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Developing bioactive composite materials for tissue replacement

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Abstract

A variety of bioactive composites have been investigated over the last two decades as substitute materials for diseased or damaged tissues in the human body. In this paper, the rationale and strategy of developing these composites are given. Major factors influencing the production and performance of bioactive composites are discussed. Some promising composites for tissue replacement and regeneration are reviewed. On the basis of past experience and newly gained knowledge, composite materials with tailored mechanical and biological performance can be manufactured and used to meet various clinical requirements.

Keywords: Bioceramics; Biomedical polymers; Composites; Bone analogue; Tissue replacement

1. Introduction

Engineering alloys such as cobalt–chromium alloys, stainless steel and titanium alloy have been extensively used in orthopaedic surgery as replacements for bone [1,2]. The implants made of these metallic materials provide the strength and toughness that are required in load-bearing parts of the body and due to these advantages, metals will continue to play an important role as orthopaedic biomaterials in the future, even though there are concerns with regard to the release of certain ions from and corrosion products of metallic implants [3]. The use of metals in human bodies has a long history and research has been continuing on modifying the compositions of metals [4] or, more recently and perhaps more importantly, changing surface properties of metals [5,6] for their biomedical applications.

Over the last 30 years, ceramics, glasses and glass–ceramics for use in the medical field, which are grouped together and termed "bioceramics", have gradually gained their recognition and some of them are now accepted as viable biomaterials for tissue substitution [7]. Bioceramics have the advantage of being compatible with the human body environment. Their biocompatibility is a direct result of their chemical compositions which contain ions commonly found in the physiological environment (such as Ca^{2+}, K^{+}, Mg^{2+}, Na^{+}, etc.) and of other ions showing very limited toxicity to body tissues (such as Al^{3+} and Ti^{2+}). Due to their excellent tribological properties and with their improved fracture toughness and reliability, structural ceramics such as alumina (high purity, polycrystalline, fine grained) and toughened zirconia (TZP and Mg-PSZ) have been used for femoral heads of total hip prostheses [8]. One remarkable success of bioceramics as implant materials over the last two decades is perhaps the emergence and clinical use of bioactive ceramics which include calcium phosphates (with hydroxyapatite being the prominent family member), Bioglass®, A-W glass–ceramic, and other bioactive glasses and glass–ceramics that elicit a specific biological response at the interface of the material resulting in the formation of a strong bond between the tissue and the material [9]. However, the brittle nature of ceramics such as alumina and the low strength of bioactive ceramics such as hydroxyapatite have limited their scope of clinical applications and hence more research needs to be conducted to improve their properties.

The medical use of synthetic polymers also has a long history and the success of polymers in medicine can be exemplified by the applications of poly(methyl methacrylate) (PMMA) and ultra high molecular weight polyethylene (UHMWPE) in total hip replacement. On the basis of years of laboratory experimentation and

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clinical investigations, the following synthetic polymers are considered "biocompatible" [10]: polyethylene (PE), polypropylene (PP), polyurethane (PU), polytetrafluoroethylene (PTFE), poly(vinyl chloride) (PVC), polyamides (PA), PMMA, polyacetal, polycarbonate (PC), poly(ethylene terephthalate) (PET), polyetheretherketone (PEEK), and polysulfone (PSU). These polymers are also considered "bio-stable" in the human body and have found wide applications in the medical field, ranging from PTFE vascular grafts to UHMWPE acetabular cups [11]. The recent emergence of "tissue engineering" has led to significant interest in biodegradable polymers which include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL), polyhydroxybutyrate (PHB), and a few other polymers [12] that can be used to construct degradable scaffolds onto which various types of cells may be seeded. Biodegradable polymers such as poly(ortho esters) have also been investigated for controlled drug release purposes [13].

The use in the medical field of aforementioned materials (i.e., metals, ceramics, and polymers) that were originally developed for general engineering applications rather than for tissue replacement in human bodies has obviously been successful and it is certain that most of these proven materials will be continuously used in the healthcare industry. However, there are also shortcomings of these materials for their intended medical applications. One of the major problems with current implant materials is that they are much stiffer than human cortical bone [1,11]. According to the load-sharing principle of the composite theory [14], if a stiff metal or ceramic implant is placed in bone, the bone will be subjected to a reduced mechanical environment, and consequently bone will resorb [1]. This is following what is known as "Wolff's Law", i.e., with the changing stress or strain imposed, bone will remodel so that the stress or strain is retained within specific levels [15]. In the case of total hip replacement, bone resorption in the proximal femur that leads to aseptic loosening of the prosthesis (which is a very common problem) is believed to be caused by the state of stress and strain in the femoral cortex after the metallic femoral hip replacement is implanted [8]. Elastic characteristics of the implant play a significant role in allowing the femur to attain a physiologically acceptable stress state. In order to overcome the problem of modulus-mismatch between existing implant materials and bone and promote the formation of a secure bond between the implant and host tissue, the concept of analogue biomaterials was introduced by Bonfield et al. in the 1980s [16]. Since then, a variety of bioactive composite materials have been produced and investigated [17]. These materials (i.e., the composites which consist of more than one type of materials (metallic, ceramic, or polymeric)), unlike the first-generation biomaterials which extended their use in engineering to medicine, are specifically designed for medical applications and hence, in this context, truly "designer biomaterials".

2. The template, the strategy and candidate materials for bioactive composites

2.1. Bone and the composite strategy

In the development of new engineering materials, apart from other required properties pertaining to specific applications, strong and stiff materials coupled with reasonable ductility are always targeted. In developing new biomaterials for tissue replacement, the structure and properties of the tissue which is to be replaced, i.e., the biological template, must be taken into consideration, because, if properties of the new material are significantly different from those of the host tissue, the material under development will cause dynamic changes of the host tissue after implantation, as has been discussed in terms of Wolff's Law, and thus will not achieve the goals embedded in the original conceptual design. It is therefore essential to have a good understanding of biological templates prior to developing new biomaterials.

Bone serves as the template for making new materials for hard tissue replacement. Bone is a natural composite material, having a complex structure in which several levels of organisation, from macro- to micro-scale, can be identified [1]. Two levels of composite structure are considered when developing bone substitutes (Fig. 1): first, the bone apatite reinforced collagen forming individual lamella at the nm to μm scale and, second, osteon reinforced interstitial bone at the μm to mm scale. It is the apatite-collagen composite at the microscopic level that provides the basis for producing bioactive ceramic–polymer composites as analogue biomaterials for bone replacement [18]. Mechanical properties of bones have been well documented [19], which serve as the benchmark upon which the mechanical performance of bone analogue materials is evaluated. As an anisotropic material, cortical bone has a range of associated properties rather than a set of unique values [18]: 7–30 GPa for Young's modulus, 50–150 MPa for tensile strength, and 1–3% for elongation at fracture.

As bone is an apatite–collagen composite material at the ultra-structural level, a polymer matrix composite containing a particulate, bioactive component appears a natural choice for substituting cortical bone. The bioactivity of the composite, which is rendered by the bioactive component in the composite, will promote the tissue growth adjacent to the implant and the formation of a strong bond between the tissue and the implant after implantation. The matrix polymer will

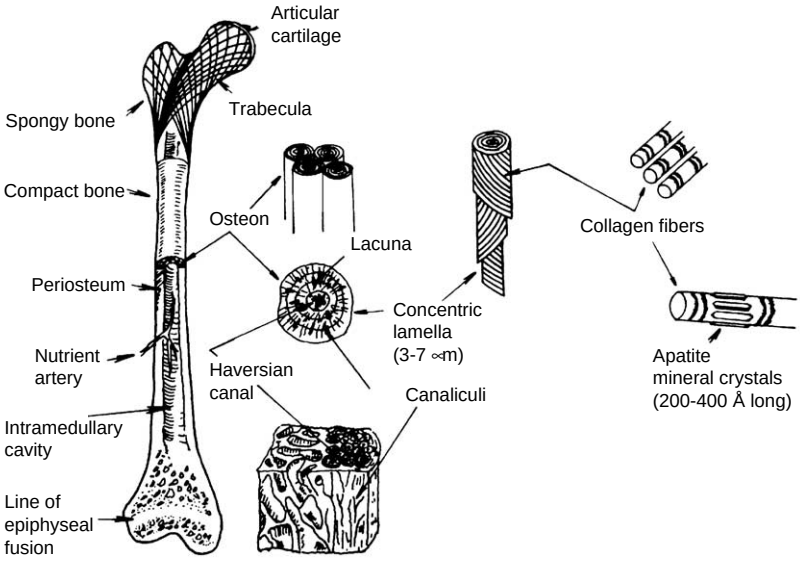


Fig. 1. Structural organisation in a human long bone [1].

provide ductility and other associated properties that are required of hard tissue replacement materials.

