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Bioceramics: Past, present and for the future

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Abstract

There have been a number of major advances made in the field of bioactive ceramics, glasses and glass ceramics during the past 30–40 years. From initial work on the development of materials that are tolerated in the physiological environment, emphasis has now shifted towards the use of ceramic materials that interact with bone tissue by forming a direct bond. It is now possible to choose, by compositional control, whether these materials are biologically stable once incorporated within the skeletal structure or whether they are resorbed over time. This paper reviews the ground-breaking work that was performed during the 1970s and 1980s in the field of bioceramics in the production and characterisation of bioactive and bioresorbable glasses, glass ceramics and calcium phosphates. The review then explores the influence of the original concepts and ideas on the more recent development of ceramic scaffolds, composites and coatings with enhanced bioactivity for bone tissue engineering.
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1. Introduction

During the past 30–40 years there has been a major advance in the development of medical materials and this has been in the innovation of ceramic materials for skeletal repair and reconstruction. The materials within this class of medical implant are often referred to as "Bioceramics" and the expansion in their range of medical applications has been characterised by a significant increase in the number of patents and publications in the field and an ever increasing number of major international conferences and themed meetings. Bioceramics are now used in a number of different applications throughout the body. According to the type of bioceramics used and their interaction with the host tissue, they can be categorised as either "bioinert" or "bioactive" and the bioactive ceramics may be resorbable or non-resorbable. The materials used include: polycrystalline materials; glasses, glass ceramics and ceramic-filled bioactive composites, and all these may be manufactured either in porous or in dense form in bulk, as granules or in the form of coatings. For the purposes of this review, focus will be placed upon the use of bioceramics as medical implants for the repair and reconstruction of diseased or damaged hard tissue and to describe some of the major developments in bioactive materials during the past 40 years. While every attempt has been made to reflect accurately the developments that have taken place it is impossible to fully acknowledge all of the very large number of researchers working in the field.

2. Early use of bioceramics

Bone is a complex living tissue which has an elegant structure at a range of different hierarchical scales. It is basically a composite comprising an organic phase (based on collagen) in which calcium-containing inorganic crystals[1] are embedded. However, although the skeleton plays a vital role in the mammalian body both in terms of support and locomotion and also the protection of vital organs, it is susceptible to fractures as a result of injury and degenerative diseases which are often associated with ageing. Therefore there has always been a need, since the earliest time, for the repair of damaged hard tissue.

The earliest attempts to replace hard tissue with biomaterials aimed to restore basic functions by repairing the defects caused by injury and disease—however the aim was to elicit minimal biological response from the physiological environment. These materials are now largely classed as "Bioinert" and the absence of a toxic response would have been considered to be a successful outcome. "Bioinert" is a term that should be used with care, since it is clear that any material introduced into the physiological environment will induce a response—however

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for the purposes of biomedical implants, the term can be defined as a minimal level of response from the host tissue in which the implant becomes covered in a thin fibrous layer which is non-adherent.

As with many biomedical implants, the material used in clinical application was originally designed for quite different purposes and the development of bone cement and some of the metallic alloys are prime examples of this. However, more recently, interest has been directed towards the advantageous properties of ceramics including their excellent levels of chemical resistance, compressive strength and wear resistance.

In the 1920s de Jong[2] first observed the similarities between the X-ray diffraction patterns of bone mineral and a calcium phosphate compound, hydroxyapatite. Later Posner and co-workers identified the crystallographic structure of bone mineral and hydroxyapatite.[3–5] A series of studies in the 1960s, revealed that the presence of carbonate in bone and tooth mineral and hydroxyapatite may be observed directly, using infra-red spectroscopy, in the form of weak peaks between 870 and 880 cm^{-1} and a stronger doublet between 1460 and 1530 cm^{-1} and also through alterations in the hydroxyapatite lattice parameters from X-ray diffraction.[6] The effects of the substitution of electronegative anions, such as fluorine and chlorine for (OH), were also reported to influence the lattice parameters of the structures.[7] However, the main thrust of these studies was characterisation and it was not until later in the 1960s and beyond that the development of bioactive ceramics came of age.

