Review

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Acrylic Bone Cements: The Role of Nanotechnology in Improving Osteointegration and Tunable Mechanical Properties

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Nanotechnology is an extremely powerful emerging technology, which is expected to have a substantial impact on biomedical technology, especially in tissue engineering and drug delivery. The use of nanocompounds and nanoparticles in the synthesis of improved bone cements to be applied in vertebroplasty/kyphoplasty and artroplasty, is of great interest due to the increasing incidence of osteoporosis and osteoarthritis. This review reports new advances in the development of acrylic bone cements, using different radio-opalescent nanomaterials taking into consideration their influence on the mechanical behavior and biocompatibility of the resulting acrylic bone cement. Furthermore, other non-radiopaque nanoparticles capable of mechanically reinforcing the bone cement as well as induce osteointegration, are also reviewed. Additionally, nanoparticles used to improve the controlled release of antibiotics contained in acrylic bone cements are briefly described.

KEYWORDS: *Acrylic Bone Cement, Vertebroplasty, Kyphoplasty, Osteointegration, Mechanical Behavior, Biocompatibily, Bone Tissue Engineering.*

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INTRODUCTION

As median age raises, orthopedic procedures as arthroplasty, vertebroplasty and kyphoplasty,[1–4] are gaining increasing importance. This can be demonstrated by merely looking over a recent clinical study on the prevalence of osteoporosis and osteoarthritis, which are the some of the major health concern faced by physicians when treating elder people.[5,6] While the first deals with prostheses fixation, the remaining two are intended to stabilize a vertebral body that has been mechanically compromised (e.g., by fracture, tumor, or metastases).[7–9] As long term results are highly required it is mandatory to develop new technologies or to improve the existing ones, as they exhibit several disadvantages.[10–17]

Poly(methyl methacrylate) (PMMA) and its derivatives have been successfully used in orthopedic surgeries as bone filler in vertebroplasty.[18,19] Also, PMMA is the most common and successful adhesive used to anchor orthopedic implants to bone, as evidenced by data from long-term national joint registries.[20] In addition to prove clinical

safety and efficacy, acrylic bone cements used in vertebral augmentation have shown to induce immediate and lasting pain relief in 80–90% of the cases.[21, 22]

Bone cement acts as a grout by filling in the voids that are left between the implant and the patient's bone, thus creating a mechanical interlock. This is why the role of the cement is directly related to its mechanical properties, especially its resistance to fracture in the mantle at the cement-prosthesis interface or the cement–bone interface. The use of acrylic bone cements present disadvantages including high polymerization temperature, neurotoxicity of the monomer and lack of osteointegration due to their bioinert nature, i.e., it does not resorb or allow bone replacement. It is therefore encapsulated by fibrous tissue,[21, 23, 24] causing instability and movements at the bone cement-prosthesis interfaces, which are considered the weak-link-zones. These micromovements can accelerate aseptic loosening, causing a failure in the cemented

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total hip arthroplasties.[25, 26] Additionally, the Young modulus of PMMA bone cement is considerably higher compared to the value obtained for cancellous bone. When used in vertebroplasty and kyphoplasty this mismatch may leads to increased fracture risk for the adjacent vertebral bodies after reinforcement.[24, 27]

Nowadays great efforts are being made in order to improve osteointegration, which is a key factor to achieve long term stability of the implant. Additionally, while the primary roles of bone cement in artroplasty are immediate fixation of the implant to the bone and force transfer from the implant to the surrounding tissue, in vertebroplasty and kyphoplasty it is fundamental for the bone cement to augment fractured vertebra. In order to adequately perform these functions, bone cement must be compatible with the host tissue as well as possess sufficient strength to withstand the large and repetitive magnitudes of load/stress to which it is exposed.[28] Mechanical properties of bone cement play an essential role in the long term outcome of a cemented joint arthroplasty and the augmented vertebra.[29]

Typically, acrylic bone cement is a two-component based formulation: a solid phase of PMMA, a radiopaque agent and an initiator; and a liquid phase of methyl methacrylate (MMA) with an amine as coinitiator and hydroquinone to inhibit autopolymerization.[30] Due to its radiolucent nature, a radiopaque substance is added to the formulation in order to monitor the bone healing process. This modification allows the identification of osteolytic lesions around an implant and the detection of fractures within the bone cement after surgery, using fluoroscopic or x-ray control.[31] These fillers, or radiopacifiers, typically dense metal powders, affect the energy attenuation of photons in an X-ray beam as it passes through the material, thus reducing the intensity of the photons by absorbing or deflecting them. As these materials exhibit higher attenuation coefficient than soft tissue or bone, they appear lighter shadow on a fluoroscope or x-ray film. Most commonly used radiopaque particles are barium sulphate ($BaSO_4$) and zirconium oxide (ZrO_2) but, as they are highly polar, phase separation is observed due to their incompatibility with low polar polymer matrix, leading to degradation of physical and mechanical properties of the cement.[32]

Compared to its applications in other fields,[33] nanotechnology applied to PMMA cement is still in its infancy. Previous studies have shown that modifications of material (such as metals, ceramics, polymers, and composites thereof) at nanoscale,[34] alter particularly the texture and the topography of the material, increase surface wettability and increase the cytocompatibility.[35] There is still ongoing research to improve the thermal, biological and mechanical properties of bone cements to increase the performance and longevity of cemented prostheses.

Theoretically, nanostructured fillers are capable of establishing interactions with the acrylic matrix of commercial orthopedic cement and may help to enhance its mechanical properties without compromising radiopacity and rheological properties by preventing phase separation.[36, 37] Moreover, chemical bonding between the acrylic matrix and the nanofillers is expected to reduce the production of abrasive nanofiller debris in tissue surrounding the prosthetic joints.[38] Much effort has been devoted to the development of acrylic bone cement with improved mechanical behavior. In this sense nanotechnology is playing a fundamental role as it has widespread the possibilities of achieving the desired material. It is known that mixing materials at the nanoscale, leads to nanocomposite materials having several properties that are not only the ones derived from the separate constituents, but new ones. This is the main reason why applying nanotechnology to acrylic bone cements is attractive.

The aim of this review is to explore different alternatives proposed by several researchers in order to overcome the above mentioned drawbacks of acrylic bone cements using nanotechnology. Mechanical and biological behavior as well as the radiopacity of the modified bone cements is analyzed and compared to those of the conventional acrylic bone cement. We believe that it is of great interest to understand the influence of the nanotechnology in the development of new bone cements, with the purpose of developing new treatments with higher efficiency compared to conventional therapies.

MODIFICATIONS IN THE ORGANIC MATRIX

Even with the aforementioned weaknesses,[39] PMMA-based bone cements are still predominantly used in different orthopedic procedures.[8, 40] The most frequently used commercial acrylic bone cements and their properties are shown in Table I.

Numerous attempts have been made to improve the properties of these bone cements with varied degrees of success. Addition of other monomers, crosslinking agents, have been reported in earlier works.[51–55] Nowadays several research groups are focused on the study of the changes on the mechanical, thermal and biological properties by modifying cement formulation.

Bioactive Bone Cements

Some authors[56–58] have reported that the development of new formulations namely bioactive bone cements is highly desirable, since they promote bone growth and the formation of a strong chemical bond between the implant and bone tissue.[59–61] More recently, Fernandes et al.[24] developed solid phase bioactive self-curing acrylic cement which was modified by the addition of different biodegradable matrices such as poly(3-hydroxybutyrate) (PHB) and its copolymer with hydroxyvalerate (PHBV). The chemical structures of these polymeric matrices are shown in Figure 1. They combined a biodegradable polymer (PHB or PHBV) with bioactive glass filler as silicate-based glass or borate-based glass.

Table I. Composition and properties of commercial acrylic bone cement.

Acrylic bone cement	Composition	Properties	Refs.
Simplex P	Powder: 75% w/w methylmethacrylate–styrene–copolymer, 10% w/w barium sulfate, 15% w/w PMMA, Liquid: 97.4% v/v MMA, 2.6% v/v DMPT, 75 + 15 ppm hydroquinone	High viscosity, maximum temperature 50 °C (curing in a mold); at the central location (61.8 °C ± 12.7, 3.6 minutes ± 2.1); however at the anterior cortex and spinal canal locations not exceed 41 °C; Fracture strain (mm/mm) 0.0162 (0.0038); Elastic modulus (GPa) 2.53 (0.33); Ultimate tensile strength (MPa) 36.19 (10.09)	[8, 41–46]
Palacos R	Powder: 81.8% w/w MA, MMA, 14.9% w/w zirconium dioxide, 0.78% w/w BPO, 2.4% chlorophyll. Liquid: 96% v/v MMA, 2.0% v/v DMPT, 0.40 mg chlorophyll	High viscosity, maximum curing temperature 53 °C; Modulus of elasticity (GPa) 4.5–4.9. Hardness (MPa) 280–300	[41, 42, 46, 47]
CMW 1 DePuy	Powder: 88.85% w/w PMMA, 9.1% w/w barium sulfate, 2.05% w/w BPO. Liquid: 98.18% v/v MMA, 0.82% v/v DMPT, 25 mg hydroquinone	High viscosity, maximum curing temperature 90 °C, Modulus of Elasticity 2.7 ± 0.1 GPa. Tensile Strengh 39 ± 1 MPa. Fracture toughness 1.44 ± 0.09 MPa	[41, 46, 48]
Osteobond	Powder: 88.75% w/w PMMA–styrene, 10% w/w barium sulfate, 0.0125% w/w BPO. Liquid: 97.3% v/v MMA,2.7% v/v DMPT, 80 ppm hydroquinone	Low viscosity, at the central location (51.2 °C ± 6.2, 1.3 minutes ± 1.4); however at the anterior cortex and spinal canal locations not exceed 41 °C; Modulus of elasticity (GPa) 4.5–4.8. Hardness (MPa) 280–300	[8, 41,42, 46]
Composite material Cortoss	Resin components: (2,2-bis-4-(2-hydroxy-3-methacryloxypropoxy) phenylpropane, (2,2-bis-4-(2-methacryloxy-ethoxy)phenylpropane, triethylene glycol diemethacrylate, 2,2′-(4-methylphenyl)imino bis-ethanol, BPO (98%), 2-hydroxy-4-methoxy-benzophenone, 2,6-di-tert-butyl-p-cresol. Different silanes as reinforcing components	Setting time from 4 to 8 min, biostability and hight compression strength: > 100 MPa	[42, 49, 50]

Pure PMMA cement and those containing PHB and PHBV, were assayed for cell viability/proliferation (MTT assay) in cells of human bone marrow, under conditions that promoted osteoblastic differentiation,[62] for twenty one days. Results are shown in Figure 2, they indicated that PHBV containing cements had performance.