2.2. Bioactive bioceramics

Bone apatite is one of the biological apatites that constitute the mineral phase of calcified tissues in the body. Using a synthetic compound that is similar to bone apatite is perceived to be advantageous for replacing the hard tissue over other synthetic materials. Hence there has been a sustained interest over the last 20 years in hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), which resembles bone apatite and is a member of the calcium phosphate family that forms part of the bioactive bioceramics group. HA possesses excellent biocompatibility and is osteoconductive [20]. It has been used clinically on its own as a bioactive material in the form of powder, porous structure, or dense body [9]. However, the most publicised success of HA is its use as a bioactive coating on total hip prostheses [21]. Another attractive member of the calcium phosphate family for medical applications is tricalcium phosphate (TCP, $Ca_3(PO_4)_2$), which plays an important role as a bioresorbable bioceramic. TCP has been used for bone repair in the form of ceramic blocks, granules or calcium phosphate cements [22]. Both HA and TCP are weak bioceramics and thus cannot be used on their own as major load-bearing implants in the human body.

Bioglass® and A-W glass–ceramic are also bioactive bioceramics that have been successfully used for tissue replacement. Bioglass® is a family of bioactive glasses that contain SiO_2, Na_2O, CaO and P_2O_5 in specific proportions. A particular advantage of Bioglass® (45S5 Bioglass®) is its ability to bond to both hard and soft tissues [7]. The primary shortcoming of Bioglass® is mechanical weakness and low fracture toughness due to an amorphous two-dimensional glass network. The bending strength of most Bioglass® compositions is in the range of 40–60 MPa, which is not suitable for major load-bearing applications. By heat treatment, a suitable glass can be converted into glass–crystal composites containing crystalline phase(s) of controlled sizes and contents. The resultant glass–ceramic can have superior mechanical properties to the parent glass as well as to sintered crystalline ceramics. The bioactive A-W glass–ceramic is thus made from the parent glass in the pseudoternary system $3CaO \cdot P_2O_5$–$CaO \cdot SiO_2$–$MgO \cdot CaO \cdot 2SiO_2$, which is produced by the conventional melt-quench method [23]. The bioactivity of A-W glass–ceramic is much higher than that of sintered HA. A-W glass–ceramic possesses excellent mechanical properties and has therefore been used clinically for iliac and vertebrae prostheses and as intervertebral spacers [23].

Bioceramics such as HA, TCP, Bioglass® and A-W glass–ceramics may be used in the form of particulates as the bioactive, reinforcing phase in bioactive tissue substitutes.

2.3. Biomedical polymers

Among biocompatible and bio-stable polymers, there are a few polymers as potential matrices of bone analogues. Although PE is the leading candidate due to its proven record as a biomaterial and its ductile characteristics, polymers such as PEEK and PSU can also be considered as matrix polymers in bone-substituting composites. If a biodegradable tissue substitute is required, composites based on polymers such as PLA, PCL and PHB may be made and used. All these polymers, bio-stable or biodegradable, have their own distinctive characteristics [10,12]. The judicious selection of a particular polymer as the matrix of a composite is

based on the consideration of clinical requirements. In this sense, the use of one polymer for a composite does not preclude the use of other polymers as matrix materials. Furthermore, in selecting a polymer, most of these factors, if not all, must be taken into consideration: structural unit(s), average molecular weight, molecular weight distribution, degree of chain branching, crystallinity, and degree of crosslinking.

3. Factors influencing the performance of bioactive composites

A composite material consists two or more chemically distinct phases (metallic, ceramic, or polymeric) which are separated by interface(s). A composite is designed to have a combination of the best characteristics of each of the component materials. The classification of engineering composite materials is based on the matrix materials (metals, ceramics, and polymers) or on the reinforcement dimensions/shapes (particulates, whiskers/short fibres, and continuous fibres) [14,24].

Most engineering composite materials are developed to provide unique mechanical properties such as strength, stiffness, toughness and fatigue resistance. For biomedical composites, even though excellent mechanical performance is desirable and often targeted for improvement, the biocompatibility of the material is of paramount concern. The biological compatibility is more important than the mechanical compatibility. Being composed of two or more types of materials, composites carry an enhanced probability of causing adverse tissue reactions. However, bioactive, tough composites do have the advantage of overcoming the problems of brittleness of bulk bioceramics while maintaining a bioactive response in vivo. The classification of biomedical composites can be based on the matrix materials or on the bioactivity of composites (at least one of the constituent materials of a composite should be bioactive, which may render the composite bioactive; in some cases, two or all of the constituent materials are bioactive.). Using the matrix material as the basis for classification, there are three types of biomedical composites:

- Polymer matrix composites, e.g., carbon/PEEK, HA/HDPE.
- Metal matrix composites, e.g., HA/Ti, HA/Ti–6Al–4V.
- Ceramic matrix composites, e.g., stainless steel/HA, glass/HA.

Using the bioactivity of composites as the basis for classification, there are also three types of biomedical composites:

- Bioinert composites, e.g., carbon/carbon, carbon/PEEK.
- Bioactive composites, e.g., stainless steel/Bioglass®, HA/HDPE, HA/Ti–6Al–4V.
- Bioresorbable composites, e.g., TCP/PLA, TCP/PHB.

Two types of reinforcements are normally used for biomedical composites: fibres and particulates. With only a few exceptions, fibres and particulates in biomedical composites are harder and stronger than the matrix and hence reinforce the composites. Because the reinforcement and matrix interact with each other in different ways in different composite systems, composites need to be treated individually.

Properties of biomedical composites are strongly affected by a number of factors, some of which are listed below:

(1) reinforcement shape, size, and size distribution;
(2) reinforcement properties and volume percentage;
(3) bioactivity of the reinforcement (or the matrix);
(4) matrix properties (molecular weight, grain size, etc.);
(5) distribution of the reinforcement in the matrix;
(6) reinforcement-matrix interfacial state.

Among these factors, properties of constituent materials are major influencing factors. However, factors such as composite architecture (the reinforcement percentage, distribution and orientation, etc.) and reinforcement-matrix bonding condition also play important roles. By carefully controlling these factors, the mechanical and biological performance of bioactive composites can be tailored so as to meet various clinical requirements. Brief discussions of major factors for bioactive particle filled polymers are given in this section.

