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ANNIVERSARY REVIEW

Bioactive ceramics: processing, structures and properties

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Abstract There is an increasing need for bone repair materials for skeletal reconstruction, due to the prevalence of diseases such as osteoporosis and to the growing number of aged and overweight people Worldwide. Although used widely, there are limitations with autograft and allograft, including issues of supply and effectiveness, respectively. This has led to the need for more suitable synthetic biomaterials to replace natural bone, which can be nearly inert or bioactive. This review aims to discuss bioactive implants, coatings and scaffolds made of ceramics, glasses, glass–ceramics and composites. These are able to form a chemical interfacial bond with tissue and can be resorbable or non-resorbable.

Introduction

Bone is one of the most complex constituents of the body and this is due to the multiple functions that it has to perform. As well as being part of the musculoskeletal system, it protects vital soft tissues of the body and plays an active role in mineral metabolism. It is a natural composite, mainly composed of inorganic bone mineral, an organic collagen matrix and non-collageneous proteins [1]. The mineral constitutes about 0.45 of the volume fraction of bone and resembles synthetic hydroxyapatite (HA) which has a stoichiometric chemical formula of $Ca_{10}(PO_4)_6(OH)_2$ and a Ca:P ratio of 1.67. Therefore, most bioactive materials are based on ceramics, glasses or glass–ceramics containing calcium and silicate ions or calcium phosphates.

For the last 50 years, there has been interest in the development of bioactive materials. In the late 1960s, Professor Larry Hench realised the potential of using glass in the body for bone repair [2]. He also coined the officially accepted definition for such materials as, 'a material that elicits a specific biological response at the material surface which results in the formation of a bond between the tissues and the materials' [3]. This direct attachment of bone to the implant takes place by means of a biologically active hydroxyl-carbonate apatite (HCA) layer, which is chemically and structurally similar to the mineral phase in bone, providing the interfacial bond [4].

There is growing need for bioactive materials to replace areas of bone which are too large to heal themselves. This problem is exacerbated by an increasingly aged, and in many circumstances, overweight population. Autografts are the first choice for bone replacement, but as the size of defect increases, alternatives need to be sought. Allografts are also a possibility, however with these come the risks of transmitted infections and transplant rejection. The final choice is therefore synthetic bone replacement materials. The use of bioactive materials can prevent the problems associated with fibrous encapsulation and the inability of an 'inert' implant to encourage bonding of natural bone via the process of osteoconduction.

I: Materials

Bioactive glasses

The technology for producing bioactive glasses was initiated in 1969 by Hench et al. [5]. This was a glass

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comprising a soda–calcium oxide–silica composition (the basic structure being that of a 2D SiO_2 network) with the addition of P_2O_5. This glass was able to promote bone bonding in a physiological environment and was denoted as 45S5 [6]. Hench established this name based on the nomenclature for the glass composition of XYZ, where *X* is the percentage SiO_2, *Y* is the glass network former (SiO_2) and *Z* is the CaO to P_2O_5 ratio in the glass composition.

Structure

The 45S5 glass known as Bioglass® consists of a silicate network which incorporates sodium, calcium and phosphorus which a composition of 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5.

Since, the first report on Bioglass® many other bioactive glasses have been developed and reported in the literature [7–12]. These materials are often based in the same system as the original formulation by Hench et al., i.e., the Na_2O–CaO–SiO_2–P_2O_5 system.

The content of SiO_2 or silicate also appears to be of importance during the formation of an apatite layer. Carlisle was the first to demonstrate that the silicon content of human bone increased proportionally with calcium at relatively low calcium concentrations suggesting that silicon was associated with calcium in an early stage of calcification [13]. This study also highlighted the importance of soluble silicon in bone formation. Several authors have reported the effect of soluble silica as a favourable site for apatite nucleation by the formation of a silica-rich gel layer [7, 14, 15]. However, Hench showed that a content of silica which was greater than 60 mol% was detrimental to the bioactivity of the material and inhibited apatite formation in simulated body fluid (SBF) [7]. Hench and Paschall [16] showed that glasses with larger amounts of phosphate than in Bioglass® would result in no bone bonding to bone and that substitutions of 5–15 wt% B_2O_3 for SiO_2, 12.5 wt% CaF_2 for CaO or crystallising the glass compositions for form glass–ceramics did not have a significant effect on the bone-bonding ability of the material. Kokubo reported that the addition of transition metal ions such as titanium, cobalt and manganese could be demonstrated to control the bioactivity of the glass and ensure better stability [16].

Processing

Preparation techniques for bioactive glasses includes both melting methods and sol–gel techniques [6, 17–22]. Processing commonly involves the use of high purity raw chemicals to ensure the quality of the final glass product. The starting materials include highly pure quartz or silica sand, reactive grade sodium and/or potassium carbonates and calcium carbonates.

The melting process involves the use of temperatures in the range of 1200–1240 °C, depending on the composition being melted. When volatile components such as Na_2O and P_2O_5 need to be incorporated, then care must be taken to avoid their loss during the heating process. The glass must be annealed to reduced thermal stresses during the casting and cooling process (commonly in the range of 400–500 °C).