These results demonstrated that PHBV-containing cements promoted the development and organization of an osteoblastic cell layer, achieving higher cell proliferation and alkaline phosphatase activity (ALP), thus indicating that the inclusion of this polymer resulted in an improved biological response compared to the one observed on the cements containing PHB. On the other hand, comparison between cements containing PHB or PHBV and pure PMMA cements showed that the behavior was quite similar for modified cements, namely a lower peak temperature and a longer setting time, which might indicate an extended time for bone cement preparation/application during surgical procedure. Therefore the authors conclude that the introduction of different polyhydroxyalkanoates into bioactive bone cement induced several beneficial changes in the general properties of the cement showing that the developed material is a potential alternative to the commercially available cements.

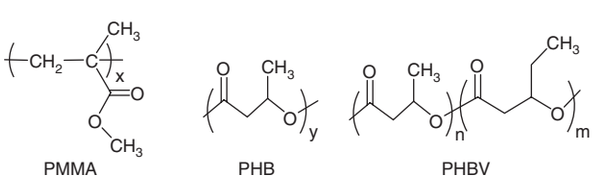

Figure 1. Chemical structure of different polymer matrices.

Likewise, different authors have recently developed a new bone cement matrix using a copolymer of PMMA and ethyl hexylacrylate (EHA) (1:1), in order to improve the commonly used formulations. The reason why this particular copolymer was chosen is that its mechanical properties and *in vitro* bioactivity were evaluated in a previous study,[63–65] showing its potential for orthopedic applications. On the other hand, Nien et al.[66] developed a novel bone cement by introducing crosslinked poly(methylmethacrylate-acrylic acid sodium

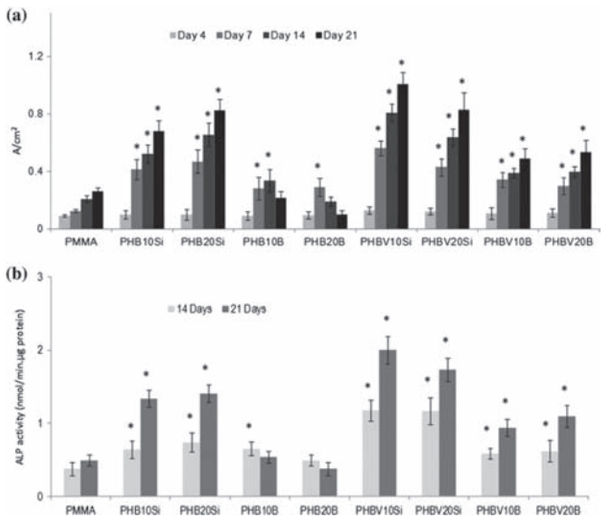

Figure 2. Cell viability/proliferation (A) and ALP activity (B) of human bone marrow osteoblastic cells seeded over the cements for 21 days. Reprinted with permission from [24], P. P. Lopes, et al., Acrylic formulations containing bioactive and biodegradable fillers to be used as bone cements: Properties and biocompatibility assessment. *Mater. Sci. Eng. C* 33, 1289 (2003). © 2003, Elsevier Ltd.

salt) particles in order increase drug release. The authors reported that the drug-loaded bone cement had enhanced hydrophilicity, which allowed the efficient motion of fluids through the cement, and supplement both the drug release rate and total release amounts of drugs.

Blends of PMMA with Natural Polymers

Another alternative to improve mechanical properties and bioactivity of PMMA, was proposed by Van Mullen et al.[67] and consisted in blending this polymer with natural polymers. In order to create porous bone cement, a biodegradable polymer, as lactose or hydroxypropylmethylcellulose (HPMC),[68] carboxymethylcellulose,[69] hydroxyapatite powder-carboxymethyl chitin composite,[70] chitosan powder[71] or biodegradable nanoparticles[72] should be added to the traditional formulation. Taking into account that the degradable phase leached after a time period, the presence of chitosan powder or nanoparticles into bone cement improve the properties or provide new ones.[73, 74]

Chitosan (CS) is a promising hydrogel material for bone tissue regeneration due to its biocompatible and biodegradable nature, whose degradation rate depends on factors such as degree of deacetylation and crystallinity.[75] Tang et al.[76] studied quaternized chitosan derivatives, such as hydroxypropyltrimethyl ammonium chloride chitosan (HACC). When loaded into PMMA it inhibited significantly the formation of biofilms caused by methicillin-resistant Staphylococcus strains. In a different work, these authors[77] investigated the surface morphology, hydrophilicity, apatite formation ability and osteogenic activity of HACC loaded PMMA. The results showed that, compared to other PMMA-based cements, HACC-loaded PMMA had improved properties such as a lower polymerization temperature, prolonged setting time, porous structures after immersion in phosphate-buffered saline, higher hydrophilicity, more apatite formation on the surface after immersion in simulated body fluid, and better attachment and spreading of the human-marrow-derived mesenchymal stem cells. They also found better stem cell proliferation, osteogenic differentiation, and osteogenesis-associated genes expression on the surface of the HACC-loaded PMMA compared to the gentamicin-loaded PMMA.[68] Therefore, this new anti-infective bone cement had improved physical properties and osteogenic activity, which may lead to better osteointegration of the bone cement in cemented arthroplasty and vertebroplasty.

Recently, some research groups have been focused on chitosan oligosaccharides (CSO) as they proved to be a bone-inducing substance to be used as bone graft material. Due to its shorter chain lengths and free amino groups in D-glucosamine units, CSO are water soluble. These oligosaccharides have positive charges which allow strong binding to negatively charged surfaces, as well as biological activity such as antitumoral,[78] antimicrobial[79] and free radical scavenging activity,[80, 81] non-toxicity, biodegradability and biocompatibility.[82] In a different study, Nie et al.[83] developed composite materials consisting of water-soluble chitosan oligosaccharide (CSO) and PMMA, which were prepared by combining freeze-drying and radical polymerization of MMA under redox conditions using benzoyl peroxide (BPO) as initiator, *N*,*N*-bis(2-hydroxyethyl)-*p*-toluidine as co-initiator and triethyleneglycol dimethacrylate as crosslink agent, resulting in two-continuous phase composites.

The incorporation of CSO highly influences the mechanical behavior of PMMA. As CSO degrades, a porous interconnected PMMA composite arises. The elimination of CSO led to lower compression modulus and strength, rendering this material ideal as bone substitute as its mechanical behavior is similar to that of cancellous bone. Tangboriboonrat and col.[84] reported the synthesis of PMMA latex by miniemulsion polymerization, using chitosan oligomer as stabilizer. These particles interacted directly with the indigenous non-rubbers at the surface of sulphur prevulcanized natural rubber (SPNR) film. The driving force was the hydrogen bond formed between carboxylic (COOH) groups of proteins on rubber surface and hydroxyl (OH) and protonated amine groups (NH_3^+) of CS chain on PMMA-CS particles at pH 2.0. The presence of PMMA-CS particles led to an increase in surface roughness of the SPNR film. The simple coating of the rubber substrate with PMMA-CS particles reduced effectively the *in vitro* cytotoxicity on L-929 cells as is shown in Figure 3.