3. Major developments during the past 40 years

The decades following the 1960s have become recognised as an extremely significant era in the development of bioceramics and we are very fortunate to have been able to work through these times of huge advances in knowledge and technology. There are a number of very important names in the field that all began their seminal work within the same time period. These major contributors include Professors Bonfield, Hench, DeGroot and Kokubo with Professors Zhang, Aoki and Jarcho, all providing major advances in the UK, Europe, the USA, Japan and China. While ideally this review would document all of the work performed across the globe during this period, it is necessary to concentrate on just a few of the most significant developments.

3.1. Bioglass®

It is reported[8] that the history of Bioglass® began in 1967 when Professor Larry Hench learned of the terrible cost of wounds sustained during the Vietnam War in terms of amputations. The need for the development of materials that would help in the repair of tissues by forming a direct bond with them, rather than the interfacial scar tissue that occurred around metallic and polymeric implants of that time. In the early 1970s, Hench et al.[9–11] reported that particular compositions with the Na_2O–CaO–P_2O_5–SiO_2 system with B_2O_3 and CaF_2 additions formed a strong, adherent bond with bone. The equilibrium phase diagram for Na_2O–CaO–SiO_2 shows a ternary eutectic near the 45S5 composition (the 45 representing 45 wt% SiO_2, S being the network former and 5 representing the ratio of CaO to P_2O_5) and this was the original basis for selecting this composition for investigation.

In vitro tests showed that the 45S5 Bioglass® composition undergoes a surface reaction which occurs very rapidly. The surface reaction is a complex, multi-stage process which results in the formation of a biologically active hydroxy-carbonate apatite (HCA) layer. This HCA phase is chemically and structurally similar to the mineral phase in bone and thus it provides a direct bonding by bridging host tissue with implants.[12,13]

In order to assess this new class of highly bioactive material, in 1991, Hench proposed an *in vivo* bioactivity index I_B (12.5), which is defined as $I_B = 100/t_{50bb}$, where t_{50bb} is the time required for more than 50% of the interface to be bonded.[14] The rate of bone bonding and the strength and stability of the bond vary with the composition and microstructure of the bioactive materials. Hench et al. reported that for their particular formulation of bioactive glass, bone formed a rapid bond when the silica levels were in the range 42–53%; glasses with 54–60% silica required 2–4 weeks for bone to bond; and bone did not form a direct bond with glasses containing more than 60% silica.

Hench also provided new understanding about the fundamental behaviour of implanted bioactive materials. He defined two classes of bioactive materials (A and B) characterised by the rate of bone regeneration and repair. Class A materials are those that lead to both osteoconduction (the growth of bone along the bone–implant interface) and osteoproduction as a result of the rapid reactions on the implant surface.[15,16] Class B bioactivity occurs when only osteoconduction occurs.[17,18] In 1981, Dr. June Wilson reported that in addition to its excellent bone-bonding properties, soft connective tissues form a bond with Bioglass®[19] Many glasses have since been developed and reported in the literature. These materials are often based in the same system as Hench's original formulation. While excellent investigations have been reported (for example by Hatton, Hoeland, Andersson and Knowles and their respective co-workers), it is not possible to cover the full range of work in this area within the scope of this paper.

3.2. A-W glass-ceramic

At around the same time that the original work on Bioglass® was being undertaken, Kokubo et al. were developing a new glass-ceramic material in Japan and they first reported the production and behaviour of A-W glass-ceramic in 1982.[20]