The physical characteristics (shape, size, size distribution, etc.) of the reinforcement are very important in determining mechanical properties of a composite. In the idealised situation for mathematical modelling of the mechanical behaviour of a particulate composite, the reinforcement is normally assumed to have a spherical shape (Fig. 2a). In reality, bioactive, reinforcing particles may have an irregular, platey or acicular shape. HA particles in commercially available, spray-dried powders can have an irregular shape shown in Fig. 2b, which are composed of tightly bonded HA crystallites. This type of irregular shape is preferred to the spherical shape, as the molten polymer can penetrate into troughs on the particle surface during high temperature composite processing and thus form mechanical interlock with the particle at the ambient or body temperature, whereas the smooth surface of spherical particles does not provide such a locking mechanism and thus in the absence of chemical bonding between the polymer and the particle, will debond from the polymer when a tensile stress is applied. TCP particles, produced

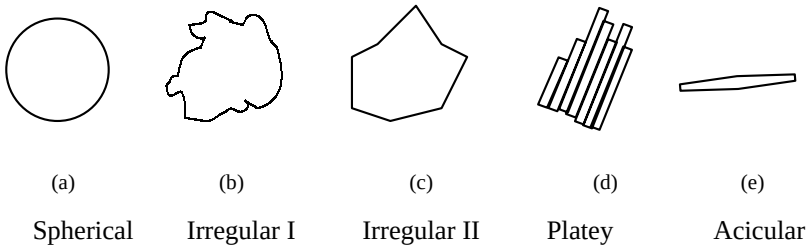


Fig. 2. Shapes of bioceramic particles for biomedical composites.

through a commercial route, can also take up this irregular shape but possess micro- or nano-pores in the particles. Therefore, under sufficient shear stress during composite thermal processing, the porous TCP particles can break up into smaller particle fragments. If the reinforcing bioactive glass (or glass–ceramic) particles are made via the conventional glass–making method (i.e., melting and quenching), the glass particles take up the shape shown in Fig. 2c, which has sharp corners. Particles of this shape cause stress concentration in the composites around the sharp corners and thus are not preferred. An additional milling process may be needed to remove (or, at least, reduce) the sharp ends of glass particles prior to composite processing. The platey shape (Fig. 2d) is not normally encountered for particles in bioactive composites. When particles of calcium phosphates produced via the precipitation method are directly used for the composites, the nanometer size particles generally have the acicular shape (Fig. 2e). In such a situation, the aspect ratio (i.e., the width to length ratio) of the particles is an important parameter and the orientation of acicular particles should be considered. Using the conventional plastics processing technology to produce bioactive composites, the average size of bioactive particles (primary particles) normally ranges from several micrometers to tens of micrometers.

Fine ceramic particles tend to combine together to from strongly bonded aggregates which may further unite to produce even larger structures, commonly termed "agglomerates". The principal adhesion forces between the particles are shown schematically in Fig. 3, together with an indication of their relative strength. To form high quality and high performance ceramic-polymer composites, the particle agglomerates or aggregates must be broken down during composite processing into primary particles (i.e., the smallest particulate pieces of the minor component existing in as-fabricated or as-received ceramic powder) which are sufficiently dispersed in the polymer matrix (Fig. 4). Dispersing particles from the condensed state (Fig. 4a) to the intermediate state (Fig. 4b) may not be sufficient as the particle contacting points will provide crack initiation sites or act to enhance crack propagation thus causing premature failure of the composite when

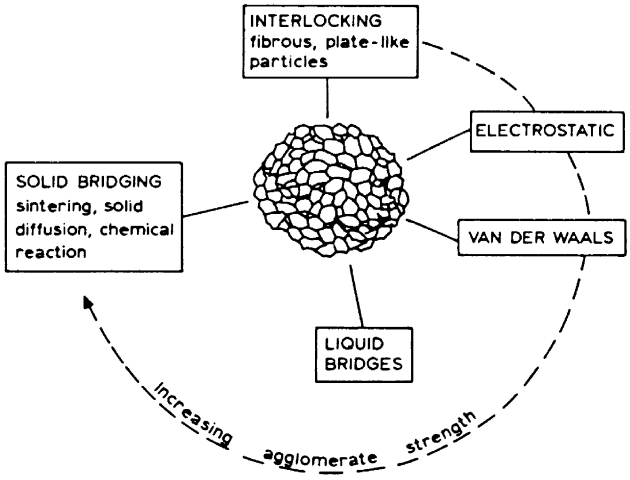
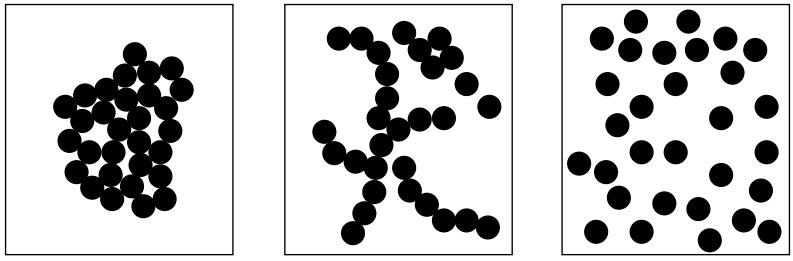


Fig. 3. Principal adhesion forces in an agglomerate of particles [25].

the composite is under mechanical stresses. Ideally, particles present in the composite should be in a dispersed state, as shown in Fig. 4c. Therefore, specially designed processing equipment is often required, which produces shear forces large enough to overcome various particle adhesion forces during composite melt-processing so that particle agglomerates or aggregates can be reduced to primary particles and primary particles can be evenly distributed in the composite [25,26].

Even with well designed machinery for dispersing rigid particles in a soft matrix, the input energy must be carefully controlled. Inadequate energy input does not lead to the breakup of particle agglomerates or aggregates (Fig. 5). On the other hand, excessive energy input can cause the fragmentation of primary particles, which may not induce any beneficial effects, and accompanied heat generation, which results in thermal degradation of the polymer. Apart from operating conditions of the machinery, which include machine design (primarily, for the generation of large shear forces), energy input (in the form of rotor or screw speed), processing temperature and pressure, other factors such as characteristics of ceramic particles (i.e., particle morphology, size, etc.), interparticle attraction, particle surface treatment, and particle



(a) Condensed state (b) Intermediate state (c) Dispersed state

Fig. 4. Possible distributions of bioceramic particles in biomedical composites.

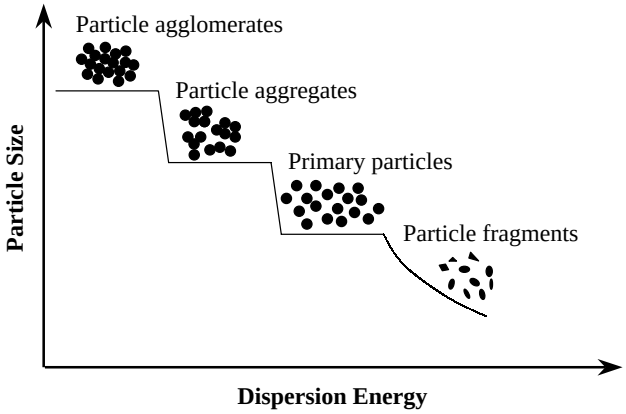


Fig. 5. Schematic diagram showing the relationship between the average size of dispersed particles (or particle agglomerates or aggregates) and the dispersion energy required.

volume fraction in the composite can significantly affect particle dispersion and distribution in the composite. Surface treatment of bioceramic particles may not ease processing difficulties and may not necessarily lead to enhanced particle dispersion [27].

The analysis of efficiency of a manufacturing process with regard to particle dispersion and distribution in a composite can be assisted by employing scanning electron microscopy and image analysis techniques [28]. At different processing stages, polished samples can be imaged and the images analysed. It should be borne in mind that polished samples only provide two-dimensional diameters (circular equivalent) of ceramic particles. For determining three-dimensional average volume diameter of these particles (spherical equivalent) in the composite, stereology together with image analysis needs to be used [28,29].

For the purpose of producing bioactive bone substituting materials, the bioactive phase in a particular composite must exceed certain volume fraction. Below this volume fraction, even though the bioactive phase is incorporated into the matrix, the composite may not possess bioactivity that is desired. It has been shown that for hydroxyapatite reinforced high density polyethylene composite, the critical HA volume percentage is around 20%, above which bone apposition could occur on composite implant [30]. Similarly, for other composites to be useful bone replacement materials, bioceramic content in these composites should be greater than the minimum amount(s) (probably around 20 vol% as well). In this respect, with regard to particulate filled polymers, bioactive composites containing 20 vol% or more of bioceramics are highly filled polymer systems. In the plastics industry, it is generally recognised that high quality highly filler polymers are very difficult to produce unless specially designed machines are used and considerable experience of plastics processing has been gained. Even faced with such problems as dealing with highly filled polymers which are highly viscous at their processing temperatures, a reasonably uniform distribution of bioceramic particles in the composite must be guaranteed. Structural defects such as micro- and macro-pores and cracks can often be present in moulded parts due to air being trapped in mouldings and differences in physical properties between the bioceramic and the polymer. However, such defects are obviously intolerable for medical devices which are meant for improving patients' quality of life without their premature failure in service.