The sol–gel method was first proposed two decades ago and has allowed for the production of bioactive glasses with increased purity and homogeneity. It has also permitted the formation of a greater range of bioactive compositions compared to melt-formed bioactive glasses [21]. The use of the sol–gel method for glass production has also led to the simplification of the composition, leading to the first bioactive glasses of the ternary SiO_2–CaO–P_2O_5 system [23]. It involves the preparation of a sol which is then transformed into a solid phase: the gel. The process involves the polymerisation of inorganic materials by the reaction of metal alkoxides. Silicon alkoxide [e.g., in the form of tetraethyl orthosilicate (TEOS)] is hydrolysed and condensed into a silica gel network, with salts such as calcium nitrate, acting as the calcium precursors [23].

Properties

Bioglass® rapidly undergoes a chemical reaction at its surface when placed in physiological media. The surface reaction results in the formation of an hydroxyl-carbonate apatite layer. This is a complex process that results in a bone directly bonding with the glass and which results in an HCA phase which in terms of its composition and microstructure, is similar to the mineral content of bone [7, 24, 25].

Clinical applications

Bioglass® has been approved by the US FDA and has been used in clinical applications for the treatment of periodontal diseases and for middle ear surgery [26–29] and under the name NovaBone® for orthopaedic applications.

Bioactive glasses have been proven to induce strong osteogenesis. The bonding of bioactive glasses to bone is initiated by the formation of a silicon-rich gel on an implant surface, followed by the nucleation of hydroxyapatite crystals. In 1981, Wilson and colleagues reported that in addition to its excellent bone-bonding properties, Bioglass® was able to form a bond with soft connective tissue [30–32].

Bioglass® has been used in middle ear implants for the treatment of chronic otitis. Merwin et al. [33] demonstrated that the long-term stability of these implants was as a result of the ability of the Bioglass® to bone to the tympanic membrane.

Following the implantation of bioactive glass and the formation of an apatite layer, there appears to be a set of processes that occur (Fig. 1). These consist of the adsorption of proteins on the hydroxyapatite layer, followed by the activity of macrophages and in turn, stem cells, on the surface of the implant. These cause the mineralisation of the matrix tissue [34].

Study performed by Wilson et al. demonstrate that the bond between Bioglass® and tissue was due to a variety of both chemical as well as mechanical factors [30, 35]. If Bioglass® was implanted next to bone tissue, leaving the implant immobilised for a critical length of time caused the strength of the bond to be equivalent to that of the natural cortical bone [36, 37]. In vivo studies on primates illustrated that the bond between a Bioglass® coating and natural bone was so strong that upon testing, the retrieved samples fractured across the implant or the bone, but never at the bone–implant interface [38, 39].

Bioactive glass–ceramics

Bioactive glass–ceramics are an important class of polycrystalline material produced by controlled crystallisation of glass. Most bioactive glass–ceramics are based on compositions which are similar to those of Bioglass®, however all have very low contents of alkali oxides.

Processing

The heat treatment employed results in the nucleation and growth of a specific crystal phase in the parent glassy matrix. The production of a glass–ceramic allows for the ability of complex shapes to be manufactured and the very fine microstructure that results, to improve the mechanical properties of the final product.

One of the most extensively studied glass–ceramic for use as a bone substitute material is glass–ceramic apatite–wollastonite (A–W), Cerabone® [40]. This has two crystalline phases; 38 wt% oxyfluorapatite $Ca_{10}(PO_4)_6(O,F_2)$ and 34 wt% wollastonite ($CaO{\cdot}SiO_2$) 50–100 nm in size and a residual vitreous phase of $MgO–CaO–SiO_2$. It is able to combine bioactivity with desirable mechanical properties for use as a bone replacement material [41]. Since, the discovery of glass–ceramic A–W, it has been successfully used in bulk, granular and porous forms in mainly spinal surgery [42–45].

Properties

The bending strength, fracture toughness and Young's modulus of glass–ceramic A–W are the highest amongst the bioactive glass and glass ceramics available for orthopaedic applications. This allows this glass–ceramic to be used in some major compression load-bearing areas of the bone [46–52].

Table 1 compares the properties of glass–ceramic A–W (Cerabone®) and other commercially available glass–ceramics with those of both cortical and cancellous bone. Glass–ceramic A–W has substantially greater mechanical properties than Bioglass®, demonstrating its suitability for use in vertebral replacements where large compressive strengths are required.

In the 1970s, Brömer and Pfeil [64, 65] developed one of the earliest glass–ceramics for clinical use. Ceravital® in the $SiO_2–CaO–P_2O_5–Na_2O–K_2O–MgO$ system contains crystalline apatite and compared with glass–ceramic A–W, showed a lower bending strength. In vivo testing debated the stability of this material in the body, but following improvements in its composition by Gross et al. [66, 67], the solubility was reduced by the use of various metals as nucleating agents.

Berger et al. [68] developed Ilmaplant-L1®, which consists of apatite/wollastonite glass ceramic. It differs from glass–ceramic A–W in terms of its alkali contents; higher proportion of CaF_2, SiO_2 and P_2O_5; and a reduced content of CaO. Due to its low bending strength, it could only be used in non load-bearing applications such as maxillofacial implants.