The results confirmed that coating natural rubber (NR) and sulphur prevulcanized natural rubber (SPNR) films with PMMA-CS particles reduced the cytotoxicity of

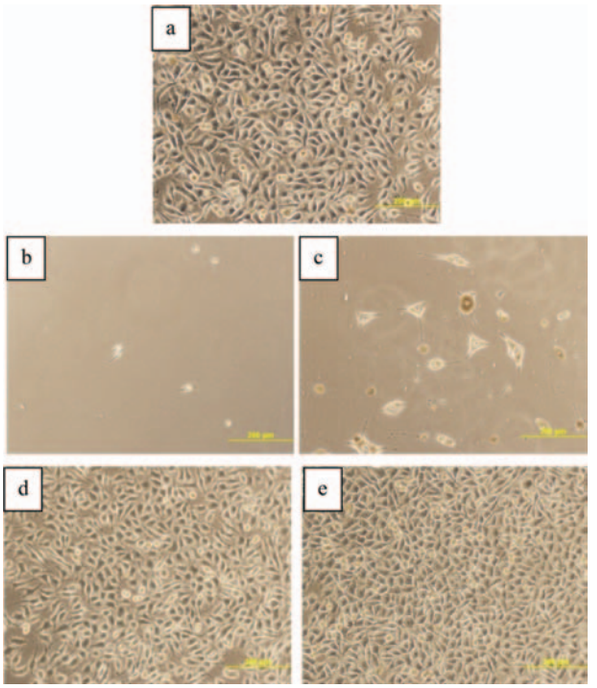

Figure 3. Morphologies of L-929 cells incubated with (a) negative control, (b) positive control of NR, (c) positive control of SPNR, (d) modified NR and (e) modified SPNR (12.5% extract concentration at day 6 after culturing). Reprinted with permission from [84], N. Kanjanathaworn, et al., Reduction of cytotoxicity of natural rubber latex film by coating with PMMA-chitosan nanoparticles. *Carbohydr. Polym.* 97, 52 (2013). © 2013, Elsevier Ltd.

mouse fibroblast cells (L-929 cells). On the other hand, interpenetrated polymer networks of chitosan (CS), polyacrylic acid (PAA) and polyacrylamide (PAM) were prepared by free radical polymerization. These hydrogeles showed no cytotoxic effects on human skin dermal fibroblasts as determined by MTT assay except for two compositions which after seven days presented a viability lower than 80% respect to the control.[85] Other variations of chitosan and nanoceramics have recently been developed and tested for bone tissue engineering. In particular, a chitosan gelatin/nano-bioactive glass ceramic composite demonstrated excellent properties for use in alveolar bone tissue regeneration.[86] It is important to notice that ceramics synthesized by a sol–gel process were osteoconductive and biodegradable. This composite was able to bond to hard tissues due to its ability to develop a surface layer of hydroxycarbonate apatite and produce no local or systemic toxicity nor inflammatory or foreign-body response.[87–89] As the chitosan/gelatin/nanoglass ceramic can be fabricated in order to have pore sizes in the range of 150–300 μm, it should be optimal for migration of cells into the interior of the scaffold and osseous ingrowths and vascularization.[90] The degradation and swelling behavior of the composite scaffold also optimized cell attachment and spreading as biomineralization occurred due to the formation of an apatite layer on the surface of the composite.[86] These properties point out the usefulness of these composites in tissue engineering applications in bone regeneration.

Modification of Liquid Phase

Flores Gallardo et al.[91] reported the fracture behavior of acrylic bone cements modified with comonomers containing amine groups. Deb et al.[92] spread the use of these compounds as activators. Additionally, different researchers.[93, 94] showed that the incorporation of comonomers containing amine groups into bone cement formulations promotes a better cell interaction between bone tissue and cement surface, as well as the reduction of the temperature peak. It was also found that bone cements prepared with these comonomers exhibited increased hydrophilicity with increasing comonomer content.

Different research groups[91, 95] prepared bone cements where the powder component consisted of PMMA beads, BPO and $BaSO_4$ while the liquid component consisted of MMA (as the base monomer), *N*,*N*-dimethyl-*p*-toluidine and either 2-(diethylamino)ethyl-acrylate (DEAEA), 2-(dimethylamino)ethyl-methacrylate (DMAEM) or 2-(diethylamino)ethylmethacrylate (DEAEM) at 2, 4, 6 and 10 wt%; these quantities were incorporated by partial replacement of MMA in the liquid phase. BPO and $BaSO_4$ were added to the solid phase at 1% and 10% w/w, respectively. A weight ratio of powder to liquid of two was kept in all cases and the cements were prepared by hand mixing without vacuum. Cements containing only MMA and *N*,*N*-dimethyl-*p*-toluidine in the liquid phase, i.e., without comonomer, were prepared for comparison purposes as control. In Figure 4 is shown the chemical structure of the comonomers used in the different formulations.

The authors concluded that the addition of monomers containing amine groups to bone cement formulations reduces both the modulus and strength in compressive

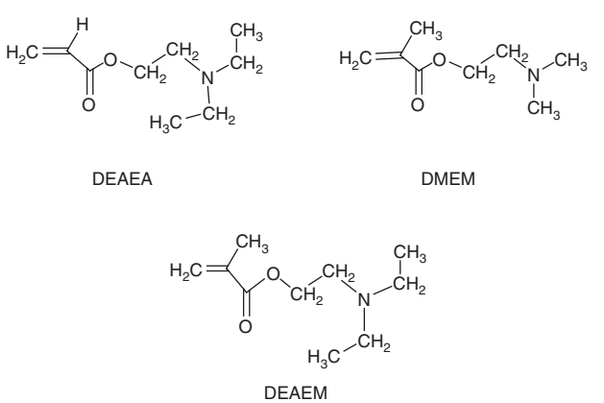

Figure 4. Chemical structure of comonomers with amine groups.

and bending tests. The incorporation of these monomers also produces a considerable improvement in their fracture properties. Almost every composite material studied showed enhanced properties, except the bone cement modified with DEAEM comonomer. Furthermore, in bone cements modified with DEAEM comonomer the decrease in the essential work of fracture with the increase of DEAEM content is related to a ductile-to-brittle transition in the crack propagation phase, i.e. an unstable crack propagation mechanism. Bone cements modified with DEAEA and DMAEM comonomers, showed increased nonspecific values compared to unmodified bone cement, this can be attributed to an increase of the absorbed energy in the crack propagation. Finally, the use of the essential work of fracture approach is suggested to determine the fracture behavior of cements that do not exhibit a linear stress–strain relationship during their mechanical characterization.

NANOPARTICLES TO ENHANCE ACRYLIC BONE CEMENTS PERFORMANCE

As it was mentioned in the introduction, using $BaSO_4$ as contrast agent has several drawbacks. In this sense several researchers have explored the possibility of modifying the liquid phase in order to achieve radiopaque cements without adding $BaSO_4$. New iodine-containing bone cements showed increased fatigue resistance[96] and decreased thermal necrosis.[97] It was also proved that iodine-cement and $BaSO_4$-cement showed analogous cytocompatibility throughout every *in vitro* experiments.[98] Despite Hernández et al.[99] reported that acrylic bone cement containing 10% bismuth salicylate in the liquid phase had overall good properties (thermal, mechanical and rheological properties) and optimum homogeneity and radiopacity, nanotechnology is a more attractive alternative to obtain reinforced composite materials due to strong interfacial interactions between the nanostructured fillers and the polymer matrix. Yet little is known on how nanoparticles in bone cements act as reinforcing and radiopaque agents, or their biocompatibility.

Improving Radiopacity

Problems associated with the use of PMMA bone cement are basically its high viscosity and radiopacity, which is insufficient to adequately observe the injection process and ensure the perfect location of the reinforcement. In a joint replacement surgery, it is vital for the bone cement to be radiologically detectable.[36] The radiopacity of PMMA can be increased by adding a contrast agent. Generally, two different micron-sized particles of heavy metal ion salts ($BaSO_4$ and or ZrO_2) have been used in bone cements formulations to increase its X-ray contrast.[100, 101] However, adding micron-sized metal ions adversely affects the biological and mechanical properties of PMMA,[100, 101] probably due to incompatibility of highly polar and ionic radiopaque substances with low polarity resin.[102] PMMA bone cements contain approximately ten per cent by weight of the radiopacifier agent, usually barium sulfate or zirconium oxide particles measuring 1–3 μm in diameter. High viscosity achieved by PMMA cements during mixing complicates the even dispersion of the radiopacifying particles throughout the polymer matrix, resulting in the presence of large domains with agglomerated filler particles. Disregarding the consequences in the mechanical behavior, the obtained fluoroscope image may not be representative of the cement distribution through out of the repaired zone.

In search of novel additives to PMMA, different kinds of nanoparticles have been used as fillers, in order to enhance its cytocompatibility and osteointegration, and decrease its exothermic reaction temperature. However, little is known on how nanoparticles act as radiopacifying agents. Instead of conventional micron-sized barium sulfate, $BaSO_4$ nanoparticles were introduced in an acrylic bone cement as radiopacifier agent as a first attempt to overcome the previously mentioned drawbacks. Webster et al.[103] showed that PMMA containing $BaSO_4$ nanoparticles (X-ray intensity 35.9%, $p < 0.01$, compared with PMMA alone) was more radiopaque than the one loaded with $BaSO_4$ microparticles (X-ray intensity 12.5%, $p < 0.01$, compared with respective conventional additive).

Nano-sized fibrous and tubular titania (TiO_2) particles, having high aspect ratio, have been introduced in the acrylic polymer matrix not only as reinforcing agent but also for its radiopacity.[104] Agglomeration of the nanofiller represents a major problem in the preparation of bone cements as it leads to an uneven distribution of the radiopacifier among the polymer matrix and poor performance of the composite. In order to avoid the nanophase agglomeration, functionalization of the nanoparticles is one of the most common strategies.

