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INNOVATIVE BIOCERAMICS

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ABSTRACT

Overall, the benefits of advanced ceramic materials in biomedical applications have been universally appreciated, specifically, in terms of their strength, biocompatibility and wear resistance. However, the amount of supporting data is not large and the continuous development of new methods is pertinent for better understanding of the microstructure-properties relationship and, in general, for obtaining new directives for their further improvement. This paper gives an overview of some of the more innovative applications of bioceramics in medicine.

1. INTRODUCTION

Trauma, degeneration and diseases often make surgical repair or replacement necessary. When a person has a joint pain the main concern is the relief of pain and return to a healthy and functional life style. This usually requires replacement of skeletal parts that include knees, hips, finger joints, elbows, vertebrae, teeth, and repair of the mandible. The worldwide biomaterials market is valued at close to $24,000M. Orthopaedic and dental applications represent approximately 55% of the total biomaterials market. Orthopaedics products worldwide exceeded $13 billion in 2000, an increase of 12 percent over 1999 revenues. Expansion in these areas is expected to continue due to number of factors, including the ageing population, an increasing preference by younger to middle aged candidates to undertake surgery, improvements in the technology and life style, a better understanding of body functionality, improved aesthetics and need for better function[1].

Biomaterial by definition is "a non-drug substance suitable for inclusion in systems which augment or replace the function of bodily tissues or organs". From early as a century ago artificial materials and devices have been developed to a point where they can replace various components of the human body. These materials are capable of being in contact with bodily fluids and tissues for prolonged periods of time, whilst eliciting little if any adverse reactions. [2]

Some of the earliest biomaterial applications were as far back as ancient Phoenicia where loose teeth were bound together with gold wires for tying artificial ones to neighbouring teeth. In the early 1900's bone plates were successfully implemented to stabilise bone fractures and to accelerate their healing. While by the time of the 1950's to 60's, blood vessel replacement were in clinical trials and artificial heart valves and hip joints were in development.

Even in the preliminary stages of this field, surgeons and engineers identified materials and design problems that resulted in premature loss of implant function through mechanical failure, corrosion or inadequate biocompatibility of the component. Key factors in a biomaterial usage are its biocompatibility, biofunctionality, and availability to a lesser extent. Ceramics are ideal candidates with respect to all the above functions, except for their brittle behaviour.

2. GENERAL CONCEPTS IN BIOCERAMICS

It has been accepted that no foreign material placed within a living body is completely compatible. The only substances that conform completely are those manufactured by the body itself (autogenous) and any other substance that is recognized as foreign, initiates some type of reaction (host-tissue response). The four types of responses, which allow different means of achieving attachment of implants to the muscular skeletal system, are given in Figure 1.

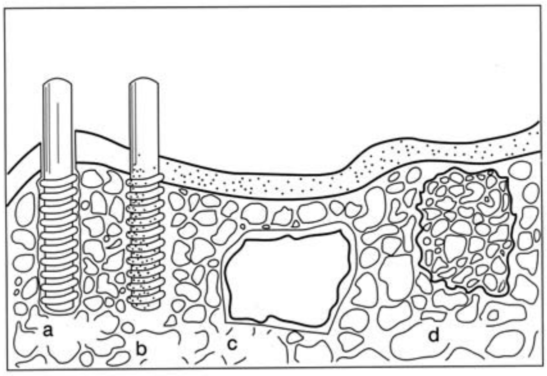

Figure 1. Classification of bioceramics according to their bioactivity; (a) bioinert, alumina dental implant, (b) bioactive, hydroxyapatite ($Ca_{10}(PO_4)_2(OH)_2$)coating on a metallic dental implant, (c) surface active, bioglass, (d) bioresorbable tri-calcium phosphate implant ($Ca_3(PO_4)_2$).

When a synthetic material is placed within the human body, tissue reacts towards the implant in a variety of ways depending on the material type. The mechanism of tissue interaction (if any) depends on the tissue response to the implant surface. In general, there are three terms in which a biomaterial may be described in or classified into representing the tissues responses. These are bioinert, bioresorbable, and bioactive, which are well covered in range of excellent review papers.[3-5]

The term bioinert refers to any material that once placed in the human body has minimal interaction with its surrounding tissue, examples of these are stainless steel, titanium, alumina, partially stabilised zirconia, and ultra high molecular weight polyethylene. Generally a fibrous capsule might form around bioinert implants hence its biofunctionality relies on tissue integration through the implant (Figure 1a).

Bioactive refers to a material, which upon being placed within the human body interacts with the surrounding bone and in some cases, even soft tissue. This occurs through a time – dependent kinetic modification of the surface, triggered by their implantation within the living bone. An ion – exchange reaction between the bioactive implant and surrounding body fluids – results in the formation of a biologically active carbonate apatite (CHAp) layer on the implant that is chemically and crystallographically equivalent to the mineral phase in bone. Prime examples of these materials are synthetic hydroxyapatite [6,7] [$Ca_{10}(PO_4)_6(OH)_2$], glass-ceramic A-W [8,9] and bioglass® [10] (Figure 1b and c)).

Bioresorbable refers to a material that upon placement within the human body starts to dissolve (resorbed) and slowly replaced by advancing tissue (such as bone). Common examples of bioresorbable materials are tricalcium phosphate [$Ca_3(PO_4)_2$] and polylactic–polyglycolic acid copolymers. Calcium oxide, calcium carbonate and gypsum are other common materials that have been utilised during the last three decades (Figure 1d)).