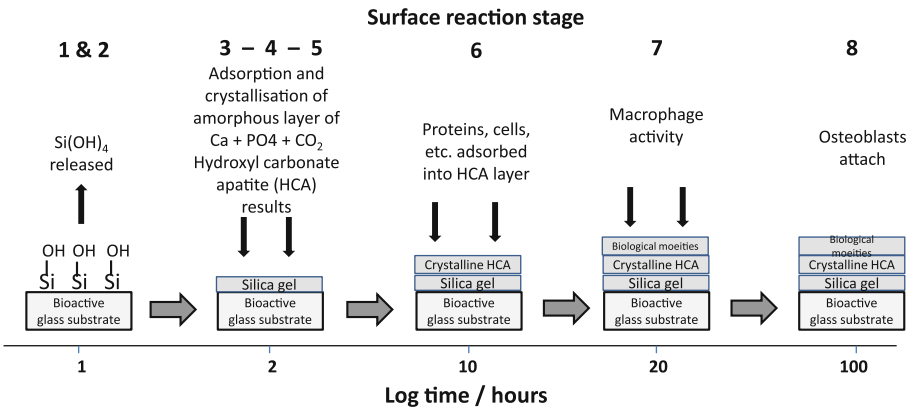

Fig. 1 Initial steps involved in the process of bone attachment to bioglass, based on the findings of Hench et al. [7]

Table 1 Properties of a variety of glass–ceramics compared with cortical and cancellous bone

Material	Density/ Mg m^{-3}	Bending strength/ MPa	Young's modulus/ GPa	Fracture toughness, K_{IC}/MPa $m^{-1/2}$
Cortical	1.80	50–150	6–20	2–12
Reference	[53]	[54]	[55]	[56]
Cancellous	0.20	10–20	0.09–0.4	–
Reference	[53]	[57]	[58]	–
Bioglass®	2.7	40–60	30–50	0.5
Reference	[59]			[60]
Ceravital®	–	150	100–150	–
Reference	–	[61]		–
Cerabone®	3.1	215	35–118	2.0
Reference	[62]			[50]
Biovert® I	2.8	140–180	70–90	1.2–2.1
Reference	[63]			

In 1983, Höland et al. [69] developed a new series of bioactive glass–ceramics, which they called Bioverit® I. This material could be machined with standard tools and retouched in the operating theatre. It is in the SiO_2–Al_2O_3–MgO–Na_2O–K_2O–F–CaO–P_2O_5 system which undergoes a controlled nucleation and growth of crystals resulting in the presence of fluoroflogopite-like mica ($Na/KMg_3[AlSi_3O_{10}F_2]$) in the glassy matrix. A second family of Bioverit®, called Bioverit® II, was produced following the success of type I which contained much lower P_2O_5 content but other crystalline phases of cordierite ($Mg_2[Si_5Al_4O_4]$). Höland alongside Vögel [70, 71] further developed the Bioverit to create a III version using a phosphate glass in the P_2O_5–Al_2O_3–CaO–Na_2O system with no silica content but doped with Fe_2O_3 and ZrO_2. By varying the crystalline content, the mechanical and biological properties of the glass–ceramics could be adapted to address a particular function.

Clinical application

Once placed in the body, glass–ceramic A–W forms an apatite layer on its surface which allows it to bond directly to the bone into which it is placed. This bonding has been found to be so strong that when retrieved samples were mechanically tested, the fracture never occurred at the implant–bone interface, but rather in the bone [42, 46–52]. The ideal mechanical properties in combination with its suitable bioactivity have meant it has been used in reconstructing iliac crests, vertebrae and intervertebral discs and, in granules form, in filling in bone defects [42].

Due to the chemical and structural characteristics of the apatite layer that formed on the surface of glass–ceramic A–W, a layer similar to that of bony tissue, it is of

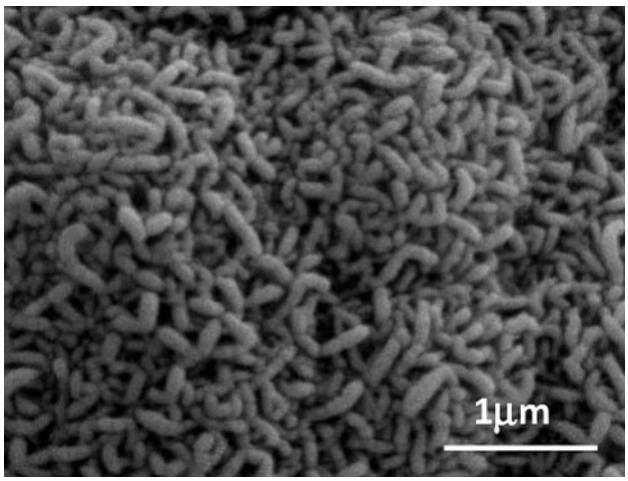

Fig. 2 High magnification image showing apatite formation using simulated body fluid (SBF)

expecting that, in the interface with the bone, osteoblasts preferentially form in place of fibroblasts. Although, no amorphous silica layer has been observed between the hydroxyl-carbonate apatite (HCA) layer and the glass–ceramic A–W, Kokubo and his colleagues believe that silanol groups form at the glass–ceramic surface since a substantial quantity of silicate ions are dissolved from the materials when tested in a simulated body fluid (SBF, Fig. 2). They are considered to be the cause of the apatite layer formation since these groups provide the favourable sites needed for apatite crystal nucleation and growth. The apatite crystals form rapidly on the surface of the glass–ceramic A–W and as they grow, they consume calcium and phosphate ions from the surrounding media. The SBF used to test the behaviour of glass–ceramic A–W was also developed by Kokubo et al. [49]. It is an acellular technique which allows the ranking of materials in terms of their bioactivity.