Nanoparticles of TiO_2 were functionalized using methacrylic acid (MA). Then, the double bond in MA was copolymerized with MMA to form a TiO_2-PMMA nanocomposite.[105] As a consequence of organophilicity provided by the functionalization of the TiO_2 nanofibres and tubes strong adhesion of the nanofibers to the PMMA matrix was observed, whereas $BaSO_4$ particles exhibited only a weak adhesion to the matrix. The TEM images of PMMA composites with 3 wt% functionalized nanofibers or nanotubes showed that most nanofibers were clumped together in bundles of nanosize range, and are uniformly dispersed throughout the polymer matrix while the functionalized titania nanotubes are uniformly dispersed in PMMA matrix. The radiopacity of cements containing 0.5, 1.0, 1.5, and 2.0 wt% loading of functionalized *n*-TiO_2 fibers was determined, using a commercially available bone cement CMW® 1 (Depuy, Warsaw, IN).[104]

It is important to notice that with the addition of 6% $BaSO_4$ particles, CMW® 1 exhibits a radiopacity value of 0.35 ± 0.01 mm Al, which does not decrease

significantly when the same commercial bone cement was loaded with n-TiO_2 up to 2% ($p = 0.05$). The obtained radiopacity values for the n-TiO_2/CMW® 1 composites were 0.36 ± 0.03 mm Al when loaded with wt 0.5% of nanofibers, 0.37 ± 0.01 mm Al for the composite containing wt 1.0%, 0.37 ± 0.02 mm Al for the one loaded with 1.5 wt% and 0.35 ± 0.04 mm Al for the composite containing 2.0 wt%. Moreover, Lewis et al.[106] reported the incorporation of strontium oxide (SrO) particles as an alternative radiopacifier in an acrylic cement matrix. In order to overcome the disadvantages observed in previous studies using titania nanotubes (n-TiO_2 tubes)[107] and to enhance its reinforcing effect and radiopacity, Khaled et al.[108] modified the mentioned nanotubes surface using strontium oxide (n-SrO–TiO_2 tubes). The surface of these nanotubes was functionalized using MA at pH 5.5, in order to introduce a vinyl functional group on nanotube's surface, providing a binding site to experimental bone cement. In this case, radiopacity of the commercial CMW® 1 specimen containing 6 wt% $BaSO_4$ as radiopacifier is 0.34 mm Al. The same composite loaded with 2 wt% n-SrO–TiO_2 tubes showed a radiopacity value of 0.3 mm Al, and 0.17 ± 0.01 mm Al when loaded with 2 wt% n–TiO_2 tubes. Although more SrO could be easily integrated into the nanotubes by adjusting the synthesis conditions, this radiopacity value is approximately an 88% of the radiopacity shown by the CMW® 1 specimen and is deemed sufficient.

Other example of chemical functionalization of ceramic nanoparticles intended to achieve better integration with PMMA bone cement was reported by Webster et al.[109] This methodology studied the effect of functionalized ZrO_2 and $BaSO_4$ particles with 3-(trimethoxysilyl)propyl methacrylate (TMS) as silane coupling agent. In this research, ZrO_2 micron particles (ZM), unfunctionalized ZrO_2 nanoparticles (ZN), ZrO_2 nanoparticles functionalized with TMS (ZNFT), $BaSO_4$ micron particles (BM), unfunctionalized $BaSO_4$ nanoparticles (BN) and $BaSO_4$ nanoparticles functionalized with TMS (BNFT), were added to commercial bone cement. The obtained results demonstrated that the radiopacity (measured by X-ray images which were then scanned for the analysis of mean gray values, (a measure of optical density) of every bone cements loaded with ceramic particles was greater than that of plain bone cements, whose mean gay value was 43.68. ZrO_2 exhibited grater radiopacity than $BaSO_4$, in every particle size whether it was functionalized or not. While functionalized ZrO_2 nanoparticles showed the lowest radiopacity for this material (72.66), functionalized $BaSO_4$ nanoparticles exhibited the highest value (63.44). Finally, unfunctionalized ZrO_2 nanoparticles exhibited similar radiopaticity compared to microparticles, where the radiopacity values obtained were 76.30 and 76.59 respectively, yet $BaSO_4$ nanoparticles were less radiopaque than $BaSO_4$ microparticles (49.81 and 54.63, respectively). Taking into account every fact reported above; it is possible to conclude that nanoparticles and especially, functionalized nanoparticles can be used instead of micro-fillers as radiopacifier agents while maintaining or even enhancing the mechanical properties of bone cement.

Improving Mechanical Behavior

In first place we will make an attempt to define bone mechanical properties, particularly vertebral structures, based on recent studies and reviews. Two different approaches will be analyze here: in first place we will discuss biomechanical factors as vertebral structure and vertebral interconnection; and secondly we will focus on bone tissue from the point of view of material science, where we will discuss bone properties in the same way we would do with polymeric and metallic materials. Every bone in human body has a morphology that is consistent and wholly depends on its function. Indeed, vertebral column is a complex structure composed of interconnecting vertebrae whose aim is to provide mobility, flexibility as well as protection to the spinal cord. Additionally, it is responsible for supporting the upper part of human body. The posterior neural arch, whose primary function is to protect the spinal cord, has also several projections which serve as attachment places for muscles and ligaments. These ones are responsible of arch bending up to 2–3° relative to the body. The Zygapophyseal joints, which arise from the superposition of two vertebrae, are responsible for the stabilization of the spine in compression as well as for preventing excessive bending and translation between them. They also bear up to 20% of the compressive force, depending on their location in the vertebral column (lumbar or cervical).[110]

Osteoporosis is the main disease that causes bone tissue degeneration by a reduction in bone mineral density. Changes in mechanical properties of this material, which will be described later, can cause vertebral compression fractures. Different types of fractures arise depending on the damage caused to the vertebral body, each one corresponding to different weakened areas in the vertebral body. The most common vertebral fractures are the anterior wedge fractures which involve the collapse of the anterior vertebral body cortex, due to "stress yielding" of the anterior vertebral body.[110] This deformation of the vertebral structure causes the spine to be positioned in a lordotic posture, which leads to a 63% of the spinal compressive force to be bearded by the neural arch. Biconcave fractures arise when vertebrae slowly develop a permanent and smooth concave shape by the processes of bone creep and fatigue damage. Finally, "crush" fractures occur most likely in vertebrae adjacent to degenerated intervertebral discs, as a consequence of a compressive over-load bearded by the vertebral body cortex. In old people these fractures can occur during normal activities as a result of cumulative "fatigue failure" (cumulative microdamage). Elder people develop an abnormal spine curvature due to vertebral deformation and posture in order to

avoid pain.[22] In disregard of cosmetic and physiological consequences, biomechanics of the vertebral column are seriously altered, leading to an abnormal distribution of the compressive load. This fact along with a reduction in bone mineral density (BMD) increases the risk of suffering additional vertebral compression fractures. Indeed, it is essential to augment fractured vertebrae and restore normal spine curvature.

It has been demonstrated that bone tissue, both cortical and trabecular bone, exhibit a viscoelastic behavior. Mercer et al.[111] described the inelastic deformation observed in cortical bone both in tension and compression. They stated the collagen formed a continuous phase whereas the mineral phase was discontinuous. If otherwise, cortical bone would exhibit brittle behavior and would crack at quite small strains. Taking into account that the mineral phase highly influences the viscoelastic behavior of bone tissue, particularly in trabecular bone, BMD is actually a critical parameter in order to establish bone tissue mechanical properties. In this sense a healthy vertebrae is highly different from an osteoporotic one, and these ones are the most prompt to suffer compression fractures.[112] However, this approach is not restricted to vertebrae as it involves every bone in human body.

Having in mind that acrylic bone cements are used in vertebroplasty and kyphoplasty for vertebral augmentation, as well as fixation material for artificial joints in artroplasty, different characteristics are needed in order to fulfill their purpose. Although commercially available bone cements have had a good success in both cases, several drawbacks are encountered, and they are related to mechanical behavior as well as osteointegration. When using it as fixation cement it should be able to serve as an interfacial phase between the high modulus metallic implant and the bone, as well as transfer and distribute body loads from the prosthesis to the bone. If the cements have an inadequate fracture resistance, which is the case as they exhibit a brittle behavior, it may lead to implant loosening.[95, 113] In vertebroplasty as in kyphoplasty, original load distribution over vertebral spine is achieved due to the injection of acrylic cement, and also restoring load-bearing of the fractured vertebrae.[110] Dissimilarities between acrylic cement and vertebral bone tissue, especially in osteoporotic vertebrae, may induce new compression fractures. PMMA for vertebroplasty has greater stiffness than vertebral cancellous bone, causing higher incidences of fracture of neighboring vertebral bodies.[114, 115]

Microparticles versus Nanoparticles

As was previously mentioned, PMMA is a radiolucent material, the addition of radiopaque particles is mandatory. However, their incomplete dispersion, i.e., the formation of agglomerates, acts as initiation sites for fatigue cracks and also decreases the tensile strength, thus leading to an overall decline in fatigue properties.[31, 116] Indeed, pure PMMA is not the ideal bone cements but PMMA containing $BaSO_4$ microparticles is clearly not better.

One of the first attempts performed to improve mechanical properties using nanotechnology was to replace micron-sized radiopaque particles by nano-sized particles. Bellate et al.[116] replaced one micrometer size $BaSO_4$ particles, present in commercial PMMA, by the same amount of $BaSO_4$ particles of 35 nm. Using low voltage scanning electron microscopy and ultra-small angle X-ray they studied $BaSO_4$ particles dispersion in the PMMA matrix as well as their mechanical properties. According to uniaxial tensile tests the nanocomposite cement had higher work-of-fracture compared to the cement with microparticles. In addition, the nanocomposite showed higher fatigue life compared the microcomposite. Plastic deformation of PMMA preceding crack propagation is the most plausible mechanism underlying the high fatigue fracture resistance of bone cements containing nanoparticles fillers. From morphological analysis, it was observed that in the inter-bead matrix region containing $BaSO_4$ nanoparticles showed a high concentration of fracture "craters" with a rim made up of "tufts" of plastically deformed PMMA, indicating that the polymeric matrix suffered plastic strain before crack propagation.[117] The authors refer to this as a "nanotoughening" effect.

In other studies carried out by Webster et al.[109] not only barium sulphate but zirconia nanoparticles were functionalized in order to achieve improved filler-matrix compatibility. They also studied the behavior of both types of unfunctionalized nanoparticles. The results of this research showed differences between failure modes for the various bone cements that were fabricated. Bone cements containing unfunctionalized ceramic micron and nanoparticles along with plain bone cements had failure modes that were in agreement with a brittle fracture behavior. Comparisons among them showed slight differences. However bone cements containing functionalized ceramic nanoparticles had failure modes that were less brittle and had a clear plastic deformation region. Morphological analysis is in agreement with mechanical tests. Webster et al.[109] demonstrate that it is possible to tweak mechanical properties of bone cements.