Apatite-wollastonite (A-W) glass-ceramic became one of the most extensively studied glass ceramics for use as a bone substitute. A dense and homogeneous composite was obtained after heat treatment of the parent glass, which comprised 38 wt% oxyfluorapatite ($Ca_{10}(PO_4)_6(O,F)_2$) and 34 wt% β-wollastonite ($CaO{\cdot}SiO_2$) crystals, 50–100 nm in size in a MgO-CaO-SiO_2 glassy matrix. Apatite-wollastonite glass-ceramic is an assembly of small apatite particles effectively reinforced by wollastonite. The bending strength, fracture toughness and Young's modulus of A-W glass-ceramic are the highest among bioactive glass and glass ceramics, enabling it to be used in some major compression load bearing applications, such as vertebral prostheses

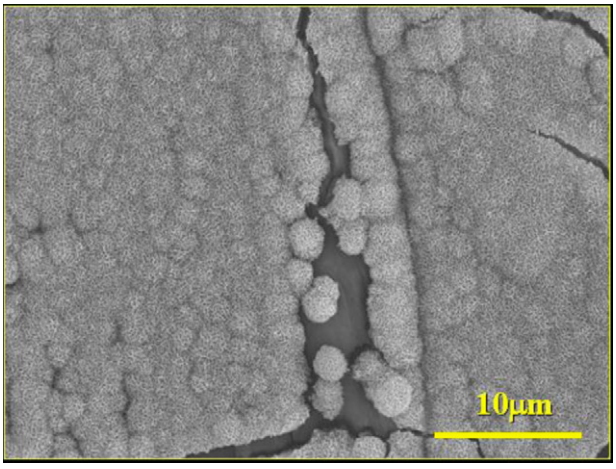

Fig. 1. A typical carbonate apatite layer formed on a bioactive substrate after soaking in Simulated Body Fluid. Image obtained by Dr. J. Juhasz.

and iliac crest replacement. It combines high bioactivity with suitable mechanical properties.[21–26]

The final product contains:

Wollastonite	28 wt% (CaO·SiO2)
Oxyfluoroapatite	34 wt% ($Ca_{10}(PO_4)_6(O,F_2)$)
Glass	28 wt% (MgO 17 wt%, CaO, 24 wt%, SiO_2, 59 wt%)

In addition to his work on glass-ceramic A-W, Kokubo is also noted for the development of a rapid method of ranking the bioactivity of bioactive ceramics. Kokubo and co-workers developed a solution of ions similar in composition to that of human blood plasma. It was found that, when samples were immersed in Simulated Body Fluid (K9), a carbonated hydroxyapatite layer formed on the surface and the rate at which this occurred could be correlated with the likely activity of the sample *in vivo*.[27,28] Fig. 1 shows a typical apatite layer formed on a bioactive substrate after soaking in SBF.

Since the initial development of Kokubo's Simulated Body Fluid, a very large number of studies have taken place to utilise the original method, and also to modify the composition of the solution either as a means of assessment of bioactivity or as method for the deposition of low temperature coatings on a variety of substrates.

3.3. Calcium phosphates

As mentioned earlier, the mineral component of bone is a calcium phosphate. There exists a family of calcium phosphates and the properties of each compound can be characterised according to the proportion of calcium to phosphorus ions in its structure. One of the most widely used synthetic calcium phosphate ceramics is hydroxyapatite (HA) and this is due to its chemical similarities to the inorganic component of hard tisuses. HA with a chemical formula of $Ca_{10}(PO_4)_6(OH)_2$, has a theoretical composition of 39.68 wt% Ca, 18.45 wt% P; Ca/P wt ratio of 2.151 and Ca/P molar ratio of 1.667. It has higher stability in aqueous media than other calcium phosphate ceramics within a pH range of 4.2–8.0.

Tricalcium phosphate (TCP) is a biodegradable bioceramic with the chemical formula, $Ca_3(PO_4)_2$. TCP dissolves in physiological media and can be replaced by bone during implantation. TCP has four polymorphs, the most common ones are the α and β forms. The stoichiometry of HA is highly significant where thermal processing of the material is required. Slight imbalances in the ratio of Ca/P can lead to the appearance of extraneous phases. If the Ca/P ratio is lower than 1.67, then alpha- or beta tricalcium phosphate may be present after processing. If the Ca/P is higher than 1.67, calcium oxide (CaO) may be present along with the HA phase. These extraneous phases may adversely affect the biological response to the implant in-vivo.