The packing behaviour of bioceramic particles in the polymer matrix is an important factor in the understanding and also design of bioactive composites, especially when highly filled systems are involved. For every filled polymer system, there is a maximum volume fraction of particles that can be incorporated before a continuous network of the particles is formed and voids begin to appear in the composite. The packing behaviour of particulate materials depends largely on particle size, shape and surface characteristics [31]. For theoretical analysis, it is normally assumed that the particles have a mono-modal size distribution with a sharp peak (Curve (a) in Fig. 6) or even just have one uniform size, which makes it difficult to achieve high packing density. In reality, most as-produced (or as-received) ceramic powders have broad size distributions, sometimes with a long tail end towards the small particle size range, as Curve (b) in Fig. 6. The other ceramic powders may exhibit bi-modal size distributions shown as Curve (c) in Fig. 6. The packing of particles having a

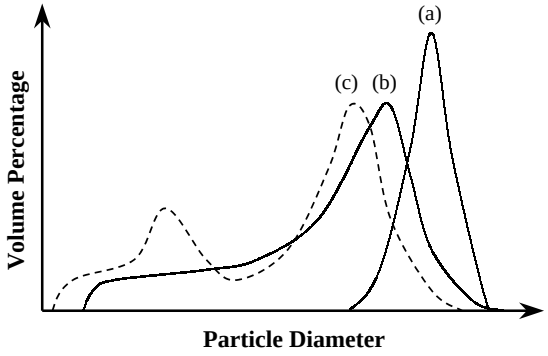


Fig. 6. Schematic diagram showing particle size distributions of particulate reinforcements: (a) mono-modal size distribution, (b) mono-modal size distribution with a long tail end, (c) bi-modal size distribution.

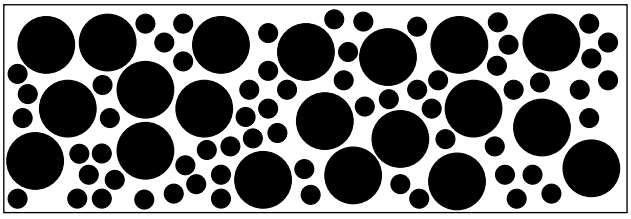


Fig. 7. Schematic diagram showing the distribution in a polymer matrix of bioceramic particles of a bi-modal size distribution.

bi-modal size distribution is more efficient (Fig. 7, the diameter of large spherical particles being three times that of small spherical particles), as the small particles can occupy the space between large particles, thereby leading to a high bioceramic content per unit volume in the composite. With such an understanding, the use of a mixture in specific proportions of two (or more) powders having respective mono-modal size distributions can be considered when composite having a high volume fraction of a bioceramic is desired. (Particles having a mono-modal size distribution can be obtained by sieving as-produced bioceramic powder. They can be useful for investigations in which the number of varying parameters needs to be limited.)

Controlling the interface (or, more appropriately in most cases, the interphase) between the reinforcement and matrix in composites is of great scientific interest as well as for practical reasons [14,32]. Mechanical behaviour and properties of composites are significantly affected (and sometimes decided) by the interfacial state, as a strong interfacial bonding can effectively transfer the load from the matrix to the reinforcement and a week interfacial bonding can deflect an advancing crack thus providing enhanced fracture toughness and avoiding catastrophic failure. For engineering composite materials, silane coupling agents are often used for glass fibres in fibre reinforced plastics (FRPs) in order to provide a strong chemical link between the oxide groups on the fibre surface and the polymer molecules of the resin [24]. In most bioactive composites, chemical bonding does not exist and the interfacial bond strength totally depends on the mechanical interlock between bioceramic particles and the polymer matrix. In a theoretical analysis [33], it was shown that if the composite is under tension, high stress concentrations (tensile stress) develop at the poles of spherical particles (Fig. 8). In the polar area, when the tensile stress exceeds the relatively low interfacial strength provided by the locking mechanism, debonding of the bioceramic particle from the polymer matrix inevitably takes place. To prevent (or delay) the debonding process, it appears necessary to provide chemical links between bioactive particles and the matrix polymer for biomedical composites.

The hard bioceramic particles in composites not only provide the reinforcement but also render the composite bioactive when there is a sufficient amount of the particles in the composite. For achieving the reinforcing effect, factors such as the size, shape and mechanical properties of the particles need to be considered. For example, Young's modulus values of bulk HA, Bioglass® and A-W glass–ceramic are 80–120 GPa [9], 30–35 GPa [7] and 118 GPa [23], respectively. If a high bioactivity level is desired for achieving a strong bond between the composite implant and the host tissue within a short period, bioceramics exhibiting high degrees of bioactivity such as Bioglass® can be selected for the composite. Different bioceramics have their own characteristics [34], and the judicious selection of a particular bioceramic for the composite is based on the clinical requirement, the composite production route, and sometimes the cost involved.

When selecting a polymer among different grades of the polymer for the matrix of a composite, attention needs to be paid to its average molecular weight, which can affect various characteristics of the polymer including melting/crystallisation behaviour, viscosity at processing temperatures, mechanical properties, and degradation behaviour if the polymer is biodegradable [35]. It is obvious that the polymer of the highest average molecular weight among different grades should be used for tissue substituting composites as strength and stiffness comparable to those of the tissue are required of the composite. However, compromises on the selection may have to be made with regard to processability of the polymer and hence the composite, as, among many practical concerns, too high a viscosity at the elevated processing temperature will not yield a defect-free, thermally non-degraded composite.

4. Production of bioactive composites

Prior to composite production, all raw materials should be characterised using a variety of techniques

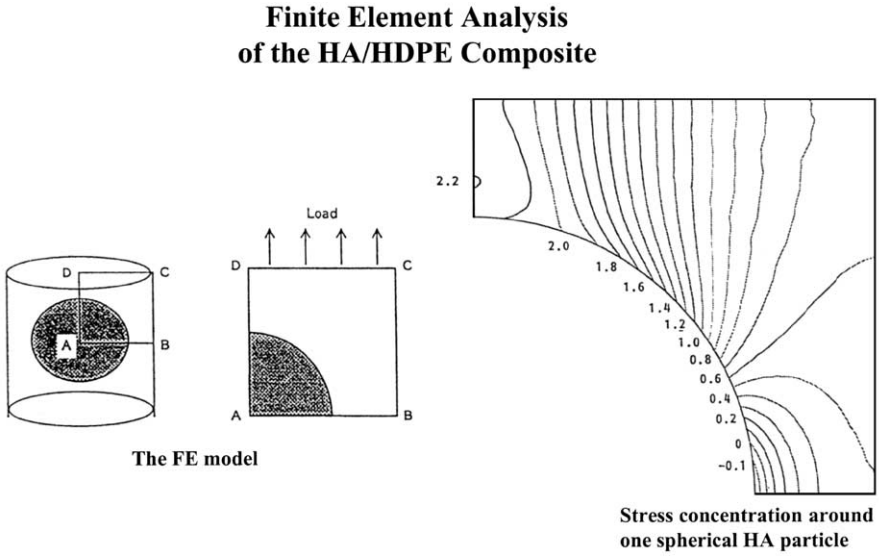


Fig. 8. Stress concentration around spherical bioceramic particles in bioactive composites [33].

such as X-ray diffraction, X-ray fluorescence, Fourier transform infrared spectroscopy, BET specific surface area analysis, particle size analysis, and scanning electron microscopy for bioceramic particles, and differential scanning calorimetry, thermogravimetric analysis and molecular weight measurement for matrix polymers. This characterisation process serves two purposes: (1) for scientific research and new composite development, the chemical compositions and purity of raw materials are checked and hence guaranteed and their physical properties recorded which will be used during materials development for systematic analyses; and (2) for producing composites for medical devices, the data obtained are used for quality control [36]. Characterisation of raw materials forms an important part in the production of bioactive composites.

