder and smaller particle size.

This extensive work performed by the group of Kokubo [292–299] originated a composite cement with excellent mechanical properties, osteoconductivity and handling properties suitable to be used as injectable materials. However, the very high loadings suggested (70% by weight) for an already brittle material increased the fracture toughness and the stiffness at the cost of decreasing the ductility, what could not guarantee a good performance of this bone cement. Moreover, this much higher modulus, when compared to the conventional bone cement, brings a negative effect: the stress shielding of bone, leading to bone resorption that was also caused by the increase in the intraosseous pressure after implantation [298]. In conventional PMMA cement, the soft tissue layer formed between it and the bone due to its lack of osteoconductivity may have alleviated this congestion, so that no bone resorption was observed. A final remark should be made regarding the lack of measurements of mechanical properties in the long-term (mainly fatigue resistance). It has already been shown that the addition of filler such as HA, although positively affecting the flexural strength and modulus, reduced the number of cycles to failure in fatigue tests [300]. An alternative to increase the fatigue resistance of bone cements is by the using of fibres such as titanium fibres, which were shown to increase both the number of cycles to failure [301] and the fracture toughness of notched specimens [302]. The reinforcing effect of the fibres increased with decreasing stress intensity and were further improved by the use of centrifugation, showing an additive effect between these two treatments [301]. However, the addition of fibres is even more limited than the addition of particles, since they severely decrease the handling and flow of the paste [291,302].

HA was studied as a filler for improving bioactivity and mechanical properties by other authors, also presenting good results. This ceramic is a well-known biocompatible, osteoconductive and osteophilic material [291,303]. These are due to the chemical similarity of the synthetic HA with the one present in the bone and to the high chemical reactivity of its surface, both characteristics resulting in its ability to strongly bond to bone (osteoconductivity). This behaviour makes the material very advantageous to be used in hard-tissue replacement composites. However, due to the brittleness of the HA and to the lack of interaction with polymer (if no coupling agent is used), the filler may present deleterious effects on the mechanical properties (when added at high loadings). Therefore only limited amounts of HA can be incorporated into PMMA bone cement. And, as the proportion which can be included while maintaining mechanical strength or handling properties are small, the increase in bioactivity (provided by the ceramic) is not likely to be very large [291]. Therefore, alternatives like efficient ways to bond HA to the matrix or the development of new matrix systems are being studied, as it will be shown in the next paragraphs.

Dalby et al. [304] studied the effects of the incorporation of only 17.5% by weight of HA into PMMA: besides providing higher levels of human osteoblast-like cells (HOB) proliferation and phenotype expression, exposed HA particles served as preferential anchoring of HOB cells and either were entrapped by these cells or induced them to produce cristalline particles. In another study [305], the authors demonstrated that, although both conventional and composite bone cements were able to support normal osteoblast cell growth, full confluence was achieved earlier (7 days) on the PMMA/HA cement, while polymer was still visible through the cell layer on the plain cement. But this increase in biological properties did not result in an increase of mechanical strength, and a balance point between the two should be found.

Similar biological behaviour was found by Moursi and colleagues [306] when studying PMMA with 20% by weight HA. After 8 days of osteoblast cell culture, proliferation on the composite was significantly higher than on PMMA and the osteoblasts showed a more distinct networked pattern of organized fibronectin. However, in this study the increase in mechanical properties was found, with the three-point bending strength almost doubling. Vallo and coworkers [303] also found increase in fracture toughness and flexural modulus with up to 15% by weight of HA in a commercial bone cement. However, the best combination of mechanical properties with workability of the paste was obtained with addition of about 3% of the ceramic.