The composition of this solution is similar in ionic content to that of human blood plasma and has been used by many groups to evaluate and analyse the bioactive response of their materials which has included modification of the original composition and methodology [72–76]. It has also been used to create a low temperature biomimetic coating on otherwise inert materials [77–84] and led to the development of bioactive organically modified silicate hybrid materials through a sol–gel processing route [85–88].

Calcium phosphates

Calcium phosphate salts with different molar ratios are used widely for orthopaedic applications (Table 2). Their solubility is increased as the Ca/P ratio is decreased, a response which is further enhanced by the reduction of the

Table 2 Calcium phosphates that can be used in medical devices [91]

Name	Formula	Ca/P ratio
Brushite	$CaHPO_4 \cdot 2H_2O$	1.0
Octacalcium phosphate	$Ca_8H_2(PO_4)_6 \cdot 5H_2O$	1.33
Tricalcium phosphate	$Ca_3(PO_4)_2$	1.5
Hydroxyapatite	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Tetracalcium phosphate	$Ca_4(PO_4)_2O$	2.00

surrounding pH. The inorganic content of bone is composed of a poorly crystalline, calcium-deficient, carbonate apatite [89]. Calcium phosphates possess bioactivity which means they are able to create a chemical bone with bone and reduce the problems associated with rejection of otherwise 'inert' biomaterials [90]. With the ability to vary the calcium to phosphorus ratio and in turn, the bioactivity and resorption rate of these ceramics, it leads to the capability of controlling the rate of bone growth as the bioceramic resorbs [91].

One of the most commonly used synthetic calcium phosphate ceramics is hydroxyapatite (HA) [91]. HA has a chemical formula of $Ca_{10}(PO_4)_6(OH)_2$ and has a Ca/P molar ratio of 1.67 (Table 2). Driessens stated that compounds which had a Ca/P ratio of less than 1.0 would not be suitable for use in the body [92].

Processing

Calcium phosphates such as HA are commonly produced using wet chemical methods including aqueous precipitation and sol–gel processing [93–95]. The aqueous precipitation technique is most often performed in one of two ways; a reaction between a calcium salt and an alkaline phosphate [96–102] or a reaction between calcium hydroxide or calcium carbonate and phosphoric acid [93, 103–108]. This precipitation process is often followed by dry die-pressing or isostatic pressing, after which sintering can be performed to densify and crystallise the material.

Properties

The route by which calcium phosphates are produced greatly influence their physical and chemical characteristics. Factors such as surface area, crystallite size and particle size can all affect the rate of resorption and bioactivity. The degradation of calcium phosphates preferentially begins at the grain boundaries which can sometimes lead to a release of individual ceramic grains or agglomerates. HA has higher stability in aqueous media than other calcium phosphate ceramics within a pH range of between 4.2 and 8.0 [90]. Hence, it is relatively insoluble at neutral pH. This slow rate of dissolution is considered by some surgeons to be a disadvantage in certain clinical applications. The other preparations of calcium phosphate, such as tricalcium phosphate (TCP; α and β forms) and biphasic calcium phosphate, have varying degrees of solubility at neutral pH, based in part on their crystalline structure and surface area. The substitution of ions such as silicates or carbonates will also alter the rate of dissolution and enhance the bioactivity of HA [109–114]. They also affect the lattice parameter, morphology, crystallinity and thermal stability of HA such as that which takes place when cationic ions are substituted for the calcium ion in the HA structure. Substitutions for the phosphate or hydroxyl ions, the anionic groups, can be achieved by the use of carbonate ions. Type A is when the carbonate group substitutes for the hydroxyl ion in HA and Type B is when the phosphate ion is exchanged.

As mentioned earlier, the rate of dissolution increases as the calcium to phosphorus ratio drops. Hence, tricalcium phosphate resorbs faster than HA. Tricalcium phosphate has four forms; α, β, γ and super α [115]. However, the most commonly used forms for medical applications are the α and β forms. Research has shown that the α form dissolves at a faster rate than β TCP. Animal studies have demonstrated that the α form degraded significantly more than the β form after 4 weeks following implantation [116].

Clinical applications

Calcium phosphates are used for a variety of orthopaedic applications for treatment of diseased and damaged bones in areas such as maxillofacial, spinal and cranial surgery. They can be used in bulk, granular, coating or composite form as described in this review.

II: Modes of use

All the bioactive materials mentioned so far can be used as dense, sintered small bone replacements, as granular bone fillers and as scaffolds in porous form to encourage osteointegration. The use of these biomaterials can be further exploited and the properties of otherwise inert materials, most commonly metals, enhanced by applying bioactive materials as coatings and by using them as fillers in composites [39, 117–200].

Bioactive coatings

The formation of a chemical bond between bone and an implant material requires there to be bone growth either on to or into a prosthesis. In the 1960s, it was noticed that calcium phosphate coatings would provide much better

fixation of load-bearing implants than using cements such as polymethylmethacrylate (PMMA) [117]. Calcium phosphates such as hydroxyapatite (HA) are suitable since they closely resemble the mineral phase of human bone which is composed of inorganic apatite crystals and organic collagen [118]. When used in vivo, HA-coated implants proved to be non-inflammatory and elicited a positive bone response [119], resulting in a strong and lasting osseoconductive bond between living tissue and the implant.