There are a number of production techniques for making non-porous, bioactive ceramic–polymer composites for tissue replacement, which are summarised below:

Route I: Physico-chemical methods
- Method 1: Precipitating mineral crystals in situ in the polymer matrix
- Method 2: Dispersing bioceramic particles in the polymer solution with subsequent consolidation

Route II: Thermo-mechanical methods
- Method 1: Impregnating a porous bioceramic matrix with a polymer
- Method 2: Incorporating bioceramic particles into the polymer matrix using conventional plastics processing technologies

Precipitating mineral crystals in situ in the polymer matrix was used to produce calcium phosphate reinforced collagen [37]. Dispersing bioceramic particles in the polymer solution with subsequent consolidation was used to make hydroxyapatite/chitin composite [38]. A combination of these two methods has produced collagen-based composites containing bone-like apatite [39]. Impregnating a porous bioceramic matrix with a polymer was investigated for manufacturing biodegradable composites [40]. The majority of bioactive ceramic–polymer composites developed so far have been produced using the last method listed above, i.e., incorporating bioceramic particles into the polymer matrix using conventional plastics processing technologies [16,26,41–48]. For achieving an enhanced mechanical performance of the bioactive composite, advanced processing technology such as hydrostatic extrusion can be employed [49]. In addition, polymer fibres may be used as the matrix material [50,51], which can provide a stronger and stiffer matrix than the isotropic polymer. However, the processing conditions during hot compaction of the composite must be strictly controlled so that in the finished product after thermal processing the fibre morphology can still be retained [50].

In the thermo-mechanical route for producing bioactive composites, the manufacturing process normally consists of compounding, milling and compression or injection moulding (Fig. 9). Composites of various geometries can be made. The compounding process is crucial in composite production for achieving a homogenous distribution of bioceramic particles in the composite. Compounding particulate bioceramics with polymers can be conducted using a compounding extruder [26,41,42], an internal mixer [44,46,48], or a two-roll mill [52]. Breakdown of polymer chains inevitably occurs during polymer thermal processing

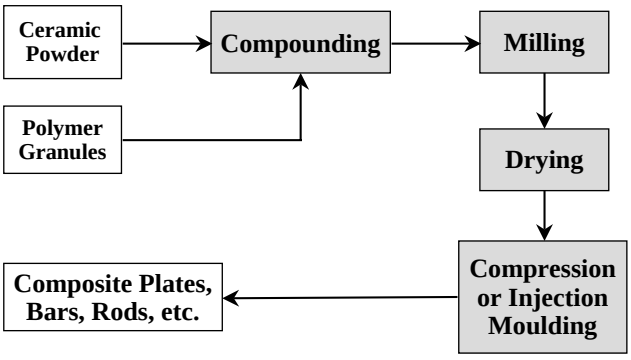


Fig. 9. Manufacture of bioactive composites using plastics processing technologies.

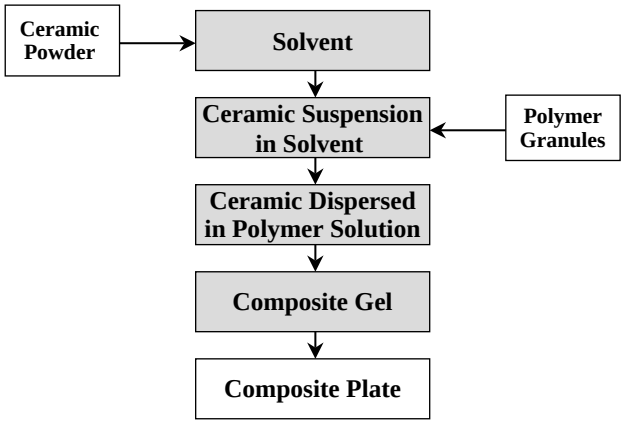


Fig. 10. Manufacture of bioactive composites using the polymer solution-casting technique.

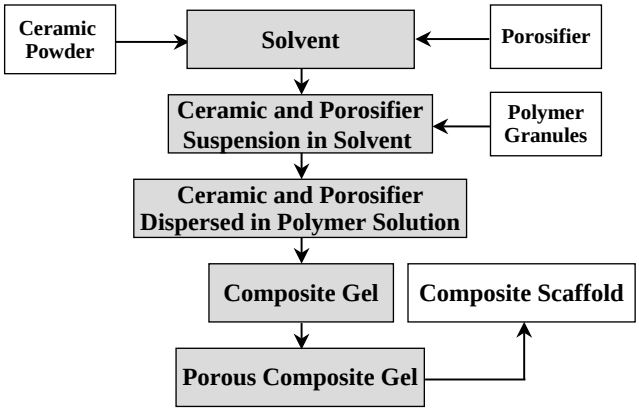


Fig. 11. Manufacture of bioactive and biodegradable composite scaffolds.

and the average molecular weights of polymers can be further reduced with the presence of bioceramic reinforcements [28,53]. The specific heat values of ceramics are much lower than those of polymers [35], which can cause severe oxidation of polymers such as polyethylene during the compounding process if cooling of the compounded material is not rapid and adequate [54]. In the compounding process, processing parameters such as temperature, screw/rotor speed and dwell/processing time should be strictly controlled. The milling process is to pelletise strands of the extruded material or to break down large chunks of compounded material into small pieces so that they can be used for compression or injection moulding. Prior to compression or injection molding, the milled, compounded materials must be dried, which drives off moisture in the materials. (If drying is not properly done, it is very likely that the moulded products will contain microvoids which have resulted from air bubbles formed at the processing temperature.) With regard to compression or injection moulding of bioactive composites, the moulding temperature and pressure are two key parameters, which depend on the melting behaviour and viscosity of the composite. For composites having heat-sensitive polymers such as PHB as the matrices, the moulding temperature must be carefully selected in order to avoid thermal degradation of matrix polymers. The moulding time, i.e., the dwell time at the moulding temperature, should also be kept short.

In the physico-chemical route of using polymer solutions with dispersed ceramic particles to form composites, the production procedure is shown in Fig. 10. In this method, the selection of a suitable solvent needs to be considered and the polymer solution concentration should be optimised. Too thin a polymer solution cannot prevent sedimentation of bioceramic particles during the gelation process, and too thick a polymer solution causes difficulties in dispersing large amounts of bioceramic particles in the solution. In both situations, unsatisfactory dispersion and uneven distribution of bioceramic particles occur in the final products [38]. The sequence of adding ceramic powder and polymer granules, as shown in Fig. 10, should be followed, especially in producing composites containing high volume fractions of bioceramic particles. Otherwise, bioceramic particles cannot be properly dispersed. Other processing parameters in this method, such as mixing mode, mixing time (stirring time) and gelation rate, also affect the quality of composites produced. It is vital that there are no residues of the solvent (and other chemicals aiding the production of composites) in the final product.

With modifications to the method described above, a simple technique, as shown in Fig. 11, can be used to produce bioactive and biodegradable composite scaffolds for tissue engineering applications [55,56]. The average pore diameter in the scaffolds is mainly decided by the diameter of porosifier used and the wall thickness of the pores can be controlled by using different polymer solution concentrations [55]. The amount of bioceramic particles incorporated in the polymer scaffolds may be limited.

Conventional manufacturing technologies for engineering composites can be used to produce composites for medical applications. However, extreme care must be taken to avoid material contamination. For a particular composite, these three aspects—processing, structure, and properties—are closely inter-related. Changes in any one of these aspects will affect either one or both of the other relationships. Optimal design of a material cannot be achieved without a comprehensive understanding of the relationships among processing, structure, and properties of the material.