3. THE MORE TRADITIONAL BIOCERAMICS

Many of the more "traditional" ceramics have been used for bioceramics applications. Alumina and zirconia, for example, have been used as inert materials for a range of applications from the 1960's. Their high hardness, low friction coefficient and excellent corrosion resistance offers a very low wear rate at the articulating surfaces in orthopaedic applications. Microstructures are controlled to inhibit static fatigue and slow crack growth while the ceramic is under load. Alumina is currently used for orthopaedic and dental implants. It has been utilised in wear bearing environments[13] such as the total hip arthroplasties (THA) as the femoral head generating reductions in wear particles from ultra-high molecular weight polyethylene (UHMWPE). Other applications for alumina encompass porous coatings for femoral stems, porous alumina spacers (specifically in revision surgery) and in the past as polycrystalline and single crystal forms in dental applications as tooth implants.[3,11-13]

Compared to alumina, PSZ has higher flexural strength, fracture toughness and high Weibull modulus (better reliability), as well as lower Young's modulus and the ability to be polished to a superior surface finish.[14, 15] The higher fracture toughness is of importance in femoral heads due to the tensile stresses induced by the taper fit onto the femoral stem.

Partially stabilized zirconia femoral heads make up about 25% of the total number of operations per year in Europe, and 8% of the hip implant procedures in USA. It has been reported that over 400,000 zirconia hip joint femoral heads have been implanted since 1985 until 2001. Most of the zirconia femoral heads (tetragonal zirconia polycrystal, TZP) consists of 97 mol%ZrO_2 and 3 mol %Y_2O_3. Although not quite as hard as alumina, PSZ still possesses excellent wear resistance and has been used for similar orthopaedic applications as alumina. Wear rates of UHMWPE against partially stabilised zirconia have been found to be low enough such that tribological debris would not be a problem in clinical applications. [14, 15]

The first x-ray diffraction study of bone was published[16] by De Jong in 1926, in which apatite was identified as the only recognizable mineral phase. He also reported marked broadening of the diffraction lines of bone apatite, which he attributed to small crystal size. It was not until the 1970's that synthetic hydroxyapatite [$Ca_{10}(PO_4)_2(OH)_2$] was accepted as a potential biomaterial that forms a strong chemical bond with bone *in vivo*, while remaining stable, under the harsh conditions encountered in the physiologic environment.

Since discovery of the bioglasses, which bond to living tissue (Bioglass®) by Hench and Wilson[17], various kinds of bioactive glasses and glass-ceramics with different functions such as high mechanical strength, high machinability and fast setting ability have been developed. The glasses that have been investigated for implantation are primarily based on silica (SiO_2), which may contain small amounts of other crystalline phases. The most prominent and successful application of this is Bioglass®, which can be found in detail in various comprehensive reviews.[5,9,18,19] Bioactive glass compositions lie in the system $CaO-P_2O_5-SiO_2$. The first development of such a bioglass began in 1971 when 45S5 Bioglass® was proposed with a composition of 45% SiO_2, 24.5% CaO, 24.5% NaO_2, and 6% P_2O_5 by weight.[10] Hench[5], and Vrouwenvelder *et al.* [20], suggested that bioglass® 45S5 has greater osteoblastic activity as compared to hydroxyapatite. Li *et al.,* [21] prepared glass ceramics with differing degrees of crystallinity and found that the amount of glassy phase remaining directly influences the formation of an apatitic layer, with total inhibition when the glassy phase constituted less than about 5 wt.%.

Due to the surface-active response of these types of materials, they have been accepted as bioactive (or surface-active) biomaterials and have found applications in middle ear, alveolar ridge maintenance implants and other non-load bearing conditions.[17] Kokubo *et al.* in 1982 produced[8] a glass-ceramic containing oxyfluorapatite $Ca_{10}(PO_4)_6(OH,F_2)$ and wollastonite ($CaO.SiO_2$) in a $MgO-CaO-SiO_2$ glassy matrix, which was named A-W glass-ceramic. It was reported that this glass-ceramic A-W, spontaneously bond to living bone without forming the fibrous tissue around them. A bioactive and machinable glass ceramic named Bioverit® has also been developed, which contains apatite and phlogophite $(Na,K)Mg_3(AlSi_3O_{10})(F)_2$. It is used in clinical applications as artificial vertebra.

4. INNOVATIVE CERAMICS

4.1 New Modified Zirconia Implants

Zirconia ceramic implants somehow have had a controversial history regarding their phase metastability, degradation in water lubricants in simulation studies and influence on friction and wear phenomena.

There have been some concerns regarding this degradation phenomenon associated with the tetragonal-to-monoclinic phase transformation under the long-term aqueous condition such as in vivo. One of the current manufacturers of zirconia femoral heads has improved the conventional zirconia, leading to the increased strength and the high resistance to the phase transformation. In addition, it was reported that in hip simulator testing demonstrated that the polyethylene wear against the improved zirconia head is lower than that against the CoCr head. When articulated with highly cross linked poly ethylene, not only zirconia heads but also CoCr heads showed very low wear rates. However, because zirconia is more scratch-resistant than CoCr, it would be more suitable implant for the long-term clinical use. [22]

Yttrium stabilised tetragonal polycrystalline zirconia (Y-TZP) has a fine grain size and offers the best mechanical properties. Low temperature degradation of TZP is known to occur as a result of the spontaneous phase transformation of the tetragonal zirconia to monoclinic phase during ageing at 130-300^{O}C possibly within water environment. It has been reported that this degradation leads to a decrease in strength due to the formation of microcracks and accompanying phase transformation.