Besides $BaSO_4$ and ZrO_2, other radiopaque nanoparticles were studied. That is the case for TiO_2 nanofibers and nanotubes studied by Charpentier et al.[32] These authors followed the hypothesis that in order to achieve a radiopaque composite without compromising mechanical properties it was necessary to employ radiopaque agents that were compatible with the PMMA matrix. The major drawback of these nanoparticles is their strong agglomeration when they are blended with the polymer matrix. In this sense, it was studied the functionalization of the above mentioned titania nanostructures using methacrylic acid and a Ti-carboxylic coordination bond, providing them with the organophylic character needed to achieve strong adhesion with the PMMA matrix. They explain

that the high surface area of fibers and nanotubes, along with good dispersion among the polymer matrix, leads to an improvement in mechanical properties.[32] This is due to the adhesion with the surrounding polymer which allows external load to be effectively transferred to the nanofillers, thus resulting in a toughter and stiffer cement. SEM micrographs of the fracture surface of the reinforced bone cements are shown in Figure 5. They also demonstrated that mechanical properties improve with higher aspect ratio as nanotubes show better performance than nanofibers. In further studies carried out by Charpentier et al.[108] titania nanotubes were functionalized using strontium oxide as it showed potential antibacterial activity and increased biocompatibility. Although both radiopacity and biocompatibility are improved, mechanical properties were not affected by the presence of strontium oxide. The authors stated that as the nanotube is an open-ended structure, the monomer may access its interior by capillary action, and subsequently polymerized inside the tube, thus leading to an additional mechanical interlocking polymer-filler. They demonstrated that aspect ratio and nanostructure highly influences mechanical behavior.

Carbon Nanotubes

Taking into consideration recent advances in material science, not only biomedical research, several alternatives should be considered in order to improve mechanical behavior. Due to their high aspect ratio carbon nanotubes (CNTs), both single wall carbon nanotubes (SWCNTs) and multiwall carbon nanotubes (MWCNTs) offer the potential to highly enhance mechanical, thermal and electrical properties of polymer systems as polyethylene,[118] polyurethane,[119] polystyrene, poly(vinyl alcohol), methyl methacrylate–styrene copolymer,[120] polyaniline,[121] styrene-butadiene rubber,[122] and polycarbonate urethane,[123] while retaining the structural capabilities of the polymer matrix. Andrews and Weisenberger[124] reported that improvements in CNT-polymer composites are a result of CNT type, dispersion, level of weight loading (wt%), alignment of the CNTs and the polymer matrix. However, chemical modifications on the nanotubes wall can generate substantial changes to the polymer matrix even when added at low weight percentages.[125] Uniform distribution of CNTs within the polymer matrix is critical for maximizing the interfacial bond between the CNTs and polymer matrix in order to achieve optimal improvements in mechanical properties.[126] It has also been reported that alignment and optimum dispersion of CNTs is important to enhance the thermal properties of a nanocomposite.[127]

Dunne et al.[128] reported the reinforcement of acrylic bone cement through the addition of funtionalized and unfunctionalized carbon nanotubes, using three different methodologies:

(1) magnetically stirring the MWCNTS in the MMA component,
(2) dry blending using a small-scale turbo blender and
(3) dispersing the MWCNTs in the MMA monomer using an ultrasonic disintegrator.

Using the first mixing method had an overall negative effect on mechanical performance of the bone cement due to the poor dispersion of the MWCNTs. On the contrary, dry blending of MWCNTs in the polymer powder and disintegrating the MWCNTs in the liquid monomer using ultrasonic agitation homogeneously dispersed the MWCNTs in the resulting nanocomposite. According to their orientation, MWCNTs were able to bridge the initial crack and prevent crack propagation, thus enhancing the longevity of the cement mantle, as can be seen from Figure 6.

In a more recent study, Dunne et al.[129, 130] demonstrated that incorporating MWCNT into acrylic bone cements significantly improves their fatigue life. Particularly, functionalized MWCNT-COOH reported the greatest improvement compared to unfuctionalized MWCNTs and MWCNT-amine; these chemical modifications improved the nanoparticles dispersion. Improvements in mechanical behavior are attributed to an enhanced mechanical and chemical interlocking between carbon nanotubes and the polymer matrix. By examining SEM micrographs, shown in Figure 7, it is clear that there was a polymer sheathing around the well-dispersed MWCNT-COOH

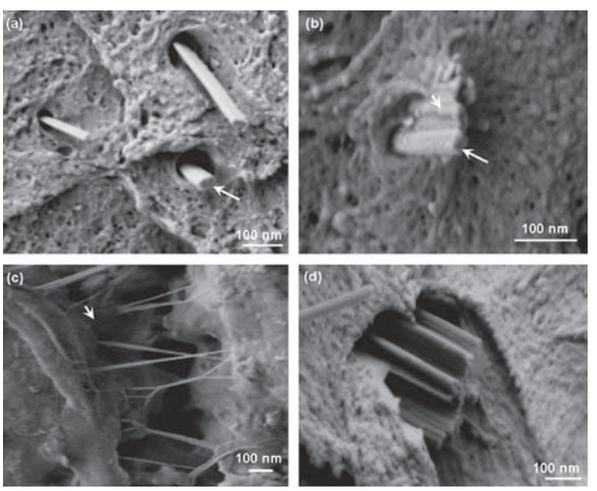

Figure 5. (a) and (b) SEM of the fracture surface showing the micro-mechanism of fracture toughness of PMMA nanocomposites reinforced with: (a) 2% non-functionalized *n*-TiO_2 tubes; (b) 2% functionalized n-TiO2 tubes. (c) and (d) Crack bridging within the PMMA nanocomposite reinforced with: (c) 2% functionalized *n*-TiO_2 tubes; (d) 6% functionalized *n*-TiO_2 tubes (the long arrow indicates polymer inside the tube while the short arrow indicates polymer outside the tube). Reprinted with permission from [108], S. M. Z. Khaled, et al., Synthesis and characterization of poly(methyl methacrylate)-based experimental bone cements reinforced with TiO_2-SrO nanotubes. *Acta Biomater.* 6, 3178 (2010). © 2010, Elsevier Ltd.

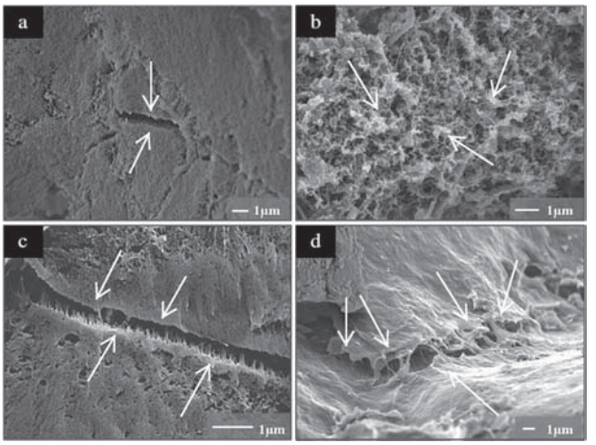

Figure 6. **SEM images showing (a) A large crack within the short rod chevron notched fracture surface of the control cement. (b) Unfunctionalized MWCNTs dry blended in the PMMA polymer powder cement showing an agglomeration of barium sulphate, which was the fracture initiation point for this specimen (c) and (d) Functionalized MWCNTs disintegrated in the MMA liquid monomer by ultrasonication, MWCNTs can be seen to bridge a micro-crackacross the cement surface, at different magnification. Reprinted with permission from [128], R. Ormsby, et al., Incorporation of multiwalled carbon nanotubes to acrylic based bone cements: effects on mechanical and thermal properties. *J. Mech. Behav. Biomed. Mater.* 3, 136 (2010). © 2010, Elsevier Ltd. Oxford, UK.**

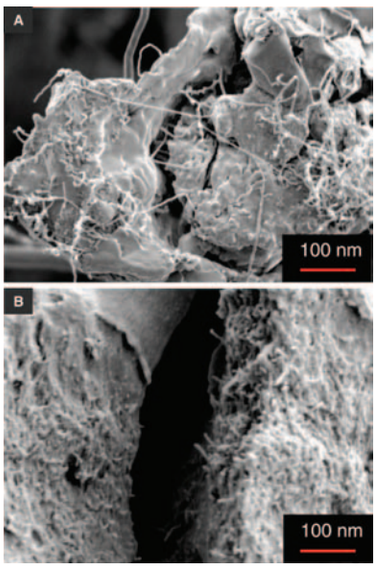

Figure 7. **SEM images showing examples of the reinforcement mechanisms of MWCNT-COOH (0.1 wt.%). (A) MWCNT-COOH can be seen bridging and reinforcing a propagating crack, perpendicular to the direction of crack growth. (B) Evidence of MWCNT-COOH pull-out from the PMMA bone cement matrix. Reprinted with permission from [129], R. Ormsby, et al., Fatigue and biocompatibility properties of a poly(methyl methacrylate) bone cement with multiwalled carbon nanotubes. *Acta Biomater.* 8, 1201 (2012). © 2012, Elsevier Ltd.**

nanotubes and a polymer coating at the end of these nanoparticles as CNT pull-out occurred. Different research groups arrive at similar conclusions and state that CNT acts as reinforcing material increasing fatigue life of the bone cement,[120] enhanced tensile and compressive strength.[131, 132]

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are a inorganic, highly porous additive which has received slight attention as reinforcing material in polymers.[133, 134] However, due to their high surface area an efficient stress transfer mechanism can be achieved, thus increasing the strength MSN/polymer composite.[135] Different research groups studied the improvement of mechanical properties of acrylic bone cements and MSNs.[136, 137] However, Shen et al.[137] described the employment of these nanoparticles as a drug delivery mechanism for gentamicine rather than mechanical reinforcement. On the contrary, Squire et al.[138] reinforced commercially available acrylic bone cement using different loading ratios of mesoporous silica nanoparticles, and determined the static mechanical properties as flexural, compressive and fracture toughness, fatigue performance and water absorption/elution. While flexural modulus and compressive strength increases with higher silica content, the flexural strength, fracture toughness and work of fracture decrease significantly. Fatigue properties are highly influenced by MSNs.