Working with the PEMA/n-BMA (n-butyl methacrylate) system, which presents the advantage of being much more ductile than conventional PMMA bone cement, Harper et al. [300,307] could add up to 40% by weight HA without a decrease in static mechanical strength. After immersion in Ringeŕs solution, the tensile strength was not altered whereas the fatigue

properties were significantly reduced. The decrease in fatigue resistance due to HA was compensated for (when tested in air) by the use of a silane coupling agent; however, after immersion in the saline solution the resistance was considerable lowered. This implied that the silane coupling agent was not as effective in the presence of Ringer's solution, due to either dissolution or hydrolysis of the coupling agent in the presence of water and/or the mineral salts. Similarly, Dupraz et al. [308], reported that only about 50% (in the best situations) of these coatings remained after 5 days of water extraction at 37 °C; primary and secondary amines were completely removed.

An alternative to improve the interaction filler–matrix is the addition of adhesion promoting agents, which also promote bonding of the cement to the bone and/or the prosthesis. Morita et al. [309], with incorporation of 4-methacryloyloxyethyl trimellitate anhydride, promoted adhesion of the polymer to HA, preventing the weakening associated with the introduction of this filler and decreasing the water uptake. After implantation, the normal cement presented adhesive failure at the interface between it and bone, while with the use of the adhesive cement there was a cohesive fracture of the bone. Shinzato et al. [310] added phosphoric ester (another adhesion-promoting agent) to the liquid component of the formulation. The strength increased, probably due to the effects of copolimerization, the same occurring with the affinity index.

Another methodology for bonding HA to PMMA was tried by Liu et al. [311,312] who after showing the ability of HA to react with organic isocyanate groups grafted acrylic polymers on these modified HA. Thermogravimetric and infrared analysis demonstrated that the polymers were chemically bonded to the particles through the isocyanate groups, making it a suitable approach to improve the adhesion matrix-filler.

4.3. Non melt-processable composites

Although melt-processing methods are usually preferrable because they do not demand the use of solvents that may be toxic and necessitate additional recovery steps to reduce solvent emission, other alternatives may be chosen for materials that degrade/decompose before melting [313]. Suitable alternatives are solution-based or precipitation methods, which allow for the preparation of composites of polymeric matrices and HA with enhanced osteogenic potential (provided by the HA), prevention of HA migration (due to the binding action of the polymer matrix) and sufficient mechanical properties for orthopaedic use. However, some of the techniques reported (mixing of HA powder in a polymer solution or coating of HA particles onto a polymer sheet, among others) gave origin to macroscopically inhomogeneous composites without enough mechanical properties and that often caused inflammation after implantation [314]. The coating of HA onto a chitosan film by a biomimetic method, for instance, [315], although turning the material more suitable to bond to bone, is not expected to increase the mechanical properties of the polymer.

However, in the case of compact and stiff materials, this methodology (coating) can be very useful when used as a way to improve the bioactivity of several kinds of polymers and even metals. Leonor and Reis [316] have developed an auto-catalytic deposition methodology to produce calcium–phosphate layers onto the surface of polymeric biomaterials (starch-based blends and HMWPE): prior to in vitro tests, specimens were immersed in either alkaline or acid baths (with controlled pH and temperature). After only 1 h of immersion the specimens have already developed a calcium–phosphate layer (which became more compact and dense after immersion in simulated body fluid—SBF), which was a considerably improvement compared to the 6–24 h of induction time needed by the biomimetic coatings [317]. Another methodology was developed by Oliveira and Reis [318,319] using a sodium silicate gel for impregnation of compact and porous specimens of starch-based blends during 24 h in a controlled atmosphere. This impregnation could or not be preceded by pre-incubation in a calcium chloride supersaturated solution (because the calcium ions increase the apatite-forming ability of a silica layer [320]). With these treatments, a clear apatite-like layer was observed after only 6 h of immersion in SBF, and the layer could be observed even inside the pores (what is not easy to get with standard biomimetic coatings). Although no mechanical characterization was reported, the coating would provide fast bonding with the surrounding bone, in this way improving the mechanical performance of the interface implant–bone and of the whole construct.