Recently degradation free new zirconia-alumina composites have been reported; TZP/alumina composite (80% TZP of [90 mol% ZrO_2-6 mol%Y_2O_3-4 mol%Nb_2O_5 composition] and 20% Al_2O_3.[12] Another potential composite comprised of 70 vol %TZP(stabilized with 10mol%CeO_2), and 30vol%Al_2O_3 and 0.05mol 5TiO_2 is currently being investigated in Japan.

Implant stability is critical in obtaining good long-term success of total joint replacements. Loss of either biological or cement fixation can lead to accelerated wear, pain, loss of function, or even fracture of the implant, each of which could potentially necessitate revision surgery. Fixation strength can be improved by using macrotextured (porous or textured) surfaces, which enhance the potential for mechanical inter-lock at the implant-bone interface.

Oxidized zirconium, a material introduced in 2000 for orthopaedic bearing applications (Oxinium™, Smith & Nephew, Inc., Memphis, TN) and reported to have beneficial wear and abrasion resistance [23, 24], cannot be easily processed using traditional porous coating techniques. Therefore, an alternative chemical surface texturing method was utilized. Chemical texturing process has been used clinically on Ti-6Al-4V total hip replacement components to create a surface morphology suitable for bone in-growth.[25] This texturing method, known commercially as ChemTex® 5-5-5 (CYCAM, Inc., Houston, PA), and a newly developed chemical texturing process, known commercially as Tecotex® I-103 (Tecomet, Woburn, MA), were selected to produce macro-textured surfaces (R_{max} > 0.4 mm) on a zirconium alloy (Zr-2.5Nb). These textured surfaces are subsequently oxidized to form a hard ceramic layer uniformly about 5 μm thick over the entire surface, which consists predominantly of monoclinic zirconia (Figure 2).[26]

4.2 Simulated Body Fluid (SBF)

One of the most promising methods in bioceramics has been the introduction of *simulated body fluids* (SBF) by Kokubo and co-workers[27, 28]. This synthetic body fluid is highly supersaturated in calcium and phosphate in respect to apatite under even normal conditions. Therefore, if a material has a functional group effective for the apatite nucleation on its surface, it can form the apatite spontaneously. It is widely accepted that the essential requirement for an artificial material to bond to living bone is the formation of bonelike apatite layer on its surface. Formation of the bonelike apatite layer on the bioactive materials can be produced in a simulated body fluid (SBF) with ion concentrations almost equal to those of the human blood plasma. Most current bioceramics research utilises this solution to measure the bioactivity of an artificial material by examining apatite-forming ability on its surface in SBF solution.

Hydroxyapatite layers can be easily produced on various organic or inorganic substrates in SBF. Kokubo *et al.* in 1989 showed after immersion in SBF, wide range of biomaterial surfaces showed very fine crystallites of carbonate ion containing apatite.[27] Osteoblasts have been shown to proliferate and differentiate on this apatite layer.

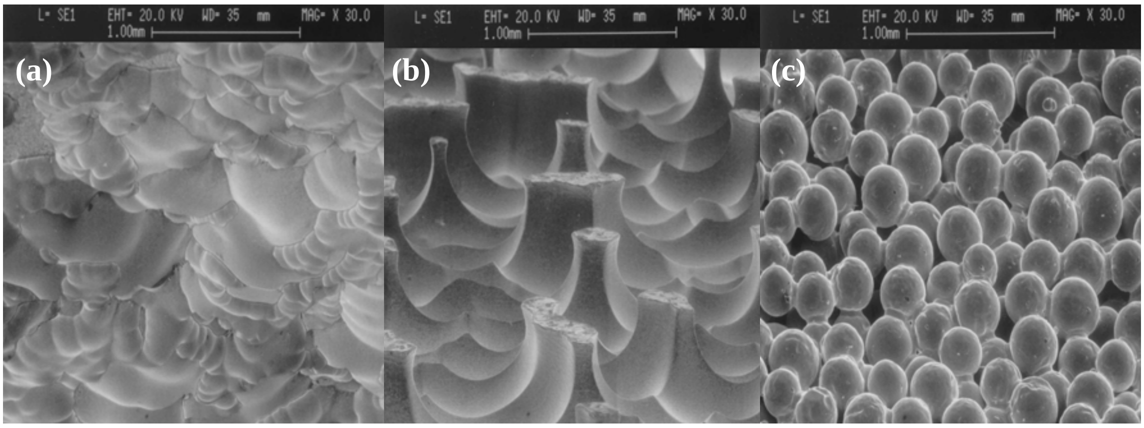

Figure 2. Surface texture SEM images of ; (a) ChemTex® textured (CT) surface, (b) Tecotex® textured (TT) surface, and (c) porous sintered bead (SB) coating (30x) (after Heuer et al.[26]).

SBF is a metastable solution and if an apatite nucleating functional group is present on a substrate within the fluid, the apatite spontaneously nucleates. It has been reported that this nucleation rate can be increased if excessive amounts of Ca^{2+} ions, PO_4H_2, and Si-OH, Ti-OH, Zr-OH, Ta-OH, Nb-OH or similar functional groups are present[28]. It has been shown that highly porous gels of SiO_2, TiO_2, ZrO_2, Nb_2O_5 and Ta_2O_5 could form apatite layers on their surfaces in SBF. This has been reported to indicate that above mentioned functional groups with a specific structure are effective for the apatite nucleation in the body environment.[28]

4.3 Coralline Apatites

Coralline apatites can be derived from the sea coral. Coral is composed of calcium carbonate in the form of aragonite. As coral is a naturally occurring structure and has optimal strength and structural characteristics. The pore structure of coralline calcium phosphate produced by certain species is similar to human cancellous bone, making it a suitable material for bone graft applications (Figure 3). Coral and converted coralline hydroxyapatite have been used as bone grafts and orbital implants since the 1980s, as the porous nature of the structure allows in-growth of blood vessels to supply blood for bone, which eventually infiltrates the implant.