Core–Shell Nanoparticles

An interesting approach proposed[139, 140] to modify mechanical properties in polymers is the addition of core–shell or multilayer nanoparticles, as they have the ability to improve fracture resistance leaving significantly unmodified its modulus.[141] Cervantes-Uc et al.[113] developed core–shell nanoparticles of poly(butyl acrylate) (PBA) rubbery core and PMMA shell, with different core–shell ratios, in order to enhance the fracture toughness of the acrylic bone cements. Although the fracture toughness was enhanced in some formulations, it was observed that the incorporation of these particles to bone cement formulations decreased both the modulus and strength in every mechanical tests performed (compressive, bending, tensile). Finally, Perek and Pilliar[142] and Murakami et al.[143] reported the use of more complex structured particles (three-stage shell structures) in bone cement formulations.

Hydroxyapatite Nanoparticles

Some researchers have studied hydroxyapatite-reinforced PMMA (PMMA/HA) as a potential bone cement.[144, 145] Due to its biocompatibility and osteoinductivity,[146–149] adding HA to the bone cement can improve its mechanical properties as a consequence of an enhanced osteointegration. However, they are highly dependent on the amount incorporated, size and aspect ratio and surface properties.[150, 151] Naderi et al. studied the effect of hydroxyapatite nanoparticles on acrylic bone cement mechanical

behavior. They found that PMMA cements containing 2.5% HA had the maximum value of ultimate compressive strength, elastic modulus of compression and compression yield strength compared to other investigated formulations. Additionally wear rate decreases with increasing HA content.[152]

OSTEOINTEGRATION AND THERMAL BEHAVIOR

As was described previously, commercial acrylic bone cement is based on a free radical polymerization reaction upon the mixing of the polymer powder and liquid monomer constituents, which is highly exothermic, reaching peak temperatures of 80–100 °C.[153] Although this temperature value is maintained for a short period (typically 1–2 s), a number of studies have stressed the importance of keeping the heat generated through the bone cement exothermic reaction to a minimum.[154, 155] Peak temperatures higher than the citotoxic temperature have the ability to cause a permanent cessation of blood flow and bone tissue necrosis. This is one of the mitigating factors for aseptic loosening of a fixed implant produced when PMMA cement is used.[156] In spite of the great efforts made to overcome this fact temperature at the bone-cement interface is still above the physiological range (43∼46 °C).

Reducing the heat amount produced during polymerization reaction of PMMA bone cement, and therefore lowering the extent of thermal necrosis has been investigated by many research groups. Lowering the temperature prior to bone cement mixing,[157] pre-cooling the femoral prosthesis before implantation into the bone cavity,[157, 158] using pre-chilled water to pulse-lavage the bone cavity prior to placement of cement[159] or preparing bone cement under vacuum[156] have significant effect on peak temperature at the cement-bone interface. Bone cements loaded with additives, such as fibers,[160–162] mineral particles,[151, 163] polymers,[24] or drugs,[66] are reported. Additionally, modifications to biocompatible materials in order to enhance their osteogeic potencial have been described.[164] Among these modifications, the addition of bioactive fillers, such as HA to enhance bioactivity has been extensively studied.[149, 165, 166] Chitosan (CS) was incorporated into the formulations to examine the effects on bone cement properties. It was observed that CS induced a reduction in curing temperature from 71.60 to 59.04 °C when 0.1 g of CS per gram of PMMA was added. In addition, CS is expected to degrade *in vivo* over time as new bone tissue develops; this will lead to a stronger bond between the host bone and bone cement and extend the survival of the implant.

Microparticles versus Nanoparticles

Due to increased surface area, Webster and al.[103] theorized that nanoparticles of MgO may reduce exothermic reactions of polymers compared to micron particles of MgO. The authors used MgO and $BaSO_4$ microparticles as well as nanoparticles in a 10% wt. ratio per total PMMA cement. Cement samples which contained either MgO or $BaSO_4$ decreased temperature of bone cement reaction although temperature reduction was significantly larger when nanoparticles were present instead of conventional (or micronsized) particles. The obtained results demonstrated that PMMA cement containing either $BaSO_4$ (conventional or nanophase) exhibited lower peak temperatures compared to pure PMMA during the curing process. For the sample containing MgO nanoparticles, the largest decrease in temperature, compared to plain PMMA, was recorded during the first 10 min, being the temperature changes of -5.31 °C, -5.46 °C, -4.01 °C, -3.65 °C, and -2.95 °C after 1 second, 1 minute, 2 minutes, 10 minutes, and 1 hour and 47 minutes of mixing, respectively. When using conventional MgO, the decreases in the temperature peak were only -1.65 °C, -1.96 °C, -1.81 °C, -1.50 °C, and -0.45 °C, measure at the same intervals of time. The temperature of PMMA after 1 second, 1 minute, 2 minutes, 10 minutes, and 1 hour and 47 minutes of mixing were 44.98 °C, 45.82 °C, 50.1 °C, 52.5 °C, and 47.85 °C, respectively.

The tests for cytocompatibility properties demonstrated that osteoblast adhesion was higher on PMMA cements with either nanophase MgO or conventional and nanophase $BaSO_4$ than pure PMMA cement, although samples with conventional $BaSO_4$ had a significantly higher cell density than those with conventional MgO. Another explored alternative to induce osteointegration and reduce thermal citotoxicitty are bone cements modified by containing unfunctionalized and functionalized ZrO_2 and $BaSO_4$ particles.[109] Some ceramic nanoparticles were left unfunctionalized while others were functionalized with a silane-coupling agent 3-(trimethoxysilyl)propyl methacrylate (TMS). In this case, no significant differences were found in the exothermic polymerization temperatures for any of the bone cements formulated. However, bone cements containing nanometer ZrO_2 or $BaSO_4$ particles functionalized with TMS showed improved cytocompatibility properties. Clearly, after 24 hours, results demonstrated greater osteoblast density all bone cements containing ceramic particles compared to unmodified bone cements. Additionally, osteoblast density was found to be greater on bone cements containing functionalized $BaSO_4$ nanoparticles ($P < 0.1$) compared to the one containing $BaSO_4$ micron particles. Finally, compared to bone cements containing ZrO_2 micron particles, osteoblast density was greater on bone cements containing ZrO_2 nanoparticles, both unfunctionalized ($P < 0.05$) and functionalized with TMS ($P < 0.1$) (Fig. 8).

Although titania is a well-known biocompatible material,[167] Khaled et al.[104] investigated the *in vitro* biocompatibility of the cement reinforced with *n*-TiO_2 fiber using primary osteoblasts obtained from rat calvarias (RCOs) as well as the maximum polymerization temperature (T_{max}) and setting time (t_{set}). Control PMMA

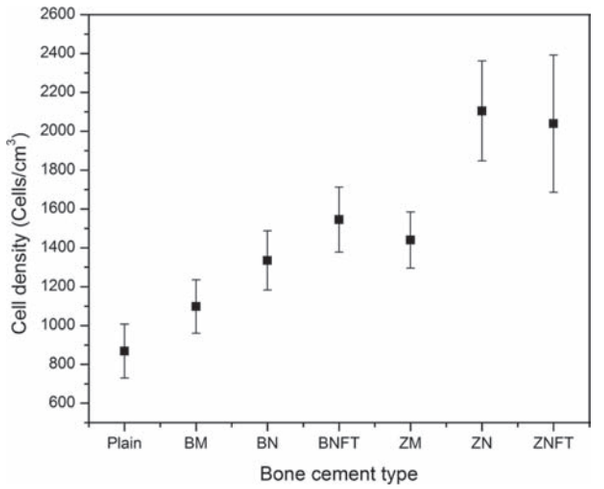

Figure 8. Osteoblast cell-density, after 24 hours for: unmodified bone cements = Plain, Bone cements with $BaSO_4$ micro particles = BM, bone cements with unfunctionalized $BaSO_4$ nanoparticles = BN, bone cements with functionalized $BaSO_4$ nanoparticles = BNFT, bone cements with ZrO_2 microparticles = ZM, bone cements with unfunctionalized ZrO_2 nanoparticles = ZN, Bone cements with functionalized ZrO_2 nanoparticles = ZNFT.

exhibited the highest T_{max} value, which was 90.33 ± 1.28 °C, compared to 0.5, 1.0, 1.5 and 2.0 wt% *n*-TiO_2 Fiber-CMW®1 composite, whose peak temperature were 87.67 ± 0.66 °C, 87.27 ± 0.18 °C, 86.30 ± 1.90 °C and 80.73 ± 3.93 °C, respectively. On the contrary, t_{set} value increased with increasing *n*-TiO_2 fibers content: 5.85 ± 0.08 min for 0.5 wt%, 5.91 ± 0.08 min for 1 wt%, 6.03 ± 0.07 min for 1.5 wt% and 6.10 ± 0.11 min for 2.0 wt%; compared to plain CMW® 1 whose T_{set} was 5.77 ± 0.08 min.