In certain circumstances it might be desirable for an implant to assist in bone repair and then be slowly resorbed and replaced by natural tissue. However, it is necessary to match the rate of resorption with that of the expected bone tissue regeneration. When the solubility of a calcium phosphate is higher than the rate of tissue regeneration, it will only be of limited use in bone cavity and defect filling. TCP with Ca/P ratio of 1.5 is more rapidly resorbed than HA. Mixtures of HA and TCP, known as biphasic calcium phosphate (BCP), have been investigated as bone substitutes and the higher the TCP content in BCP, the higher the dissolution rate.

It is only in the past 20–30 years that interest in the use of dense hydroxyapatite for implantation has developed and important work was reported in the 1980s and 1990s by the groups led by DeGroot, Jarcho, Driessens, Bonfield and Zhang. Calcium phosphates are now used for a variety of different applications covering all areas of the skeleton including spinal fusion, craniomaxillofacial reconstruction, treatment of bone defects, fracture treatment, total joint replacement (bone augmentation) and revision surgery. Only certain compounds are useful for implantation in the body, compounds with a Ca/P ratio less than 1 are not suitable for biological implantation due to their high solubility. Calcium phosphate implants (and hydroxyapatite, in particular) are used in the form of coatings on metallic implants, as fillers in polymer matrices, as self setting bone cements, as granules or as larger, shaped structures.

The crystal structure of HA can accommodate substitutions by various other ions for the Ca^{2+}, PO_4^{3-} and OH^- groups. The ionic substitutions can affect the lattice parameters, crystal morphology, crystallinity, solubility and thermal stability of HA.

Cationic substitutions occur in the sites normally occupied by the calcium atoms and include sodium, magnesium, potassium, strontium and manganese. Imbalances in the charges of the substituting ion can cause disorder within the crystal structure of HA. The difference in valency caused by such a substitution requires a reduction in anionic charge to maintain charge balance.[29]

Anionic substitutions can either occur in the phosphate- or hydroxyl positions. Fluorapatite and chlorapatite are common examples of anionically substituted HA. They display a similar structure to HA, but the F^- and Cl^- ions substitute for OH^-.

It was probably Raquel LeGeros who first started the work on the characterisation of carbonate substituted HA (carbon-

ate HA, CHA)) for biomedical application, back in the 1960s. Since then, this has become the most extensively studied synthetic substituted HA and this is principally because carbonate is the most abundant substitution in bone mineral (3–8 wt%).[6,1,30] There are two types of carbonate substitution proposed in the literature, these being the substitution of CO_3^{2-} for OH^- (type A) and CO_3^{2-} for PO_4^{3-} (type B) and both of these substitutions influence the crystallographic lattice parameters of the material. Carbonate ion substitution has been shown to increase rates of bone apposition around dense HA implants as compared to pure HA. The increased bioactivity of CHA has been attributed to be due to the greater solubility of the CHA.[31–33] More recently work has been performed to optimise the production and sintering behaviour of CHA for biomedical application.[34–36]

3.4. Plasma-sprayed HA coatings

The clinical application of calcium phosphate ceramics was, for many years, largely limited to non-major load bearing parts of the skeleton due to their inferior mechanical properties. One of the major innovations in the last 20 years has been to plasma spray the femoral stems of hip prostheses with hydroxyapatite. Clinical results for hydroxyapatite-coated implants reveal that they have much longer life times after implantation than uncoated devices and they have been found to be particularly beneficial for younger patients. In the 1980s de Groot et al.[37] published their work on the development of plasma-sprayed hydroxyapatite implants. At the same time Furlong and Osborn,[38] two leading surgeons in the orthopaedics field began implanting plasma-sprayed stems in patients.