Pore interconnection sizes are of utmost importance when hard and soft tissue in-growth is involved. Kühne *et al.*, showed[29] that implants with average pore sizes of around 260 μm had the most successful in-growth as compared to no implants (simply leaving the segment empty). It was further reported that the interaction of the primary osteons between the pores via the interconnections allows propagation of osteoblasts.

The hydrothermal method was first used in 1974, for hydroxyapatite formation directly from corals by Roy and Linnehan.[30] It was reported that complete replacement of aragonite ($CaCO_3$) by phosphatic material was achieved less than 533 K and 103 MPa by using the hydrothermal process. In 1996, HAp derived from Indian coral using hydrothermal process was reported.[31] However, the resultant material was in the form of a powder and required further forming and sintering.

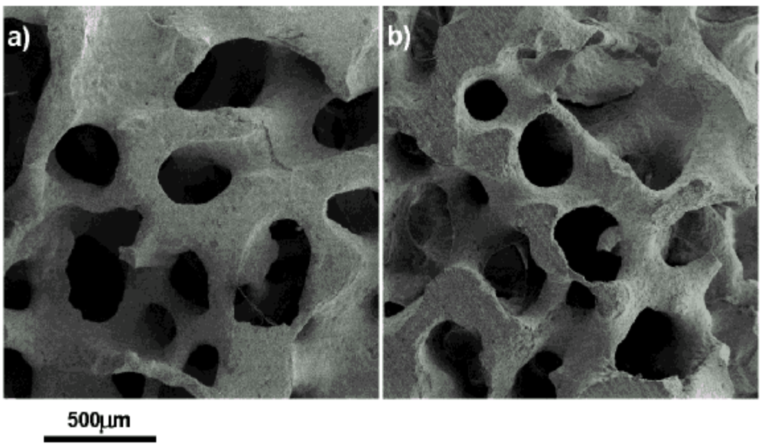

Figure 3. Comparison of the Australian coral (a) in original state and (b) after hydrothermal conversion.[33]

During the hydrothermal treatment hydroxyapatite replaces the aragonite whilst preserving the porous structure. The following exchange takes place:

$$10CaCO_3 + 6(NH_4)_2HPO_4 + 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 6(NH_4)_2CO_3 + 4H_3CO_3 \quad (1)$$

The resulting material is known as coralline hydroxyapatite, whether in the porous coralline structure or in powdered form.

Aragonite to carbonate hydroxyapatite was achieved by using microwave processing technique. Higher extends of conversion were reported.[32]

Hu *et al.*, [33] succeeded to convert Australian coral to monophasic hydroxyapatite by using a two-stage process where the hydrothermal method was followed by a patented hydroxyapatite sol-gel coating process based on alkoxide chemistry. They reported 120% increase in the biaxial strength of the double-treated coral in comparison to only converted one.

4.4 Calcium Phosphate Coatings

Porous hydroxyapatite has been accepted that due to its unfavourable mechanical properties it cannot be used under load bearing purposes. For this reason hydroxyapatite has been used as thin film coatings on metallic alloys. Of the metallic alloys investigated titanium based alloys have shown to be the material of preference for thin film coatings.[34] Titanium alloys possesses good mechanical strength and fatigue resistance under load bearing conditions. They are lightweight, with high strength to weight ratios.

Of the coating techniques utilized, thermal spraying tends to be the most commonly used and analysed. This technique has been faced with challenges of producing a controllable resorption response in clinical situations. Besides the set backs, thermally sprayed coatings are continually being improved by using different compositions and post heat treatments which converts amorphous phases to crystalline calcium phosphates. Other techniques are being investigated. Techniques that are capable of producing thin coatings include pulsed-laser deposition[35] and sputtering[36] which, like thermal spraying involves high - temperature processing. Other techniques such as electrodeposition [37,38], and sol-gel[39] utilise lower temperatures and avoid the challenge associated with the structural instability of hydroxyapatite at elevated temperatures.[40]

The advantages of sol-gel technique are numerous; it results in a stoichiometric, homogeneous and pure coating due to mixing on the molecular scale; reduced firing temperatures due to small particles sizes with high surface areas; it has the ability to produce uniform fine-grained structures (Figure 4); the use of different chemical routes (alkoxide or aqueous based); and their ease of application to complex shapes with a range of coating techniques those being dip, spin, and spray coating. The lower processing temperature has another advantage; it avoids the phase transition (~1156 K) observed in titanium based alloys used for biomedical devices.

4.5 Synthetic Bone Graft Ceramics

Bone grafting is currently used in orthopaedic and maxillofacial surgery for the treatment of bridging diaphyseal defects, non-union, filling metaphyseal defects and mandibular reconstruction. Autogeneous bone graft is osteogenic (which forms bone, due to living cells such as osteocytes or osteoblasts), osteoconductive (have no capacity to induce or form bonebut they provide an inert scaffold which osseous tissue can regenerate bone), osteoinductive (stimulate cells to undergo phenotypic conversion to osteoprogenitor cell types capable of formation of bone). There are no substitutes for autogenous bone; there are, however, synthetic alternatives.