Cell adhesion and proliferation results, obtained by florescence microscopy, revealed that osteoblast adhesion to CMW® 1 and 1% *n*-TiO_2-fiber-CMW®1 surfaces are similar after 24 h. Moreover, the percentage of live osteoblast cells after 48 and 72 h are not significantly different for the cement reinforced with 1% *n*-TiO_2 fibers compared to the control at $p = 0.05$. Therefore, CMW®1 retains its biocompatibility even after being reinforced with *n*-TiO_2 fibers. Strontium oxide (SrO) showed potential to act as bacterial growth inhibitor and increase the biocompatibility of the cement.[105] Basically, strontium (Sr) is a natural bone seeking trace element that accumulates in the skeleton.[168] Due to its chemical similarity to calcium (both are in the same group in the periodic table), Sr enhances the proliferation and growth of bone cells *in vitro*, stimulates bone formation and inhibits bone resorption.[169] Khaled et al.[108] found that adding functionalized *n*-SrO–TiO_2 tubes to a PMMA matrix improved its biocompatibility.

The results of the *in vitro* biocompatibility using RCO cell showed that the surface of *n*-SrO–TiO_2 tube-PMMA composite exhibited the highest degree of cell spreading after 24 h, reflecting excellent cell viability compared to unfilled PMMA and the composite reinforced with 2 wt% *n*-TiO_2 tubes. After 72 h a higher extent of cell growth was observed on the *n*-SrO–TiO_2 tube-PMMA surface compared with the unfilled PMMA and *n*-TiO_2 tube-PMMA surface (Fig. 9). Moreover, analysis of the live/dead RCOs after 72 h revealed a cell survival (viability) between 92% and 98% for the composite reinforced with 2 wt% *n*-SrO–TiO_2. Thus, indicating that *n*-SrO–TiO_2 tubes significantly enhance cytocompatibility of PMMA matrix compared with a matrix containing *n*-TiO_2 tubes alone at $P < 0.05$.

Carbon Nanotubes

Nowadays there is still no conclusive data about the biocompatibility of MWCNTs. Investigations about the cytotoxic response of CNT-containing biomaterials have reported promising results confirming their potential use in orthopedic materials. Although Smart et al.[170] reported that unfunctionalized CNT exhibit some degree of toxicity when evaluated both *in vitro* and *in vivo*, they attributed these adverse effects to the presence of transition metal oxide ions (used as catalysts in CNT production). The authors also highlighted that carboxyl-functionalized CNT did not demonstrate any cytotoxic response from human cells. Despite the lack of information, a reductions in temperature peak reduces tissue necrosis, indirectly favouring the osteointegration.

In an attempt to determine the possibility of using carbon nanofibres (CNs) as either neural or orthopedic prosthetic devices, Webster et al. used carbon nanofibres as reinforcement of a polycarbonate urethane composite.[123] They observed an increased osteoblast adhesion and a concomitant decreased adhesion of fibroblasts suggesting that carbon nanotubes display promising properties for bone applications. Dunne et al.[128, 130] incorporated MWCNTs unfunctionalized or functionalized with carboxyl group both in the liquid monomer phase and the polymer powder phase prior to mixing. A significant effect on the exothermic polymerization reaction is observed. T_{max} and the setting properties exhibited during polymerization were significantly reduced by including 0.1 wt% MWCNTs into the PMMA cement. It was proposed that the MWCNTs could act as heat sinks within the PMMA bone cement and help dissipate the heat produced during the polymerization reaction by increasing the thermal conductivity of the PMMA bone cement. In a more recent study which was mentioned earlier,[129] different loading levels of MWCNT (0.1, 0.25, 0.5, and 1.0 wt% loading) were incorporated into the MMA prior to mixing and unfunctionalised (MWCNT-UNF), carboxyl functionalized (MWCNT-COOH) (4 wt.% COOH concentration) and amine functionalized (MWCNT-NH_2) (0.5 wt.% NH_2 concentration) MWCNT were used. A reduction in T_{max} of 5–26% was observed for PMMA cements containing unfunctionalized MWCNT, with the greatest reduction ($p < 0.001$) obtained for a loading of 1.0 wt%.

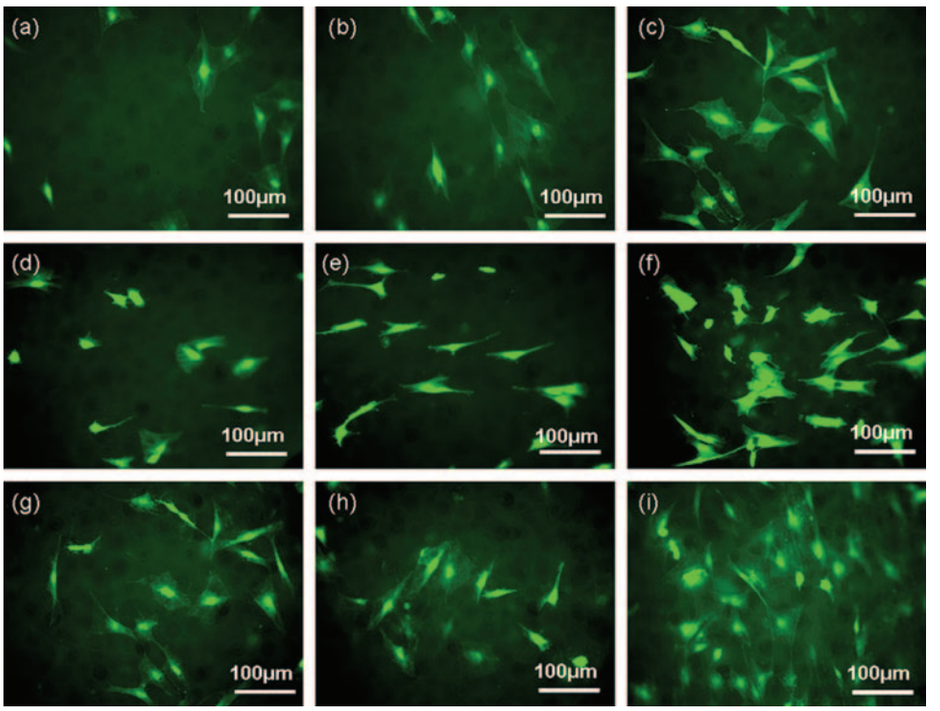

Figure 9. **(a) and (b) RCO proliferation for 24 h on the surfaces of: (a) unfilled PMMA matrix; (b) 2% *n*-TiO_2 tube-PMMA; (c) 2% *n*-SrO–TiO_2 tube-PMMA. (d)–(f) RCO proliferation for 48 h on surfaces of: (d) unfilled PMMA matrix; (e) 2% *n*-TiO_2 tube-PMMA; (f) 2% *n*-SrO–TiO_2 tube-PMMA. (g)–(i) RCO proliferation for 72 h on surfaces of: (g) unfilled PMMA matrix; (h) 2% *n*-TiO_2 tube-PMMA; (i) 2% *n*-SrO–TiO_2 tube-PMMA. Only live cells are shown. Reprinted with permission from [108], S. M. Z. Khaled, et al., Synthesis and characterization of poly(methyl methacrylate)-based experimental bone cements reinforced with TiO_2-SrO nanotubes. *Acta Biomater.* 6, 3178 (2010). © 2010, Elsevier Ltd.**

Similar linear trends were observed in PMMA cements prepared with MWCNT functionalized with amine or carboxyl groups, with reductions ($p < 0.001$) of (4–34%) and (4–28%), respectively. Adding 0.1–1.0 wt% MWCNT to the PMMA cement increased the setting time (t_{set})[171] of the bone cement linearly. On the contrary, adding 0.1–1.0 wt.% MWCNT to the PMMA cement resulted in a linear decrease in polymerization reaction rate.

The MWCNT used within this study have thermal conductivity values of ~ 3000 Wm^{-1} k^{-1}, therefore the MWCNT could act as a heat sink within the PMMA bone cement and thus assist in the dissipation of the heat generated during the polymerization reaction. This behavior is also a function of the extent of MWCNT dispersion and distribution throughout the PMMA bone cement matrix, such that uniform dispersion of MWCNT within the cement will dissipate the thermal energy throughout the cement matrix. This is further aided by the interconnectivity of MWCNT entanglements and the very large surface area of MWCNT.