Processing

Typical calcium phosphate coating techniques include ion beam-assisted deposition, plasma spray deposition, magnetron sputtering and non-thermal biomimetic methods performed under normal atmospheric conditions. Plasma spraying techniques are the main route used commercially to coat metals such as titanium. Plasma spraying was established as the most widely used commercial method of preparing calcium phosphate coatings in the 1980s. Since then, numerous research groups and companies have used this technique to coat biomaterials such as titanium and cobalt-chrome alloys due to being a reproducible and cost-effective technique [39, 120–145]. Plasma spraying is a high temperature process which is more complex and expensive than other techniques such as biomimetic routes, but which has also be used to apply glass and glass–ceramic coatings onto ceramics and metals for maxillofacial reconstruction, e.g., as coatings on alumina substrates [39, 120–122] and bone prostheses, e.g., as coatings on titanium alloy, cobalt-chrome and stainless steel substrates [123–135].

The spraying process involves injecting the bioactive powder into a plasma flame at high temperature. The powder is heated and forced at high pressure and velocity, towards the substrate material causing the surface of the molten particle of HA to be exposed to very high temperatures for a fracture of a second (Fig. 3). Due to this very high external temperature, the thin outer layer of each HA particle will inevitably undergo phase transitions. This surface may be sufficiently large to be able to plasticise the outer layer and allow a dense and strongly adhesive coating to be formed. However, it must also be small enough not to affect the overall crystalline phase deposited on the substrate material [146, 147]. Optimising the performance of the coating can be achieved primarily via three methods: controlling of the plasma spraying parameters, controlling the spray powder microstructure before deposition and finally, applying a bioinert bond coating [148].

Calcium phosphates similar to those found in natural hard tissues can be produced spontaneously in physiological, supersaturated solutions at low temperatures. This

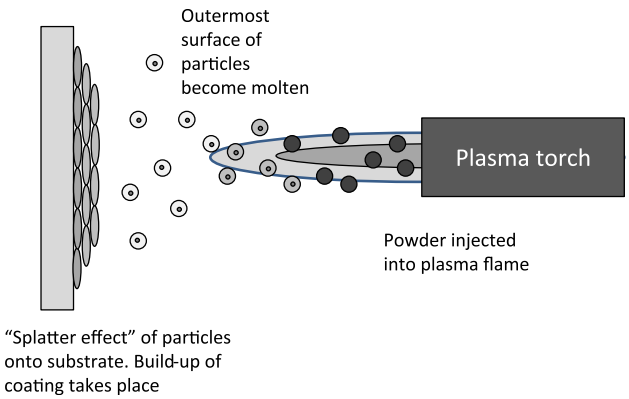

Fig. 3 Diagram showing coating formation using plasma spraying technology

process can be used to grow bone-like apatite on potential implant materials and is particularly suitable for the coating of biodegradable polymeric materials and degradable tissue engineering scaffolds [77–84].

It appears that there is now a tendency to apply relatively thin plasma-sprayed coatings (<50 μm) or even thinner biomimetic coatings (5–30 μm) due to their higher adhesive strengths and experiencing lower residual stresses which can lead to microcracking and delamination.

Properties

Using a bioactive coating for an otherwise 'inert' material may prevent the formation of a fibrous capsule of connective tissue around the implant. These coatings can allow for a faster bone apposition rate via the adsorption of proteins on the surface and promote the ability to form an osteogenetic bond creating a continuous and strong interface between an implant and human bone. This interface is one which can transmit compressive, tensile and shear loads and can accelerate the healing of an implant compared to a non-bioactive-coated material. The use of a coating can also reduce the likelihood of a cytotoxic response to metallic ions released into the surrounding tissue [6, 149–154].

Animal studies have shown that plasma-sprayed HA-coated implants allow rapid bone ingrowth with a higher percentage of bone contact on the samples plasma sprayed with HA in comparison to no bioactive coating [155, 156]. As well as these in vivo results, there has been much clinical success with HA plasma-sprayed metals [157]. A recent report indicated that implants remained well accepted in patients after 13 years implantation [158]. Plasma spraying is the most commercially used technique for producing bioactive coatings on orthopaedic and dental implants. However, this process suffers from drawbacks such as poor adhesion properties, non-uniformity and cracking due to their brittle nature and greater thickness.

For these reasons, and due to the high temperatures that are required during processing, other routes are being explored which would also potentially allow the inclusion of biologically active molecules during the apatite layer deposition.

One alternative technique being studied is micro-arc oxidation (MAO). This is a process that can be carried out at room temperature for components with complex geometries [159–163]. It is a simple, economical technique for producing calcium phosphate coatings with different surface textures on metal substrates. The production of a porous coating using the MAO technique can enhance the anchorage of the implant to the adjacent bone tissue and can allow the incorporation of antibiotics to reduce infect and implant rejection.