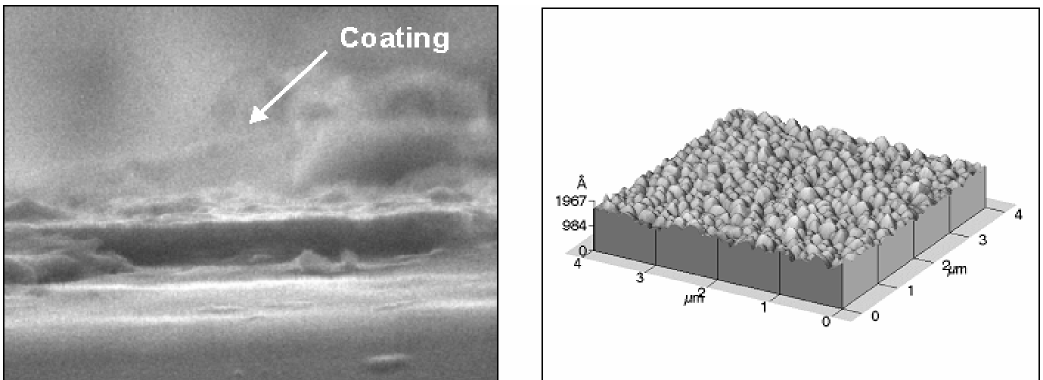

Figure 4. SEM and AFM images of sol-gel (alkoxide) derived hydroxyapatite coatings.

Allografts have been used as an alternative, but it has low or no osteogenicity, increased immunogenicity and resorbs more rapidly than autogenous bone. In clinical practice, fresh allografts are rarely used because of immune response and the risk of transmission of disease. The frozen and freeze-dried types are osteoconductive but are considered, at best, to be only weekly osteoinductive. Freeze drying diminishes the structural strength of the allograft and renders it unsuitable for use in situations in which structural support is required. Allograft bone is a useful material in patients who require bone grafting of a non-union but have inadequate autograft bone. Bulk allografts can be utilised for the treatment of segmental bone defects.[41] Their use is well documented for reconstruction after resection of bone tumours, however not common in reconstruction after trauma in which bone lengthening and transport are usually required.

Demineralised bone matrix (DBM) was first observed by Urist in 1965 to induce heterotopic bone.[42] The active components of DBM are a series of glycoproteins, which belong to a group of transforming growth factor family (TGF-β). The members of this group are responsible for the morphogenic events involved in the development of tissue and organs. Urist later isolated a protein from the bone matrix, which was termed as the bone morphogenic protein (BMP).[42] DBM is commercially available and used in management of non-union of fractures. They are not suitable where structural support is required. To date, the main delay in developing clinical products has been the need to find a suitable carrier to deliver the BMP to the site at which its action is required. New generation ceramic composites/hybrids could fill this gap. Experimentally, BMP-2 and OP-1® (BMP-7) have been shown to stimulate the formation of new bone in diaphysical defects in the rat, rabbit, dog, sheep and non-human primates.[43] The use of BMP's with new calcium phosphate derivatives or composites could be used for bone remodelling where bone regeneration and remodelling is needed such as therapeutic applications in osteoporosis.

Bovine collagen mixed with hydroxyapatite is marketed as a bone-graft substitute, which can be combined with bone marrow aspirated from the site of the fracture. Although no transmission of disease has been recorded, their use will continue to be a source of concern. This material is osteogenic, osteoinductive and osteoconductive however it lacks the structural strength required.

4.6 Titanium Metal Surface Modifications

Ti metal forms a sodium titanate hydrogel layer on its surface, when it is soaked in 5M-NaOH solution at 60ºC for 24 h. The gel layer is stabilized as an essentially amorphous and sodium titanate layer without giving significant change in its graded structure, when the Ti metal is subsequently heat-treated at 600ºC for 1 h. It was reported that these treatments with NaOH and subsequent heat treatment gave no adverse effect on mechanical properties of the Ti metal.[44] This kind of bioactive metal is believed to be useful as bone substitute even under load bearing portions such as artificial total hip and knee joints, spinal cages and dental implants. More than 70 patients have been reported to receive artificial total hip joints of Ti alloy, modified with titanium beads subjected to NaOH treatments in Japan.[45]

4.7 Nanoapatite-Polymer Fibre Composites

Bone is a composite in which nanosized apatite particles are deposited on organic collagen fibres. Similar composites could be prepared without the aid of living cells, if synthetic organic fibres are fabricated into a three-dimensional structure modified with functional groups effective for the apatite nucleation on their surfaces, and then soaked in SBF. The resultant composite is expected to exhibit bioactivity as well as analogous mechanical properties to those of the living bone.

For example, ethylene-vinyl alcohol copolymer (EVOH) fibres constituting two dimensional fabrics were modified with a calcium silicate on their surfaces by being subjected to silane coupling treatment and subsequent soaking in a calcium silicate solution with a molar ratio of $Si(OC_2H_5)_4/H_2O/C_2H_5OH/Ca(NO_3)_2$ of 1.0/4.0/4.0/0.014/0.2. Kokubo et al.[45] in their recent work demonstrated that nanosized bonelike apatite particles deposited uniformly on individual fibres constituting a fabric when soaked in SBF for 2 days. In another case, the same fibres were modified with an anatase-type titania on their surfaces by being subjected to silane coupling treatment, soaking in a titania solution with a molar ratio of $Ti(O\textit{i}C_3H_7)_4/H_2O/C_2H_5OH/HNO_3$ of 1.0/1.0/9.25/0.1 and subsequent soaking in 0.1M-HCl solution at 80ºC for 8 d. Nano-sized bonelike apatite particles deposited uniformly on individual fibres constituting a two-dimensional fabric in SBF.[45]

As these pioneering works shows, if these kind techniques could be successfully applied to three-dimensional fabrics, bioactive materials similar to those of the living hard and soft tissues could be obtained.