A number of factors influence the properties of plasma-sprayed HA coatings including coating thickness (this will influence coating adhesion and fixation—the agreed optimum now seems to be 50–100 μm), crystallinity (this affects the dissolution and biological behaviour), phase purity, chemical purity, porosity and adhesion.[39,40] Methods for the production of coatings and their properties are now largely standardised and plasma-sprayed coated implants have found highly successful clinical application, particularly in younger patients, over recent years.[41–43]

3.5. Calcium phosphates as fillers in composites

During the 1980s and 1990s, Bonfield et al. realised the potential of the use of calcium phosphate as a filler in polymer-matrix composites and the move was envisaged towards improved mechanical performance of HA ceramics.[44] Based on the concept that the structure of bone comprises mineral crystals embedded in a collagen matrix, a method for the twin screw extrusion of composites with a high density polyethylene matrix with homogeneously distributed micron-scale hydroxyapatite particles was developed.[45,46] The material was successfully developed and marketed under the name HAPEX® and used in middle ear implants. Composites of polymer and ceramic can confer favourable mechanical properties, including strength via the ceramic phase, toughness and plasticity via the polymer phase, and graded mechanical stiffness. Another advantage of the materials is that they are sufficiently soft and ductile to be shaped by a surgeon in the operating theatre.

3.6. Calcium phosphate bone cements

Calcium phosphate bone cements first appeared in the literature during the 1980s and these materials offer the potential for in situ moulding and injectability. There are a variety of different combinations of calcium compounds (e.g. α-tricalcium phosphate and dicalcium phosphate) which are used in the formulation of these bone cements but the end product is normally based on a calcium deficient hydroxyapatite.[47,48]

4. The present—current research and development

4.1. Calcium phosphates for bone grafting and tissue engineering

The increase in the biomedical application of bioactive ceramics is occurring simultaneous with the growth of interest in tissue engineering. This is a process whereby cells are delivered to a particular clinical treatment site via a scaffold. The requirements for the scaffolds are very high porosity (greater than 70–80%) with full interconnectivity. The fenestrations between the pores need to be sufficiently large to allow the movement of cells into the scaffold and should also permit vascularisation. Fig. 2 shows a scanning electron micrograph of a typical hydroxyapatite bone graft granule showing high levels of porosity at both the macrostructural and microstructural levels and also pore interconnectivity (sample supplied by ApaTech Ltd, UK). Whether a bioceramic scaffold is seeded with cells prior to implantation or whether it is intended that cells will invade and populate the structure after implantation will influence the precise terms of reference to the material. However, there is a major need in orthopaedic surgery for bone grafts.

Bone grafting currently mainly relies on the use of natural materials—often bone from another operation. One of the biggest problems with these types of procedure is the limited

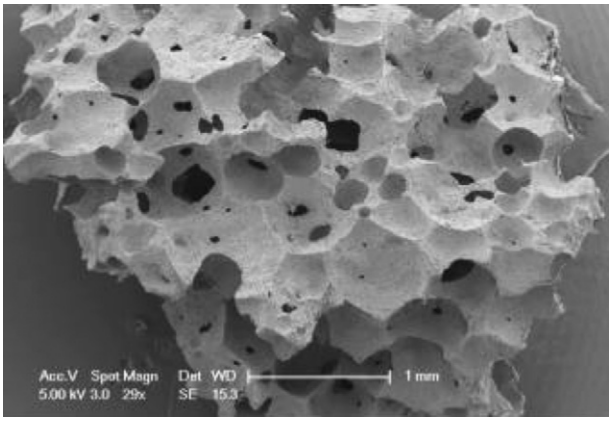

Fig. 2. A hydroxyapatite bone grafting granule. (Sample supplied by ApaTech Ltd.).

availability of the natural material and consequently there is a need for alternative sources of bone graft material. To ensure adequate supply and reproducibility, there is a need for the development of chemically synthesised materials with reproducible structures and chemical composition.