5. Bioactive composites for tissue replacement and regeneration

Beginning with Bonfield's pioneering work of using hydroxyapatite (HA) as the bioactive and reinforcing phase in high density polyethylene to produce a bone analogue [16], a number of bioactive composite systems consisting of bioceramics and biomedical polymers have been investigated. In this section, only some systems shown in Fig. 12 are briefly reviewed. There are other bioceramic-polymer systems that have been or are being investigated for tissue replacement [43,45,47,57–59]. The particular combination of a bioceramic with a polymer for a composite is based on important factors controlling composite performance and composite production, most of which have been discussed in previous sections.

Producing bone analogues using polymers as matrices has been extended to producing bioactive composites for tissue replacement using metallic matrices [60–62] or ceramic matrices [63–66]. In the case of bioactive metal matrix composites, metal matrices provide the necessary strength and toughness. In the case of ceramic matrix composites, bioactive ceramics are most likely to be the matrices and the incorporation of a glassy material [65,66] or metal fibres [63,64] leads to the toughening of the ceramics. Both bioactive metal matrix composites and bioactive ceramic matrix composites have their attractiveness and disadvantages as tissue replacement materials. It is nonetheless worthwhile to investigate possibilities of developing these materials for their intended applications.

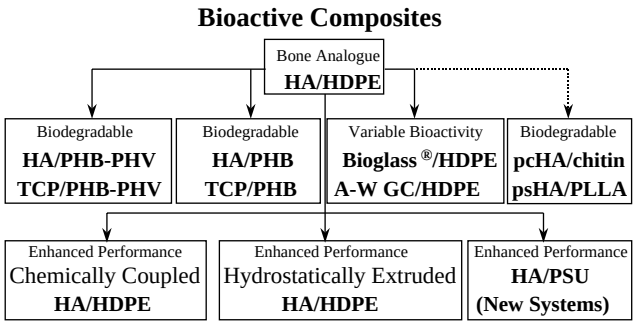


Fig. 12. Development of bioactive composites for medical applications.

The utilisation of bioactivity of bioceramic particles in composites for tissue replacement has led to investigations into producing new materials such as bioactive bone cement [67–71] and bioactive dental materials [72,73]. These new materials, with the incorporation of bioceramic particles, could induce or enhance the formation of tissue adjacent to them and finally establish a strong bond with the newly formed tissue.

Tissue engineering has emerged in recent years as a promising and viable means in solving problems of tissue loss and organ failure [74]. One of the key issues in tissue engineering is the development of suitable biodegradable scaffolds for seeding cells and for the subsequent growth of tissues. There are a number of candidate polymers for tissue engineering scaffolds [12] and various techniques have been used to produce polymer scaffolds [75]. With appropriate modifications, some commonly used manufacturing techniques have been employed to make bioactive scaffolds, which contain bioceramic particles, for tissue engineering applications [56,76–78]. These bioactive scaffolds are expected to enhance cell adhesion and tissue formation while possessing higher strength and stiffness than their polymer counterparts at the initial stages of cell-seeding and subsequent tissue growth.

5.1. *Hydroxyapatite reinforced high density polyethylene (HAPEX™)*

Hydroxyapatite reinforced high density polyethylene (HA/HDPE) composite (also known as HAPEX™ from 1995 when Smith & Nephew Richards Inc. introduced their series of middle ear implants made of the composite [79]) is the first bioactive ceramic–polymer composite that is designed to mimic the structure and match properties of bone [16], which has given rise to the research and development of other bioactive composites (Fig. 12) using the same rationale. Main advantages of using polyethylene as the matrix material include the following: it is a proven biocompatible polymer widely used in orthopaedics; it is a ductile polymer which allows the incorporation of a large amount of bioceramic particles in the system; the polymer having high content of bioceramic particles can still be melt-processed using current plastics technology; and HDPE is a linear polymer whose molecular chains can be aligned for property enhancement when advanced processing technology is used. The development of HA/HDPE composites involved the use of calcined bone ash (CBA) [80], commercially available synthetic HA [26] and synthetic HA produced in-house [52] and may involve the use of carbonated apatite or other substituted apatites which are more similar to

bone apatite and hence more bioactive than HA. Different polyethylenes [81] and different grades of HDPE [26,52,80] were also used for scientific research and for product development. The HA-HDPE system has progressed, according to the modern day development path of a new biomaterial, from conceptual design, through materials production, evaluation (physical, mechanical, and biological), intellectual property (IP) protection, clinical trial, industrial involvement, regulatory approval, to final use in medical devices for patients. Some research activities on HA/HDPE composites are continuing, focusing on a few issues which will help to understand the system better and optimise the composites.

The production of HA/HDPE composites generally follows the process shown in Fig. 9. HA/HDPE composites containing up to 45 vol% (i.e. 73 wt%) of HA can be routinely made through standardised procedures [26,52]. Either a twin screw extruder [26] or an internal mixer [52] can be used for compounding the materials effectively and efficiently. Compounding using two-roll mills appeared to be unsuitable due to their inability to cope with composites of high HA volume fractions and also polymer degradation [52]. Composite plates as thick as 20 mm may be made by compression moulding using composite powders. These plates were voids-free, as was revealed by X-ray radiographs [36,52]. Rheological studies revealed that the incorporation of particulate HA into HDPE resulted in an increase in the viscosity of composites at their processing temperatures [82,83] and that there were processing windows for HA/HDPE composites containing various amounts of HA. The die swell ratio of HA/HDPE composite was reduced as the HA content was increased.

It was shown that, by following the standardised production procedure, the difference between the actual mass percentages of HA in the composites produced and the intended amounts of HA in the composites was negligible and hence HA/HDPE composites of right compositions had been achieved [52,84]. Microscopical examination of composites revealed that HA particles were well dispersed in HDPE [26,36,52] and that the composites had a uniform distribution of HA particles (Fig. 13a). Structural analysis using stereology indicated

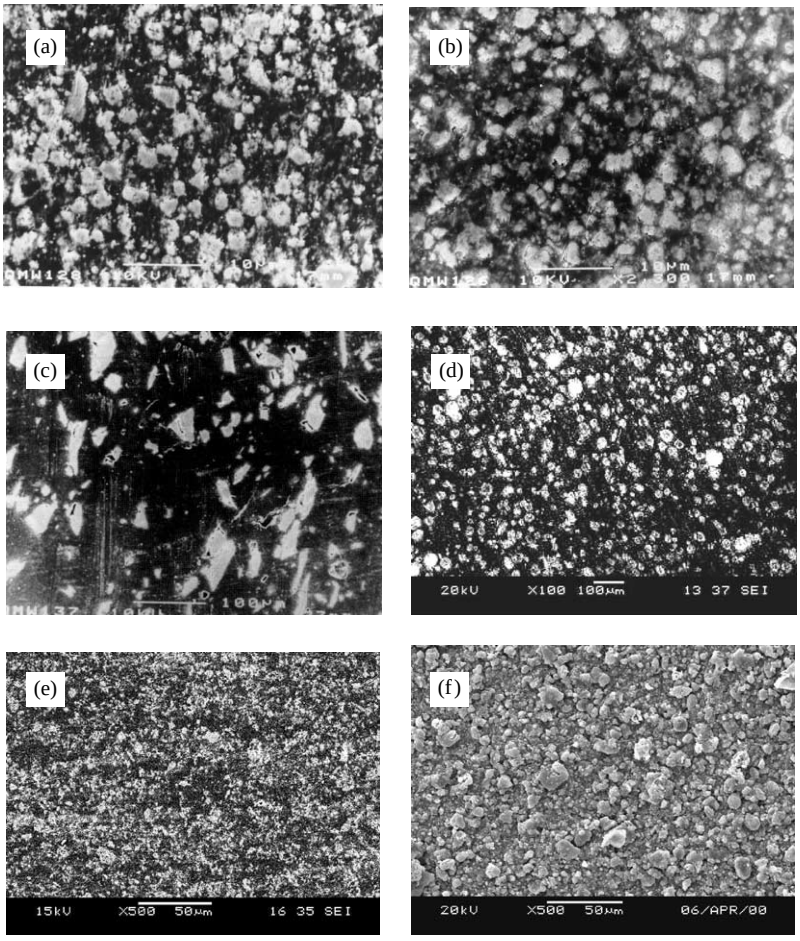


Fig. 13. Microstructure of various bioactive composites: (a) HA/HDPE [26], (b) hydrostatically extruded HA/HDPE [49], (c) Bioglass®/HDPE [120], (d) HA/PSU [116], (e) TCP/PHB [46] and (f) pcHA/chitin [38].