4.8 Bioceramics in In Situ Radiotherapy and Hyperthermia

One of the most common approaches in cancer treatment is the removal of the diseased parts, however unfortunately recovery or return of full function is seldom achieved. Noninvasive treatment techniques where only the cancer cells are destroyed were introduced in mid 80's. In 1987, microspheres of $17Y_2O_3$-$19Al_2O_3$-$64SiO_2$ (mol%) glass, 20-30 μm in diameter were shown to be effective for *in situ* radiotherapy of liver cancer[46]. ^{89}Yttrium in this glass is non-radioactive but can be activated by neutron bombardment, to ^{90}Y, which is a β-emitter with halflife of 64.1 h. They are usually injected into diseased liver through the hepatic artery, and entrapped in small blood vessels, which block the blood supply to the cancer and directly irradiate the cancer with β-rays. Since the β-ray transmits living tissue only 2.5 mm in diameter and the glass microspheres have high chemical durability, the surrounding normal tissue is hardly damaged by the β-rays.

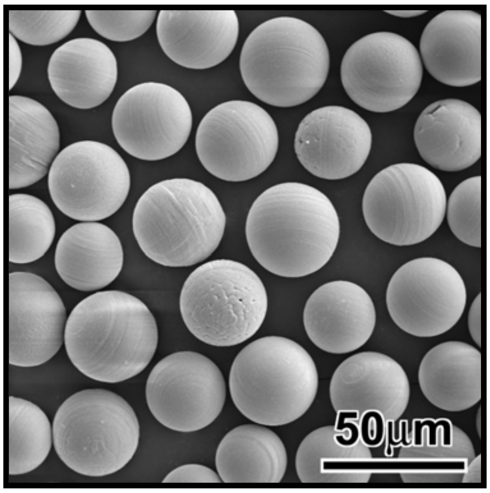

Figure 5. SEM image of Y_2O_3 microspheres for radiotherapy applications (after Kokubo et al.[45]).

These glass microspheres are already clinically used in Australia, Canada and U.S.A. The content of Y_2O_3 in the microsphere is, however, limited to only 17 mole%, as they are prepared by conventional glass melting techniques. Recently, Kokubo et al. successfully prepared pure Y_2O_3 polycrystalline microspheres 20 to 30 µm in diameter by high-frequency induction thermal plasma melting technique[47], (Figure 5). It was reported that they observed higher chemical durability than the Y_2O_3-containing glass microspheres. It was further reported that these ceramic microspheres are more effective for *in situ* radiotherapy of cancer.

Oxygen is known to be poorly supplied to cancerous cells to produce lactic acid, and hence can be destroyed around 43ºC, whereas the normal living cells can be kept alive even around 48ºC. If ferri- or ferromagnetic materials are implanted around cancers and placed under an alternating magnetic field, it is expected that cancer cells locally heated can be destroyed by magnetic hysteresis loss of the ferri- or ferromagnetic materials.

Kokubo and co-workers prepared a ferrimagnetic glass-ceramic containing 36 wt% of magnetite (Fe_3O_4) 200 nm in size in a CaO-SiO_2 matrix. It was reported that cancerous cells in medullary canal of rabbit tibia were completely destroyed when this glass-ceramic is inserted into the tibia and placed under an alternating magnetic field.[48] This kind of invasive treatment, however, cannot be applied to humans, since cancer cells metastasize. In the case of humans, ferri- or ferromagnetic material must be injected to the cancer in a form of microsphere 20 to 30 µm in diameter through blood vessels similar to the radioactive microspheres. For this purpose, heat-generating efficiency of the ferrimagnetic material must be further increased. Recently microspheres of 20 to 30 µm in diameter in which magnetite particles 50 nm in size deposited on silica microspheres 12 µm in diameter, through deposition of β-FeOOH in a solution and its subsequent transformation into Fe_3O_4 at 600ºC under CO_2-H_2 gas atmosphere. It was reported that its heat generating efficiency was about four times that of the glass-ceramic described above.

Unlike other molecules that are used to encapsulate drugs, fullerenes resist breakdown by the body. This stability is especially important for holding compounds that would cause harm if released in healthy cells, for example, radioactive metal atoms.

L. Wilson[49] have modified 60-carbon fullerenes, called buckyballs, to home in on bone when injected into the body. Gonzalez and Wilson designed their compound to stick to hydroxyapatite. They also got a surprise when characterizing the compound: The molecule has one unpaired electron, making it magnetic. This property makes the compound a potential contrast agent for magnetic resonance imaging (MRI). A contrast agent injected into a patient can sharpen an MRI picture, revealing otherwise invisible features.

S. R. Wilson[50] is working on fitting radioactive metals inside thebuckyball, which as they travel through the bloodstream, will emit radiation. But since they are excreted intact, they will completely remove the radiation from the body after the procedure. He is also working on fullerenes that will deliver bone-building drugs for osteoporosis. Currently, most of those drugs are not well absorbed and are toxic. Buckyballs might offer a nontoxic molecular ship to deliver the materials safely to fragile bones. And on a more distant horizon, buckies may someday carry light-activated and/or cancer-killing drugs to tumor cells. Smalley would love to see this last application happen soon. The discoverer of buckyballs has recently suffered a recurrence of lymphatic cancer.