Magnetron sputtering is another alternative coating deposition technique. It is a high-rate vacuum coating technique that allows a faster deposition rate at lower pressures compared with other techniques and is able to create strongly adhesive coatings on complex geometries including those made of heat-sensitive substrates such as polymers. It has demonstrated to be a promising method for forming a biocompatible coating on metal, plastic and ceramic substrates since a wide variety of materials can be used and the processing parameters and post-procedure heat-treatments such as post deposition or in situ annealing can be applied [164–166].

Biomimetically deposited calcium phosphate coatings are much thicker and uniform that those produced by other processes. This is especially apparent when coating porous substrates which, with plasma techniques as well as electrochemical treatments, is difficult to achieve. However, there exist differences in morphology which lead to several forms of apatite crystal growth; the edges of samples inhibiting apatite growth due to increased surface energy. Coatings formed via biomimetic methods are preferred by cells due to better proliferation and growth when compared with other deposition techniques [167].

Repeated dipping of substrates into a supersaturated calcium phosphate solution and removing and air-drying allows the growth of calcium phosphate crystals on substrate materials. The mechanism of apatite growth is thought to be via an evaporation-induced surface crystallisation process. However, the mechanical stability and bioactivity of these types of coatings need to be analysed. A similar dipping technique to form a nanoCaP rich hydrogel composite coating on substrates has demonstrated good adhesive strength and promising results when tested in vitro in SBF and with human osteoblast-like cells (Fig. 4) [168].

The success and continuing development of biomimetic techniques are due to the ability to form apatite on a wide variety of surface topographies and geometries. It is able to incorporate biomolecules and drugs which can promote cell adhesion and growth and can help to miminise the problems associated with implant rejection such as infection. Alternative biomimetic methods have also grown out of the standard techniques mentioned earlier in this chapter. Routes such as layer-by-layer assembly and self-assembled monolayers (SAMs) to incorporate biomolecules such as proteins are all at promising, developmental stages of research [169, 170].

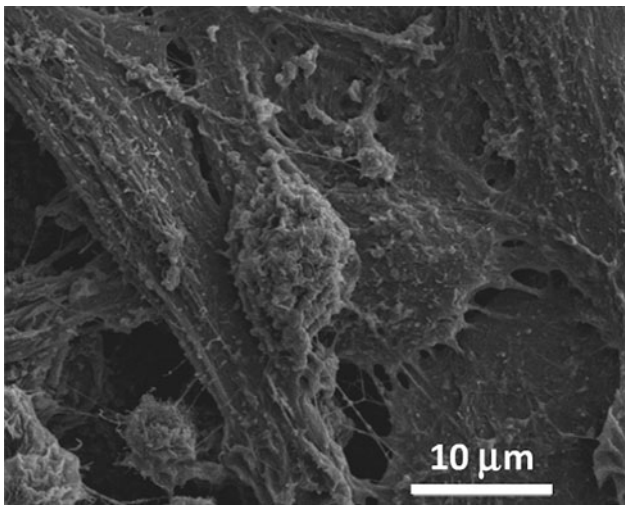

Fig. 4 Human osteoblast-like cells on the surface of a nano-hydroxyapatite (nHA)-reinforced polyhydroxyethylmethacrylate/polycaprolactone (pHEMA/PCL) composite

Bioactive organic–inorganic hybrids

As stated previously, the formation of an apatite layer in SBF on bioactive silicate glasses led to the idea of producing bioactive organically modified silicate hybrid materials [85]. The sol–gel method of forming bioactive hybrid organic–inorganic materials has been applied to produce polydimethylsiloxane (PDMS)–CaO–SiO_2, poly(tetramethylene oxide) (PTMO)–CaO–SiO_2 hybrids, amongst others [86–88, 171]. In all these hybrid materials, the bioactive inorganic component chemically bonds to the polymer and is homogeneously distributed in this organic phase. Other hybrids have also been successfully produced by the polymerisation of methacryloxypropyltrimethoxysilane (MPS) and 2-hydroxyethylmethacrylate (HEMA) with the addition of a calcium salt. This hybrid material demonstrated tailorable bioactivity and mechanical properties [172, 173].

Adaptation of the hybrid system has also demonstrated its suitability during production of bioactive poly(methylmethacryalte) (PMMA) bone cements [174, 175].

The polymerisation of MPS with MMA allows Si–OH groups to be chemically bonded to the PMMA matrix and with the appropriate calcium salts such as calcium

hydroxide, a bioactive and mechanically stable, hybrid material can be produced, which will potentially alleviate the problems associated with PMMA cement loosening and will require much lower concentrations of inorganics in comparison to previous techniques.

Bioactive composites

The composite nature of cortical bone can be characterised at a variety of different structural scales and this led Bonfield et al. [176–179] to realise the potential of creating materials which would provide synthetic bone analogues with both bioactivity and desirable mechanical properties. Initially, calcined bone ash was the bioactive phase used to reinforced high density polyethylene (HDPE) [176]. Later, synthetic hydroxyapatite (HA) particles were used to reinforce HDPE and act as the equivalent of the mineral crystals embedded in a collagen matrix. This composite was successfully developed and marketed under the name, HAPEX™, and was used in a variety of minor load-bearing applications, including orbital floor reconstruction and otologic implants [180–182].