4.2. Chemically and physically modified hydroxyapatite

HA implants have the disadvantage that, in comparison with bioactive glasses and glass ceramics, the rate of bone bonding after implantation is relatively low[49] and this has implications for the time required for patient recovery. Approach towards improving the integration rates of HA with bone have included the incorporation of biological entities such as growth factors, proteins and cells, into the HA implant.[50,51] As an alternative to modifying the biology of the implant, HA may also be chemically doped with small amounts (up to 20 mol%) of elements which are commonly found in physiological bone.[1] These substitutions influence the dissolution rate of apatites, and this has been shown to enhances the proliferation of human osteoblast-like cells *in vitro* and may encourage osseointegration.

In the 1970s, Carlisle[52] reported that dietary silicon influenced the growth and development of chicks. This led Bonfield, Best and co-workers to begin their studies on the development of silicate-substituted hydroxyapatites (Si-HA).[53,32,54,55] *In vivo* studies, comparing the rates of bone apposition to HA and Si-HA ceramic implants, demonstrated a significant increase in amount of bone apposition and organisation to around silicon-substituted HA (Si-HA) implants, illustrating their potential as bone graft materials.[32]

Attempts have been made to prepare silicon-substituted HA (Si-HA) using a number of different synthesis routes. In terms of optimising bioactivity, is important that the ionic substitution of silicon does not result in the thermal instability of the Si-HA, where sintering would result in the decomposition of the Si-HA to undesirable second phases. Gibson et al.[53] produced phase-pure Si-HA by an aqueous precipitation of a calcium-containing solution and a phosphate-containing solution at high pH, using silicon acetate as the source of silicate ions. They proposed the substitution mechanism given in Eq. (1) below:

$$10Ca^{2} + (6-x)PO_4{}^{3-} + xSiO_4{}^{4-} + (2-x)OH^{-} \rightarrow Ca_{10}(PO_4)_{6-x}(SiO_4)_x(OH)_{2-x} \quad (1)$$

Structural analysis has demonstrated that silicate ($SiO_4{}^{4-}$) ions can substitute for the PO_4 sites in HA. The effect of silicate substitution on the crystal structure is to cause a decrease in the a-axis and an increase in the *c*-axis of the unit cell of HA.[53,32,54]

4.3. Thin calcium phosphate coatings

Although the plasma-sprayed coatings are highly successful, their thickness has sometimes led to problems with interfacial shear strength between the coating and the substrate. For this reason, a number of other, "low temperature" and thin film deposition techniques are also being investigated including electrophoresis, sol–gel routes, electrochemical routes, biomimetic routes, electrohyhdrodynamic spray deposition, sputter techniques and bone-like apatite coatings through Simulated Body Fluid treatments. These new coating technologies offer the potential for control of composition- and phase purity. A few of these areas of research will now be described.

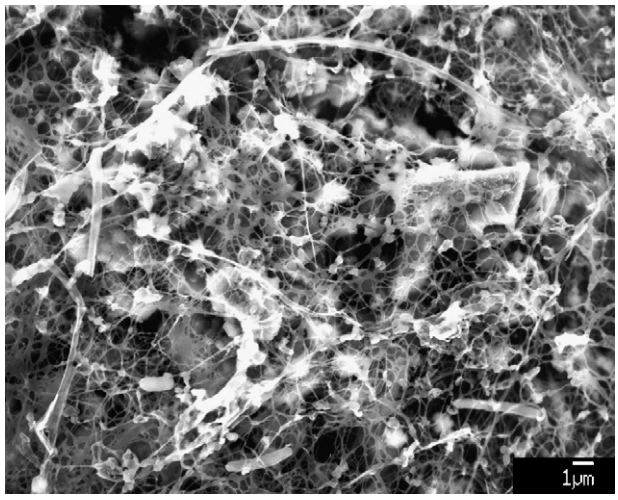

Fig. 3. Mineralised extracellular matrix surrounding osteoblast cells cultured on a magnetron co-sputtered Si-HA thin film for 56 days (image courtesy of Dr. E.S. Thian).