that the high shear forces generated during the compounding process broke up HA particle agglomerates into unit particles in the polymer matrix [28]. The average volume diameter of HA particles in moulded HA/HDPE was nearly the same as the mean particle size of HA powder used for producing the composites. It was found that the average molecular weight of HDPE was slightly decreased in the composite production process, with the level of decrease being dependent on the HA volume fraction [53]. The incorporation of HA particles also caused decreases in the degree of crystallinity of HDPE, with composites of higher HA contents having lower degrees of crystallinity for the polymer matrix [52,85].

Various aspects of the mechanical performance of HA/HDPE composites have been investigated [16,26,33,52,53,81,84–97]. By varying the amount of HA in the composite, a range of mechanical properties can be obtained. An increase in the HA volume percentage leads to increases in the Young's modulus, shear modulus, storage modulus (in the dynamic mechanical analysis), microhardness, and tensile strength of HA/HDPE, with corresponding decreases in the strain to fracture and impact energy for fracture. The particle morphology and average particle size of HA were found to affect mechanical properties of HA/HDPE composites. HA/HDPE with 45 vol% of HA possesses a Young's modulus value of 5.54 GPa, which approaches the lower bound for human cortical bone. Examination of fracture surfaces of HA/HDPE composites suggested that in the composites there was only mechanical bond between HA particles and HDPE matrix resulting from the shrinkage of HDPE around individual HA particles during thermal processing. In the aqueous environment, the uptake of water by HA/HDPE composites was small ($<1\%$ at 37°C) [98] and the strength and modulus of the composites were not significantly affected after prolonged contact with physiological fluids [99]. The incorporation of HA particles in HDPE improved the short-term creep resistance when specimens were subjected to similar stresses and an increase in the HA volume fraction increased creep resistance. However, creep failure of composites could occur at long times due to debonding at the HA-HDPE interface. Generally, the fatigue life of HDPE and HA/HDPE composite was reduced with an increasing shear stress in the biaxial stress condition. HA/HDPE composite appeared unsuitable for implants with articulating surfaces.

The in vitro and in vivo biological performance of HA/HDPE composites has also been assessed extensively [98,100–104]. In in vitro experiments using human osteoblast cell primary cultures, it was observed that the osteoblast cells attached to HA particles of the composite and subsequent proliferated, which clearly showed the biocompatibility and bioactivity of HA/HDPE composites. In in vivo experiments using adult New Zealand white rabbits, it was shown that after 6 months implantation in the lateral femoral condyle, 40% of the composite implant surface was covered by newly formed bone, displaying good osteoconductivity of the composites. The biological performance (i.e., the bioactivity) of the composites depended on the HA volume percentage of the composites.

HA/HDPE composites were firstly used for subperiosteal orbital floor implants in the correction of volume deficient sockets and in orbital floor reconstruction following trauma [105,106]. Post-operative clinical examinations reported good patient satisfaction and computerised tomograms of patients revealed integration of implants with the orbital floor 6 months after implantation. In recent years, middle ear implants made of HA/HDPE composite have become available [79,107], making use of the combined advantage of bioactivity, flexibility and trimmability of the composites, and satisfactory clinical results have been obtained [107,108].

5.2. *Chemically coupled hydroxyapatite reinforced high density polyethylene*

As there is only mechanical bond between HA particles and the HDPE matrix in HA/HDPE composites [26,52,53] and theoretical analysis has shown that debonding of HA particles from the matrix can take place at polar areas [33], silane surface treatment of HA particles and acrylic acid grafting of polyethylene were investigated for improving the reinforcement-matrix bonding of the composites [27,109,110]. Only limited improvements in tensile strength and ductility were achieved while Young's modulus was slightly decreased. It was observed that the chemical bond established between HA and HDPE delayed the debonding process but could not prevent debonding which caused eventual failure of the composites.

5.3. *Hydrostatically extruded hydroxyapatite reinforced high density polyethylene*

Hydrostatic extrusion is one of several technologies that can be used to align polymer chains so that mechanical properties of the polymer can be significantly enhanced [111]. This technique has been used to align polyethylene chains in the HA/HDPE composites [49,112–115], which is made possible due to the linear molecular structure of the polymer. It was found that higher extrusion ratios led to higher modulus and strength of HA/HDPE composites which are inside the bounds for mechanical properties of cortical bone (Table 1). The fracture strain of HA/HDPE was also substantially increased by hydrostatic extrusion. Extruded HA/HDPE containing 40 vol% of HA possessed

Table 1
Mechanical properties of hydrostatically extruded HA/HDPE composites

Extrusion ratio	HA volume (%)	Young's modulus (GPa)	Tensile strength (MPa)	Flexural modulus (GPa)	Flexural strength (MPa)
1:1	0	0.65	17.9	1.1	23
5:1	0	2.59	61.2	2.2	52
8:1	0	4.08	158.2	2.2	48
1:1	40	4.29	20.7	4.7	32
5:1	40	5.89	64.8	7.2	73
8:1	40	9.91	91.2	9.0	88

a strain to fracture which was far greater than that of human cortical bone (9.4% vs. 1–3%). Hydrostatic extrusion did not alter the even distribution of HA particles in the composites (Fig. 13b) and the bioactivity of the composites was retained after extrusion. Therefore, HA/HDPE further processed via hydrostatic extrusion has great potential for major load bearing applications.

5.4. *Hydroxyapatite reinforced polysulfone*

Apart from polyethylene, there are a few other biomedical polymers that could be used for producing bone analogue materials. Polysulfone (PSU) is an amorphous polymer which possesses high specific strength and modulus. To develop bioactive composites for load bearing prostheses, PSU may be a better choice for the matrix of a composite than HDPE as its strength and modulus are significantly higher [10], which can provide a higher level of mechanical properties for composites. Other favourable properties of PSU include low creep rate, resistance to oxidation, excellent resistance to hydrolysis or reduction of molecular weight, stability in aqueous inorganic acids, alkalis and salt solutions, and bioinertness. Furthermore, PSU has high resistance to β-, γ-, X- and IR-radiation and can be steam-sterilised. Therefore, HA/PSU composite has been developed as a new hard tissue replacement material [44,116–119]. The production of HA/PSU composite follows the same procedure as that for HA/HDPE composites (Fig. 9). HA/PSU composite containing up to 40 vol% of HA was produced. HA particles were also well dispersed in the PSU matrix (Fig. 13d) and the intended amount of HA in the composite was confirmed. Density close to the theoretical value was achieved for the composite, indicating a void-free structure. Rheological analysis revealed that HA/PSU composite exhibited pseudoplastic flow behaviour at processing temperatures. With an increase in HA content, the stiffness of HA/PSU composite also increased. Mechanical properties of HA/PSU composite are within the lower bound for bone. Just as with HA/HDPE composites, in biaxial fatigue testing, the torsional stress significantly reduced the fatigue life of HA/PSU composite. It was found that HA/PSU composite is not suitable either for implants with articulating surfaces.