Wan et al. [313] developed a new solution-based method to incorporate HA in chitin solutions in which the ceramic particles were uniformly dispersed and originated an intimately blended material with no sedimentation/aggregation. However, as usual with non-melt processed materials, it was difficult to obtain uniform dimensions, especially for the specimens with lower amounts of HA (that presented higher shrinkage). The mechanical properties were also not good, with tensile strength and modulus decreasing with an increase in HA amount (due to poor adhesion between the filler and the matrix). Microscopic examination confirmed these results, showing that HA particles were intervening between the polymer chains, weakening their interactions and decreasing the strength.

A composite of collagen and HA was developed as bone substitute [321]. The collagen solution used was shown to have been imbibed into the pores of HA and to be loosely attached to the pores walls, but, because of

the high viscosity of these solutions, the pores were not fully filled. The mechanical properties reflected this fact and increased only until a certain concentration of collagen. The decrease (at higher concentrations) was attributed to the difficulty of filling the pores. The in vitro degradation behaviour showed that degradation roughly matched the growth rate of bone.

Yamaguchi et al. [314] used a co-precipitation method to prepare the composites by using chitosan dissolved in different organic acids. They found that growth of HA crystals was inhibited by organic acids with more than two carboxyl groups, which strongly bind to HA surfaces via a COO–Ca^{+2} bond. Transmission electron microscopy images showed that HA forms elliptic aggregations with chemical interactions between calcium on its surface and amino groups in chitosan molecule (probably coordination bond); the HA nanocrystals align along the chitosan molecules, with the amino groups working as the nucleation sites. In case of pure HA, the crystallites did not form aggregations. Heat treatment at increased temperatures improved strength and elongation to failure, but the modulus decreased dramatically, making the composite less suitable for orthopaedic applications. Finally, an histological (preliminary) examination showed no inflammation and appearance of new bone around the composite.

Chitosan was also used as the matrix for the incorporation of β-TCP and calcium–phosphate invert glass by a solid–liquid phase separation of the polymer solution and subsequent sublimation of the solvent [322]. The composites had improved compressive modulus and strength (due to complexation of the functional groups of chitosan with calcium ions present in β-TCP). Only the composite with β-TCP was bioactive in SBF, due to the nucleation sites provided by this ceramic. These composites were suggested as suitable materials for tissue engineering, with macroporous structures and properties being adjusted by β-TCP/glass ratio and ceramic/polymer ratio.

Another procedure used to prepare composites was developed by Akashi and co-workers [323] by alternately soaking hydrogels in calcium and phosphate solutions during 2 h, and repeating this procedure 5 times, in order to produce HA on/in the hydrogels. The procedure was applied to chitosan [324]; the 3-D shape of the resulting composite was controlled by the shape of the starting chitosan hydrogel and the swelling was reduced with increase of the amount of incorporated HA (up to 70% by weight of ceramic could be added to the composites). Although this method is an improvement to the previously referred coating of HA onto polymers, because the formation of ceramic inside the material could possibly provide strengthening, no mechanical characterization was reported on that particular work.

5. Final remarks

Polymer matrix composites have the advantage of being very versatile, allowing for the tailoring of its final properties. Composites can be designed and produced with specific requirements, using a wide range of polymeric matrixes, reinforcements and processing routes. Several alternatives have been proposed for both temporary and permanent long-term applications. Furthermore, many injectable systems have been developed. Most of these systems are typically biocompatible and believed to be able to perform their function when implanted. But it is also true that almost all of them have some drawback. There is a great interest in continuing to explore the possibilities of those materials. However, and in-spite of the fact that many patents have been filled and granted in this field, so far, no relevant commercial application of composites in hard tissue replacement is available in the market. It is the authors' opinion that new applications with a strong clinical impact will be emerging soon, by means of joining the efforts on composite development, with new inputs from the fields of nano-technology, biomimetics and tissue engineering. In fact, novel generation biomedical composites are expected not to be conventional, becoming hybrid, biofunctional and containing a biological living part.

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