5. Magnetron sputtering

Magnetron sputtering has been used in the electronic- and device industries for many years, but its potential for bioactive coatings on medical implants has only recently been recognised. Sputtering offers the potential to produce dense, uniform and well-adhered coatings on metallic, ceramic or polymeric substrates and the ability to produce thin coatings (<1 μm thickness) with controlled microstructure also reduces the risk of third body wear and osteolysis.

In vivo studies have shown improved bone strength and osseointegration around magnetron-sputtered coatings as compared to plasma-sprayed coatings or non-coated implants.[56–58] However, further investigation of the sputtered CaP coatings is required to provide a better understanding of the likely long term clinical performance of these films.

Based on the success of the silicon-substituted apatite bone grafts, the production of magnetron co-sputtered coatings has been investigated using a combination of HA and Si targets.[59,60] *In vitro* studies have shown that these coatings exhibit enhanced bioactivity and biomineralisation over uncoated samples and pure HA coatings.[61–63] Fig. 3 shows a typical example of osteoblast response to a magnetron co-sputtered Si-HA thin film.

6. Electrospray techniques

Recently, research has been directed towards the development of electrostatic spray deposition technique, allowing the fabrication of dense, porous or nanostructured CaP coatings.[64–68] Fig. 4 shows a typical osteoblast response to nanoscale hydroxyapatite particles deposited on to a glass surface using

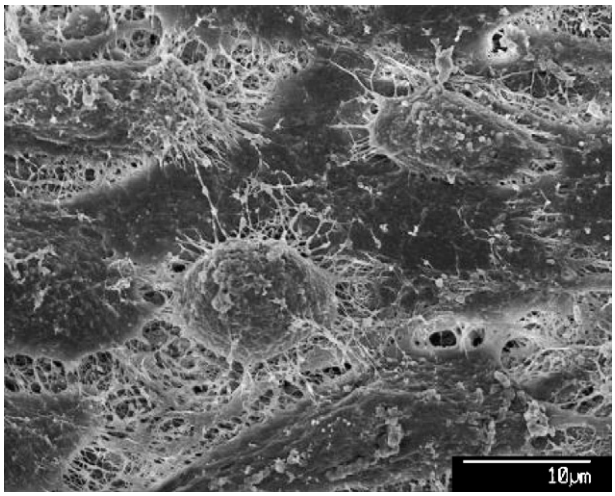

Fig. 4. Osteoblast cells on a glass substrate coating with nanoscale HA deposited via electrohydrodynamic atomisation (image courtesy of Dr. E.S. Thain).

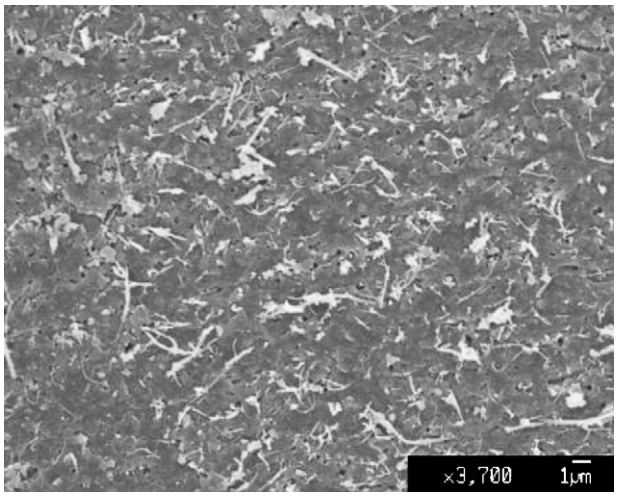

Fig. 5. The surface of a carbon nanotube reinforced HA sample (image courtesy of Ms. A.A. White).

electrohydrodynamic atomisation. Reports in the literature suggest that the special properties of these coatings are likely to influence protein interactions and subsequently, control *in vitro* cell proliferation and differentiation.[69,70] Research has shown that the incorporation of transforming growth factor—beta 1 results in enhanced cellular function.[71] Thus, this route appears to offer the potential for chemical and topographical control of cell behaviour and also drug delivery.