Bianco et.al at the CNRS Institute in Strasbourg[51], have shown that carbon nanotubes are adept at entering the nuclei of cells and may one day be used to deliver drugs and vaccines. They have modified nanotubes to transport small peptide into the nuclei of fibroblast calls. This gives hope that the nanotubes may be useful for forming the basis of anti-cancer treatments, gene therapies and vaccines.

4.8 Bone Cement Composites

During the last 5 years bone cement materials has grown in popularity and are a very promising osteoconductive substitutes for bone graft. They are prepared like acrylic cements and contains range of powders such as monocalcium phosphate, tri calcium phosphate and calcium carbonate, which is mixed in a solution of sodium phosphate. These cements are produced without polymerisation and the reaction is nearly non-exothermic. The final compounds are reported to have a strength of 10-100 MPa in compression while 1-10 MPa, in tension although very weak under shear forces. These composites are currently used in orthopaedics in the management of fractures. It has been suggested that these materials could improve the compressive strength of the vertebral bodies in osteoporosis. Injection of calcium phosphate cement has been shown to be feasible and it does improve their compressive strength.[52]

Preparation of hydroxyapatite/ceramic composites through the addition of various ceramic reinforcements has been attempted, metal fibres[53], Si_3N_4 or hydroxyapatite whiskers[54], Al_2O_3 platelets[55] and ZrO_2 particles.[56] In many cases, the composites could not be successfully prepared and, because of problems related to a poor densification the mechanical properties could not be improved.

Hydroxyapatite/metal and hydroxyapatite/polymer composites are two typical classes of materials, which have been examined for improving the toughness characteristics of synthetic hydroxyapatite.[56-58] In both cases, a toughness improvement can be found, due to a crack-face bridging mechanism operated upon plastic stretching of metallic or polymeric ligaments. Zhang *et al.*[57] proposed a toughened composite consisting of calcium hydroxyapatite dispersed with silver particles. This material was obtained by a conventional sintering method. It was reported that the toughness of these composites increased up to 2.45 MPa $m^{1/2}$ upon loading the mixture, with (30 vol%) silver. The use of silver is not only for taking advantage of the ductility of silver in terms of fracture toughness, but also because silver is inert and has anti-bacterial properties.[58] Attempts to supersede metal alloys by carbon-fiber reinforced plastics and by various composites to stabilize fractures have met with limited success. Although a new titanium metal core-composite hip implant has been clinically assessed in Europe with promising results.[44, 59]

4.10 Biomimetic Hybrid Composites

The conventional way to synthesize an inorganic material-based composite is to subject a mixture of the constituent phases to heat treatment. This process is also common in the biomaterials production arena; however, it is conceptually far from the biomineralization process, which occurs in nature. The natural process produces fine hybrid structures, which are hardly reproducible by classic consolidation processes. Traditional sintering route is not directly applicable to produce ceramic/polymer composites because no polymer will stand at the densification temperature of any ceramic material. Hydroxyapatite/polyethylene composites have been obtained by loading the polymeric matrix with the inorganic filler. In recent years, several research groups have demonstrated the feasibility of *in vitro* techniques for the synthesis of biomimetic material structures.[27, 56-58, 60-63]

The sophistication of the biomimetic route has not been paired yet and these techniques, so far, have not proved to be fully applicable for clinical applications although various companies started to produce a range of clinical products.[62] It can be easily predicted that more and more dense hybrid materials will be introduced, opening a completely new perspectives in biomaterials production and application methods.

A new alternative route, -based on an *in situ* polymerization process, carried out into an inorganic scaffold (with submicrometer-sized open porosity)-, have also been recently proposed.[58] This method is an intermediate one between conventional sintering and biomineralization *in vitro*, because it still employs sintering for the preparation of the inorganic scaffold, but the subsequent hybridisation of the scaffold with organic phases is carried out through a chemical route. This method enables the synthesis of biomimetic (hybrid) inorganic/organic composites, while aiming at relatively complex structural designs; it is rather simple and easily reproducible process. A schematic of this efficient synthesis route is given in Figure 6.

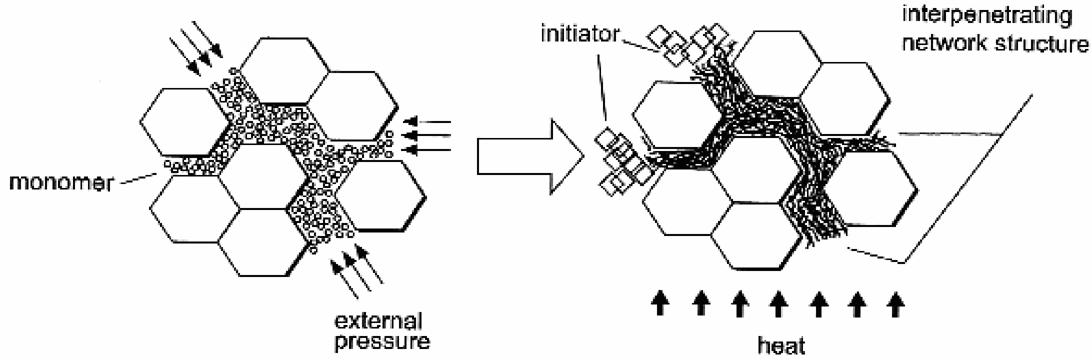

Figure 6. Schematic representation of the *in situ* polymerization synthesis route of new generation hybrid materials.