5.5. *Bioglass® reinforced high density polyethylene*

In order to establish a stronger bond between the implant and the tissue within a shorter period of time, glass or ceramics that are more bioactive than HA, such as Bioglass® and A-W glass–ceramic, could be used as the bioactive phase in composites. After implantation, Bioglass® implants can elicit specific physiological responses, including the provision of surface-reactive silica, calcium and phosphate groups, and alkaline pH levels, at interfaces with tissues, thus providing high bioactivity and conditions for establishing a strong tissue-implant bond [7]. Using the technology for HA/HDPE composites, Bioglass® reinforced polyethylene composites were produced [41,120,121]. It was found that Bioglass® particles were well dispersed and a reasonably homogeneous distribution of the particles in the polymer matrix was achieved (Fig. 13c). Composite containing up to 30 vol% of Bioglass® exhibited levels of elastic compliance, tensile strength and fracture strain comparable to those of soft connective tissues. Composite having Bioglass® volumes in excess of 30 vol% possessed mechanical properties comparable to cancellous bone. In in vitro experiments using simulated body fluid [99,122–124], it was found that it took a shorter time for bone-like apatite to form on Bioglass®/HDPE composite surfaces than on HA/HDPE composite surfaces, indicating higher bioactivity of the Bioglass®/HDPE composite. However, mechanical properties of Bioglass®/HDPE composite decreased with time in the aqueous environment. In in vitro experiments using human osteoblast-like (HOB) cells [103,124,125], the cells were observed to attach to Bioglass® particles in the composite, indicating excellent biocompatibility and bioactivity of the composite. Recent TEM examination of the interface between HOB cells and the composite indicated direct bonding between the hydroxy carbonate apatite (HCA) layer, which formed on Bioglass® particles in vitro, and HOB cells.

5.6. A-W glass–ceramic reinforced high density polyethylene

Bioglass® is highly bioactive but its mechanical properties are low due to the amorphous two-dimensional glass network forming the glass. A-W glass–ceramic (AWGC) has excellent mechanical properties while possessing high bioactivity [23]. Particulate AWGC can be used as a stiffer reinforcement in the composite while still providing the composite with a much higher bioactivity than HA particles. Therefore, the processing technology established for HA/HDPE composites was used for producing AWGC/HDPE composite [42]. As with HA/HDPE and Bioglass®/HDPE composites, a homogenous distribution of AWGC particles in the polyethylene matrix was achieved using the standard production procedure (Fig. 9). Young's modulus and microhardness of the composite also increased with an increase in AWGC volume fraction while the tensile strength and fracture strain decreased. Even with 40 vol% of AWGC particles, the composite still exhibited considerable ductility. Current investigations of this composite system are concentrating on its mechanical properties and in vitro bioactivity [126,127].

5.7. Calcium phosphates reinforced polyhydroxybutyrate and its copolymer

Biodegradable materials have been attracting attention in the research and development of new biomaterials. These materials are designed to degrade gradually in the body and will be replaced eventually by newly formed tissues. They could provide time-varying mechanical properties and their use may ensure complete dissolution of the implant, eliminating long-term biocompatibility concerns or avoiding secondary surgical operations. The requirements for biodegradable materials include the following: they should degrade in the body at a rate that can be controlled; and the degradation products should be non-toxic, biocompatible, and easily excreted entities. After implantation in the body, a biodegradable bone substituting material will have gradual decreases in strength and stiffness over a clinically determined optimal period. As bone repairs itself, the external load will be transferred from the biodegrading implant to bone. This approach provides the best biomaterials solution to short-term tissue replacement and eventual tissue regeneration, if requirements for the initial stiffness and strength and other short-term properties can be met. Composites consisting bioactive (and bioresorbable) ceramics and biodegradable polymers have great promises for such purposes.

Polyhydroxybutyrate (PHB) is a naturally occurring β-hydroxyacid (a linear polyester) [12]. Its ability to degrade and resorb in the human body environment makes it a suitable candidate as the matrix for bioactive and biodegradable composite implants that will guide tissue growth and can be replaced eventually by the newly formed tissue. Being a thermoplastic, PHB can be processed using conventional manufacturing technologies such as extrusion, injection or compression moulding [128]. Therefore, using the technology for HA/PSU composite (Fig. 9), particulate HA and TCP were incorporated into PHB separately to form composites for tissue replacement and regeneration applications [46,48,129]. Particulate bioceramics (HA or TCP) could be homogeneously distributed in the PHB matrix for both HA/PHB and TCP/PHB composites (Fig. 13e). The stiffness of the composites increased with an increase in bioceramic content. In in vitro experiments using simulated body fluid (SBF), bone-like apatite formed on HA/PHB and TCP/PHB composites [130], which was indicative of bioactivity of these materials in vivo. With prolonged immersion in SBF (i.e., beyond 2 months), both HA/PHB and TCP/PHB composites exhibited decreases in storage modulus (from DMA analysis), indicating the degradation of composites in the simulated body environment. The structure and mechanical properties of bone-like apatite formed in vitro on HA/PHB and TCP/PHB composites are similar to those formed on other bioactive materials [131].

5.8. Calcium phosphate reinforced chitin

Chitin is another naturally occurring polymer that can be used for biodegradable composites. It is an important constituent of the exoskeleton of crustacea, molluscs and insects. Chitin as a natural polymer is biodegradable due to its β-1,4 glycosidic linkages being susceptible to the lysozyme present in the human body [132]. Poorly crystallised HA (pcHA), which is more bioactive and soluble than fully crystallised HA, was used as the bioactive and biodegradable phase for chitin [38]. pcHA/chitin composite could be produced using the solution casting technique (Fig. 10), with a homogeneous distribution of pcHA particles in the composite being achieved (Fig. 13f). The solution casting process did not change the crystalline structure of chitin. Tensile testing results revealed that the strength and modulus of pcHA/chitin composite decreased with an increase in the amount of particulate pcHA in the composite. In vitro mineralisation experiments showed that pcHA particles rendered the composite bioactive and significantly improved the ability of composite to induce the formation of bone-like apatite on its surface [133].

5.9. Bioactive and biodegradable scaffolds

Using chitin or poly(L-lactic acid) (PLLA) as the matrix polymer, composite scaffolds containing plasma sprayed HA (psHA) particles were produced [55,56]

following the procedure described in Fig. 11. The pore size of the scaffolds could be well controlled by the utilisation of porosifier particles of different sizes. The concentration of the polymer solution in scaffold production should be carefully selected, as it was found that with an increase in polymer concentration, the pore interconnectivity decreased together with an increase in the thickness of pore walls. Highly porous scaffolds containing 20 wt% of bioactive ceramic particles could be made. In vitro experiments showed evidently that psHA particles enhanced the formation of bone-like apatite on the surface of psHA/PLLA composite scaffolds when they were immersed in SBF. Degradation of the scaffolds in SBF was also observed. The introduction of bioactivity into biodegradable scaffolds by incorporating particulate bioceramics may enhance cell-seeding and hence the subsequent tissue growth. Scaffold (production and selection) is only part of the "tissue engineering triad" [134]. The other two parts of the triad, namely, cells and signalling (molecules), are equally important components which decide on the ultimate success (or failure) of a tissue engineering strategy. Seeking a suitable scaffold for a particular application constitutes the construct technology which underpins the development of tissue engineering [135], and different application situations require scaffolds of different characteristics.

6. Concluding remarks

Hard tissues in the human body are natural composite materials and they serve as templates in the development of tissue replacement materials. Over the last two decades, various bioactive composites have been investigated for tissue replacement and tissue regeneration purposes. Each of these composites has its distinctive characteristics and may be used in specific clinical situations.

The successful clinical use of bioactive composites has paved the way for further developing this type of biomaterials for various applications. With new knowledge being gained of natural tissues and the human body and the advancement of composite science and technology, newer and better composite materials will become available for substituting diseased, damaged or worn-out body parts.

Natural tissues such as bone have the exceptional ability of self-repair. It remains a great challenge for man to produce what nature has made for us.

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