7. Other methods

There have been a number of other recent reports on the preparation of thin bioactive films on biomedical substrates. Si-HA films have been prepared via sol–gel route[72] and pulsed laser deposition[73] techniques. Studies have focused on developing fluoride-substituted HA coatings on metallic surfaces using a sol–gel method, and these results demonstrated a stimulatory effect on cell proliferation and differentiation *in vitro*.[74] Other researchers have concentrated on a biomimetic approach for coating a CaP layer on any suitable substrate surface (metallic, ceramic or polymeric) [75,76]. The biomimetics methodology is based on the immersion of substrates in a supersaturated or metastable solution with ion concentrations and pH value similar to the human blood plasma at a body temperature of 37 °C for several days, in order to induce the formation and growth of several micrometer-thick 'bone-like' apatite layer. Biomimetic coatings are generally produced using simple, low cost, low temperature processes. However, long induction and growth periods are required to form the coatings and adhesion strength between the coating and substrate still require optimisation.

7.1. Composites

Following the successes reported by Bonfield and co-workers with their development of HAPEX® other approaches have been made to produce both biodurable, bioactive composites and biodegradable bioactive composites. Work has included the incorporation of glass-ceramic A-W and Bioglass® within polyethylene and a wide variety of other matrices (see Refs.[77,78]). Other research has been directed towards the improvement of the mechanical performance of hydroxyapatite ceramics through carbon nanotube incorporation.[79] Fig. 5 shows a typical as-pressed surface of a hydroxyapatite sample reinforced with functionalised carbon nanotubes. A recent advance has been in the development of functionally and compositionally graded, mineralised collagen-GAG scaffolds for cartilage and ligament repair.[80] The area of composites for tissue engineering has emerged as a huge field over recent years—but the scope of this range of developments falls outside the main thrust of this review.

7.2. Sol–gel glasses

Based on the earlier work of Hench and co-workers, an alternative approach to the production of glasses has been to use sol–gel techniques and this route can produce high purity glasses, which are more homogeneous than those obtained by melting, and require relatively low processing temperatures. The glasses obtained exhibit higher surface area and porosity, these are the critical factors in their bioactivity.[81]

While bioglasses produced using the conventional melt-processing route have bioactivity with limited compositional ranges, using the sol–gel process, the compositional range of bioactivity was extended up to 100% of SiO_2. It is thought that this is a result of more rapid dissolution and hence the presence of many more silanol groups on glass surface acting as nucleation sites for formation of a carbonated apatite layer.

8. The future

While the past 40 years has seen a major move forward both in the quantity of bioceramics used in clinical application and also the quality of bone repair that they offer, there is still potential for major advances to be made in the field. These include a requirement for the

- Improvement of the mechanical performance of existing bioactive ceramics.
- Enhanced bioactivity in terms of gene activation.
- Improvement in the performance of biomedical coatings in terms of their mechanical stability and ability to deliver biological agents.
- Development smart materials capable of combining sensing with bioactivity.
- Development of improved biomimetic composites.

However, there still needs to be better understanding of the biological system. There is still doubt as to the exact bonding mechanism between bone mineral and collagen. It is also not clear whether the rapid repair that is elicited by the new generation of bioactive ceramics is as a result of the enhancement of mineralisation per se or whether there is a more complex signalling process involving the proteins in collagen. If we were able to fully understand the fundamentals of bone response to specific ions and the signals they activate, then we would be able to design better bioceramics for the future.

9. Conclusion

This paper aimed to provide a broad overview of the development of bioceramics and in particular, bioactive ceramics, glasses and glass ceramics over the past 30–40 years. It is clear that there have been major advances during this time and these have stemmed from seminal work performed by key workers around the world. While the benefits of the use of the novel materials that have been developed is clear, further research is required to fully optimise the performance of the materials in clinical application. We can only hope that over the next 40 years, the new generation of researchers can match the exceptional progress that was made in the last 40 years.

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