A common characteristic of natural biomaterials such as bone, nacre, sea urchin tooth and other tough hybrid materials in nature is the strong microscopic interaction between the inorganic and the organic phases. This characteristic allows the organic phase to act as a plastic energy-dissipating network, forming stretching (bridging) ligaments across the faces of a propagating crack in a nanoscale level. Such complexity has led to the common perception that, to mimic natural designs, *in situ* synthesis techniques should be adopted. Precipitation of calcium carbonate or hydroxyapatite into a polymeric matrix, for example, has been proposed as a novel synthetic route to biomimetic composites. [61, 64] Despite significant advances in understanding biological mineralization and developing new fabrication processes, the composites to date obtained by these methods are by far *in embryonic stage* for actual applications, due to their low structural performance.

The results of fracture tests carried out on two natural biomaterials, bovine femur and Japanese nacre (*Crassostrea Nippona*), in comparison with a synthetic hydroxyapatite/nylon-6 composite obtained by *in situ* polymerisation of ε-caprolactam infiltrated into a porous apatite scaffold showed that the high work of fracture achieved is about two orders of magnitude higher than that of monolithic hydroxyapatite, and it is due to stretching of protein or polymeric ligaments across the crack faces during fracture propagation.

Although the nanoscale modelling of synthetically manufactured hybrids and composites is still in infancy, mimicking natural microstructures while using strong synthetic molecules may lead to a new generation biomaterials, whose toughness characteristics will be comparable with the materials available in the nature. A formidable challenge remains on the optimisation of their morphology and bioactivity in these novel hybrid composites. [57]

5. FUTURE OF BIOCERAMICS

As discussed in this chapter, the properties of bioceramics are strongly influenced by the raw materials selected for preparation, by the method used to fabricate, processes used to consolidate and final machining processes utilized. All of these factors contribute to their final structures and hence to their long-term performance as bioceramics. The optimization of bioceramics in medical applications can be achieved by further studies of the effects of processing conditions on their structures and hence on their long- term properties.

In particular, the nature and effect of additives, whether to improve biological performance or to ease processing, on the local and systemic responses needs further investigation. Sometimes improvement of one property could be detrimental to other properties.

The scope for biomaterials development will include the synthesis of novel materials, the modification of those currently available, and the exploration of new hybrid and composite materials.

In the early 70's, bioceramics were employed to perform singular, biologically inert roles, such as to provide parts for bone replacement. The realization that cells and tissues in the body perform many other vital regulatory and metabolic roles has highlighted the limitations of synthetic materials as tissue substitutes. Demands of bioceramics have changed from maintaining an essentially physical function without eliciting a host response, to providing a more integrated interaction with the host. This has been accompanied by increasing demands from medical devices to improve the quality of life, as well as extend its duration. Bioceramics potentially can be used as body interactive materials, helping the body to heal, or promoting regeneration of tissues, thus restoring physiological functions. This approach is being explored in the development of a new generation of bioceramics with a widened range of applications.

Recently the tissue engineering has been directed to take advantage of the combined use of living cells and tri-dimensional ceramic scaffolds to deliver vital cells to the damaged site of the patient. Feasible and productive strategies have been aimed at combining a relatively traditional approach such as bioceramics implants with the acquired knowledge applied to the field of cell growth and differentiation of osteogenic cells. A stem cell is a cell from the embryo, fetus, or adult that has the ability to reproduce for long periods. It also can give rise to specialized cells that make up the tissues and organs of the body. An adult stem cell is an undifferentiated (unspecialized) cell that occurs in a differentiated (specialized) tissue, renews itself, and becomes specialized to yield all of the specialized cell types of the tissue from which it originated. Cultured bone marrow cells can be regarded as mesenchymal precursor cell population derived from adult cells. They can differentiate into different lineages: osteoblasts, chondrocytes, adipocytes and myocytes, and undergo limited mitotic divisions without expressing telomerase activity. When implanted onto immunodeficient mice, these cells can combine with mineralized tri-dimensional scaffolds to form a highly vascularized bone tissue. Cultured-cells/bioceramic composites can be used to treat full-thickness gaps of bone diaphysis with excellent integration of the ceramic scaffold with bone and good functional recovery. Excellent innovative work is in progress and clinical applications is becoming quite common.

Ultimately, the field of bioceramics is fundamental to advances in the performance and function of medical devices, and is a critical part of medicine and surgery. Bioceramics science is truly interdisciplinary. Therefore, the development of improved bioceramics can only be the outcome of advances in physical and biological sciences, engineering and medicine. The correlations between material properties and biological performance will be useful in the design of improved bioceramics, particularly to overcome the problems of implant rejection and related infection.

The challenge remains to provide safe and efficacious bioceramics with the required properties and an acceptable biocompatibility level. As the field of biomaterials finds increasing applications in cellular and tissue engineering, it will continue to be used in new ways as part of the most innovative therapeutic strategies.

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The aim of the 2001 edition of MF is to highlight the broad range of materials-based research carried out within various Cooperative Research Centres (CRC's) throughout Australia. The CRC scheme was introduced in 1990 by the federal government to bring together researchers from universities, government laboratories, and private industry or public sector agencies, to carry out long-term collaborative research and development of national economic and social significance. Over sixty CRC's are in operation in 2001 which are grouped into the following research fields: Manufacturing Technology; Information and Communication Technology; Mining and Energy; Agriculture and Rural Based Manufacturing; Environment, and Medical Science and Technology. Considering the importance of materials-based research throughout the world, it is not surprising that a significant fraction of CRC's have a strong research emphasis in mineral processing, process metallurgy, mechanical and physical metallurgy, materials science and polymer engineering. These include:

- Cooperative Research Centre for Cast Metals Manufacturing
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