Following the success of HAPEX™ other bioactive composites and biodegradable bioactive composites have been produced [183–188]. This has included the incorporation of glass–ceramic apatite–wollastonite (A–W) and Bioglass® in an HDPE matrix [189–197], as well as other matrices such as chitin, polysulfone (PS) and polymethylmethacrylate (PMMA) [198–206]. The latter being used to provide bioactivity to bone cement for fixation of prostheses such as hip replacements [207, 208].

Recent research has been focussed on expanding the use of hydroxyapatite ceramics into load-bearing applications and addressing the issue of their poor fracture toughness. This has been attempted by the incorporation of carbon nanotubes (CNTs) [209–211]. Recent studies have suggested that CNTs may induce a bioactive response when tested in the presence of bone cells [212, 213]. Hence, their incorporation in a HA matrix appear to be a promising method of improving the mechanical properties of HA and retaining the bioactivity of the resultant material. However, inspite of the apparent suitable bioactivity of CNTs that has been quoted, there is still little known about the potential toxicity of these nanostructures. With time, the biological stability of CNTs will be further evaluated and better understood.

Processing

The technique used to make HAPEX involved the twin screw extrusion of high density polyethylene with particles of HA that resulted in strands of composite. The strands are subsequently powderised and compression moulded into plaques which helps to break down the agglomerations, creating a material with a good distribution of bioactive particles in the HDPE matrix. Since, the production of HAPEX, this and other techniques have been employed to make a variety of other biocomposites [179, 184, 187, 199, 200].

Properties

Composites comprising a polymer matrix and ceramic filler particles can allow control of the mechanical properties, including strength and stiffness, toughness and plasticity [58, 176, 177]. The stiffness, toughness, bioactivity and ease of shaping during surgery which have been found desirable for biomedical applications [176, 178, 179] are suitable for non-major load-bearing applications. The in vitro stability and degradation were tested and their effects observed on the mechanical properties of HAPEX™. It was found that the tensile strength was reduced with immersion time [189, 190] but the Young's modulus and fracture strain were not significantly altered.

Bioactive scaffolds

The success of bulk bioactive materials and coatings has meant the extended survival of otherwise inert implants in the body, such as bioactive-coated metallic hip prostheses. However, these are still unable to last the entire lifetime of a patient; an issue which will set to be more prevalent this century. Hence, increasing emphasis is being placed on the use of materials which will encourage vascularised bone to replacement the implant over time rather than the material being a permanent feature following insertion. Such materials form a scaffold structure, helping natural tissue to grow into the interconnected pores and gradually replace the osteogenic material. Both the structure and design of the scaffold, as well as the material it is composed of, are important parameters to consider. Increasing the porosity of the scaffold will encourage better cellular ingrowth, but can be detrimental to the mechanical strength of the material [214–218].

When creating a bioactive scaffold, the design of the porous structure is vital. In addition to the composition of the scaffold material, the porosity, pore size and shape and interconnectivity are all important parameter which control the mechanical and biological properties of a scaffold [218–236]. The porosity must be such that cells can migrate into the structure where they can attach to the scaffold, and processes such as neovascularisation can take place [218–221, 224–226, 228, 229, 231]. The scaffold pore structure will significantly affect cell binding and migration and influence the rate and distance that cells can grow into the scaffold [235]. These parameters have also been observed to vary depending on what cells are used and the composition and pore size of the scaffold. The pore

size and interconnectivity must be larger than 50–100 μm to allow neovascularisation and cell infiltration [222, 224, 225, 229, 232]. It has been noted that an increase in porosity does not necessarily lead to increase cellular activity in vivo, but that the pore size and distribution can have an influence on cell differentiation [236].

The rising number of scaffolds for orthopaedics are indicating the success and potential development of these materials for tissue engineering however, as yet, there is no scaffold that is able to be implanted into bone and withstand the full physiological forces encountered in the bones of the lower limbs and spine. The ideal scaffold would be able to allow sufficient loads to be transferred to stimulate osteoblast activity and new bone tissue formation, but not require external cast/fixation to mechanically protect the site from extreme loads. However, ceramic-based scaffolds would possess adequate properties in compression, hence would be suitable for applications such as impaction grafting.

Bioglass scaffolds

As noted earlier, bioactive glass is an ideal material for osteoconduction due to its ability to promote bone formation and degrade over time, releasing soluble calcium and silica ions in the process which are assumed to act as the activators of bone growth. Bioglass® is produced by a melting process, however scaffolds can also be formed using a sol–gel foam process which avoids any issues of crystallisation during sintering as with the melt-derived glasses and enhances the bioactivity of the resultant material [237–242]. It has been found that using a variety of particle size ranges and fibre diameters and foam textures allowed for the ideal dissolution properties of the bioglass to be attained [242–245]. The interconnected macropores (in excess of 100 μm) allow for bone ingrowth and the nanoporosity allows for the attachment of osteoprogenitor cells. In fact, there is evidence which indicates the biological and mechanical benefits of having a nanostructure in biomaterials since they are able to guide cell attachment, migration and differentiation [246, 247]. The formation of nanopores, such as those which are inherent to the sol–gel methods of glass fabrication, can be used to tailor the degradation process of the scaffold, since they dramatically increase the surface area available for cellular interaction [248]. However, as with CNTs, there remain concerns regarding the use of nanostructured materials in the body [249, 250].

Glass–ceramic scaffolds

As with bulk glasses and glass–ceramics, the development of glass–ceramic scaffolds are to try and overcome the limitations of glass scaffolds in terms of mechanical properties and to widen their applications beyond small defect sites and minor load-bearing applications [251–254]. These bioactive, biodegradable glass–ceramic scaffolds exhibit oriented microstructures and mechanical properties which can be tailored and are in the lower range for cortical bone along with controlled porosity [252–259]. The 3D foam-like glass–ceramic scaffolds are formed using polyurethane sponge as the sacrificial templates and silicate glass powders (produced via a melt-quenching process) as the final scaffold material. The scaffolds have great potential for bone reconstructive surgery, including load-bearing applications, due to the ease with which they can be produced and how their strength, bioactivity and bioresorption can be tailored. More recently, a study has been performed by this group observe the effect of adding silver ions to the surface of the scaffold to install antibacterial properties and broaden the effectiveness of the glass–ceramic scaffold [260, 261].

Composite scaffolds

Alongside ceramic, glass–ceramic and bioglass scaffolds, composite scaffolds are also being investigated. Prior to the formation of composite scaffolds, degradable polymers were extensively researched for tissue engineering applications. They were selected due to their biological acceptance and controllable degradation rates. A recent review discussed the benefits and limitations of degradable polymer systems for use as scaffolds in tissue engineering [262]. The ability to seed and grow cells on the surfaces of such biodegradable polymers was shown to be vital to promoting tissue growth and bone remodelling. Therefore, in an attempt to mimic the natural system and provide enhanced bioactivity, biodegradation and mechanical properties, bioactive composite scaffolds based on bulk bioactive composites were developed [242]. Composites of degradable polymers reinforced with bioactive and biodegradable materials would ensure total resorption and replacement of the material by natural bone cells.

Processing

A variety of processing techniques can be used to develop porous structures. These can include the use of porogens which can melt, dissolve or produce gas bubbles. Sugar and salt are the most commonly used dissolution technique porogens [263–267], whereas waxes which can be melted out are used less often since there may be issues with complete removal of the wax upon heating [268]. The third method of producing gas bubbles occurs when the scaffold production involves the release of carbon dioxide gas during the chemical reaction [269].

Other methods of generating porosity in bioactive and biodegradable composites include electrospinning [270], supercritical processing [271] and freeze-drying directly from suspensions [272, 273], and fused and rapid laser deposition [274–282].

The freeze-drying of poly-L-lactide (PLLA) with collagen and nanosized hydroxyapatite (*n*HA) created suitable porous structures. By the further addition of chitosan fibres, the hydrophobicity of the composite was increased which enhanced the attachment of mesenchymal cells [272]. Composites, such as degradable polycaprolactone (PCL), polyhydroxybutyrate (PHB) and the natural polymer, collagen combined with tricalcium phosphate (TCP), bioglass and carbonate apatite, respectively, produced using fused deposition and have been shown to have suitable degradation rates, better than the porogen technique, and could be used to carry and release BMP-2 to enhance osteoblast activity [274–277].

Methods have also been employed which allow the deposition of bioactive materials, such as ceramics and glasses, onto polymers, as well as the coating of polymers onto ceramics to toughen the ceramic substrate [283, 284]. The former involves the use of a technique such as soaking in simulated body fluid (SBF) or calcium and phosphate-containing solutions [49, 285–287].

As well as optimising the composition and processing route of bioactive and biodegradable scaffolds, researchers have incorporated bioactive peptides such as growth factors and proteins to enhance cell proliferation and growth [288–290]. However, the incorporation of peptides is fraught with challenges which include the problems of stabilising the chemical and geometric structure of the macromolecules and the mode of interaction of the biomolecules with the surface of the material which can alter or inhibit their activity [291].

Conclusions

There have been major advancements in biomaterials since the 1960s. Considerable amounts of study have been performed by researchers all over the World advancing the properties and applications of bioactive materials. Various chemical combinations, processing routes and modes of application have allowed novel and biologically suitable medical materials to be formed (Fig. 5).

However, greater developments can still be made by the adoption of tissue engineering approach, including the creation of 'smart biomaterials' which can incorporate and stabilise such factors as cells, bioactive agents and sensors. Research on these types of bioactive materials is already being performed [292–296], but the limiting factors of short half-life, controlled release and potential toxicity are still to be verified and optimised.

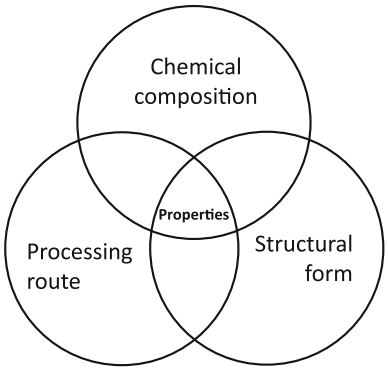

Fig. 5 Basic factors involved in optimising the biological and mechanical properties of a material for specific medical applications

There appears to be a move towards profiting from the combinatory benefits of composite materials, in particular for use as scaffold materials. Composite production techniques are allowing improved control and greater reproducibility of scaffold microstructures with desired levels of porosity, bioactivity and degradation rates. However, there is still much to be learnt and understood in the field of bioactive materials and scaffolds to fully optimise bone cell scaffolds and allow their structural and biological requirements to be better conquered.

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