Dunne et al.[130] reported that the inclusion of MWCNT had an important effect on the thermal necrosis index (TNI).[156] Adding 0.1–1.0 wt% MWCNT to the PMMA cement resulted in a linear decrease in the TNI. Significant reductions in TNI values at > 44 °C and > 55 °C were observed when unfunctionalized MWCNT (MWCNT-UNF) were added to the cement. The extent of the reductions increased as the level of MWCNT-UNF loading increased. Similarly, significant reductions ($p < 0.001$) in TNI values at > 44 °C and > 55 °C trends were also observed for the MWCNT-NH_2-PMMA ($\approx$2–99%) and MWCNT-COOH-PMMA ($\approx$6–92%) cements. More recently,[129] different loadings of MWCNT (0.1 and 0.25 wt.%) were incorporated into the MMA monomer prior to mixing, using MWCNT-UNF, MWCNT-COOH and MWCNT-NH_2 with the aim of investigating the biological response of human cells to MWCNT–PMMA cements and if such MWCNT–PMMA cements had increased biocompatibility. Every MWCNT–PMMA bone cements showed greater cell attachment compared with the control cement without MWCNTs. It was also observed that cell attachment for each MWCNT–PMMA cement increased with MWCNT loading, particularly when MWCNT-COOH was used as filler, tested over a seven day period. Fluorescence microscopy analysis confirmed that osteoblast-like MG-63 cells were attached to the surface all the MWCNT–PMMA cements and that these cells appeared not to show any significant differences in cell morphology, compared to control cement surfaces (Fig. 10). From SEM images the authors concluded

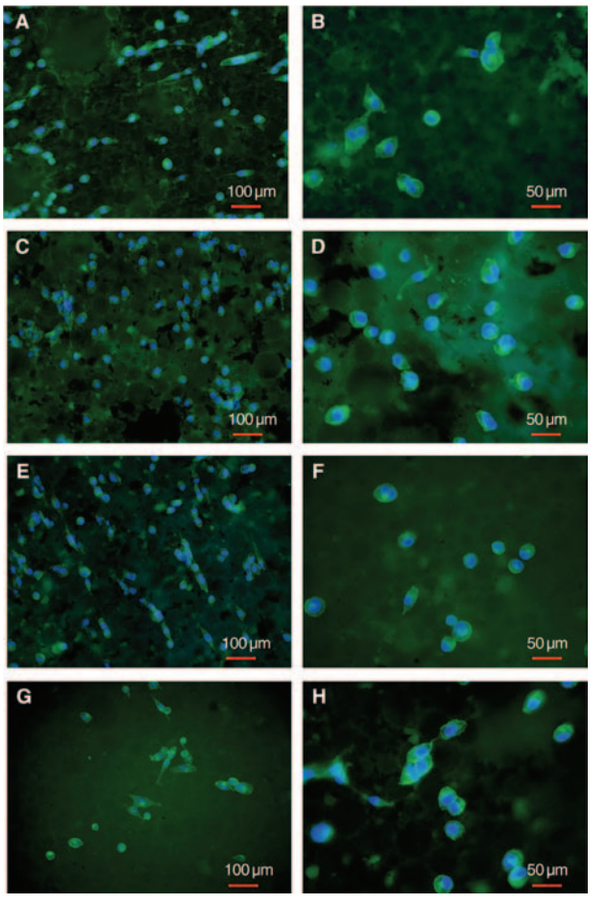

Figure 10. Fluorescence images of MG-63 cells on control and different 1.0 wt.% MWCNT–PMMA bone cements after 1 day *in vitro*. (A), (B) MWCNT-COOH; (C), (D) MWCNT-NH_2; (E), (F) MWCNT-UNF and the (G), (H) PMMA control cement. Reprinted with permission from [130], R. Ormsby, et al., Fatigue and biocompatibility properties of a poly(methyl methacrylate) bone cement with multiwalled carbon nanotubes. *Acta Biomater.* 8, 1201 (2012). © 2012, Elsevier Ltd.

that after seven days, the cells seemed to be adhered more intensely compared to the three day-assay. These results indicated that PMMA bone cements reinforced with MWCNT possess the necessary biocompatibility to permit growth and adherence of cellular material, which would allow for bone integration.

Silver Nanoparticles

A potential method to prevent post surgical infections is incorporating Ag into the bone cement due to their antimicrobial activity. However, silver nanoparticles (AgNPs) were found unsuitable for medical and dental applications[172–175] as a result of their inability to be homogenously dispersed. Whang et al. developed an antimicrobial implant material with well-dispersed AgNPs, by synthesizing AgNPs *in situ*.[176] Although AgNP-PMMA nanoparticles released Ag ions and had antibacterial activity *in vitro,* this methodology interfered with the curing process of the material and decreased mechanical properties of the bone cement. In a more recent study, the authors developed a broad-spectrum and long-term antimicrobial acrylic resin which showed great potential in preventing post-surgical implant infections in medical and dental applications. The AgNP were generated *in situ* by dissolving Ag benzoate in dimethylaminoethyl methacrylate. Afterwards, they were blended with PMMA, BPO and DMPT. After mixing, with the powder portion, specimens were self-cured for 24 h. All samples tested for *in vitro* antibacterial activity showed significant inhibition of bacterial growth. Long-intermediate-term antibacterial study showed that AgNP-PMMAs were effective up to 28 days.[177]

Tayebi et al.[178] described the synthesis of gelatin/bioactive-glass/silver nanoparticles, employed to prepare antibacterial macroporous scaffolds with potential applications in bone tissue engineering. Its enhanced antibacterial activity proves its potential as a substitute to antibiotics, thus being an attractive alternative to be used in acrylic bone cements. Recently, Prokopovich et al.[179] developed a novel type of silver nanoparticles capped with tiopronin in two different concentration:$AgNO_3$:tiopronin in a 1:3 molar ratio and other nanoparticules with a 1:0.5 molar ratio. Nanoparticles synthesized with a larger quantity of tiopronin had a mean diameter of 5.3 ± 2.2 nm; whilst the nanoparticles synthesized with a lower tiopronin to silver ratio (which had the highest amount of Ag in the nanoparticles) had a mean diameter of 11.4 ± 4.3 nm. Both types of nanoparticles were added to PMMA based bone cement at various ratios to achieve 1, 0.5, and 0.1% (w/w) silver concentration in the cement. No aggregates were observed with both nanoparticles; they were uniformly distributed in the matrix.

The antimicrobial properties of the bone cements embedded with the Ag nanoparticles were determined through the lag phase and growth rate of the Gram-positive bacteria MRSA (methicillin resistant *Staphylococcus aureus*) cells detached from the bone cement samples. When incorporated in bone cement, the smaller nanoparticles did not have antimicrobial activity, whilst the bigger ones were capable of reducing the contamination of MRSA at concentrations as low as 0.1%. The antimicrobial activity increased with increasing amount of nanoparticles encapsulated in bone cement therefore, the antimicrobial effect is dependent on the concentration of Ag nanoparticles. The possibility of Ag nanoparticles having a cytotoxic effect was investigated on osteoblast cells and the presence of Ag nanoparticles capped with tiopronin did not impact on the outcome of the enzymatic activity tested by the MTT assay kit ($P > 0.05$). The authors concluded that it is possible to prepare bone cement with antimicrobial activity using Ag nanoparticles without relying on antibiotics, and therefore, reducing the risk of inducing resistance in bacteria.

NANOPARTICLES IN BONE CEMENT FOR ANTIBIOTIC DELIVERY

The postoperative infection remains a considerable problem in orthopedic surgery.[74, 180] Upon infection, the complete removal of the artificial joint and re-implantation are often necessary. In order to reduce the risk of postoperative infection, current therapies are focused on the local release of antibiotics using drug-loaded bone cement and implants.[181–185] Different alternatives to drug delivery systems have been widely investigated and reported by different researchers,[186, 187] even in bone cement.[188–193] Currently, commercially available local antibiotic delivery systems are based on antibiotics-loaded PMMA bone cement.[194, 195] As the different drugs can only be loaded into the composite by mechanical mixing, impregnation or adsorption by the polymer–ceramic matrices, these techniques only allow drug release for a few days.

As reported in literature,[196] the release of antibiotic from bone cement is a complex process that depends on several variables, such as chemical formulation of the cement, its viscosity, the mixing conditions and the type of antibiotic itself. Several studies[190, 194] point out the fact that antibiotic release is mainly a surface mechanism, even if physiological fluids seem to enter the polymeric structure of acrylic matrix leading to antibiotic elution across cracks and pores. Furthermore, only a small portion of the loaded antibiotics can be released and more than 90% may still remain entrapped within the PMMA matrix.[197–199] Recently, more attempts have been undertaken to develop techniques to enhance the antibiotic elution from acrylic bone cements by incorporation of hydroxyapatite,[200] polyvinylpyrrolidone,[201] xylitol and glycine[202] fillers to PMMA bone cement. The additions of fillers to the bone cement have been intensively investigated to improve the controlled release of the drug without affecting the mechanical properties.[14] Mesoporous silica has shown the potential to act as a convenient reservoir for various controlled drug delivery systems.[203–205] Shen et al.[137] employed mesoporous silica nanoparticles (MSN) as functional filler for loading antibiotics into acrylic bone cements thus developing new PMMA-based bone cements with enhanced drug release.

Among other drugs, gentamicin (GTMC) a highly appreciated antiobiotic as it has a good spectrum of concentration-dependent bactericidal activity, thermal stability and high water solubility.[206, 207] An antibiotic-loaded bone cement was prepared by dispersing MSN in an aqueous solution containing GTMC. Subsequently, commercial bone cement powder CMW Smart GHV (DePuy International Ltd. UK) and Simplex P (Stryker Co, UK) were used in this study was immersed into the aqueous suspension to form slurry under stirring. The wet mixture was dried under vacuum at room temperature. The original PMMA-based bone cement powder is a non-porous material with low pore volumes and low surface areas. As compared with directly mixing GTMC crystal particles with PMMA powder, adding the MSN loaded GTMC enhances drug distribution homogeneity in the bone cement matrix. Released gentamicine concentration was measured by a UV-Vis spectrophotometer at 332 nm, using the derivatization methodology of the amino groups of the antibiotic with o-phthaldialdehyde yielding a chromophor product.[208]

It is noticed that the commercial Smartset GHV exhibits a very limited drug release. Only about 5% of GTMC is observed to be released in the first day of immersion in phosphate buffered saline (PBS) solution. No GTMC release was detectable in the following 80 days of investigation. When the sample is formulated with 8.15 wt% of MSN in the bone cement the total release of GTMC reaches about 70% in 80 days, and only a 10% of the antibiotic is released during the first day. It is noteworthy that the bone cement formulated using MSN with the smallest particle size exhibits the highest release rate. These results suggest that larger particles fail to build up an effective diffusion network by particle–particle contact, thus the release profiles of GTMC is far below the one observed for the antibiotic-loaded bone cement using mesoporous silica nanoparticles.

The MTT cytotoxicity of the modified bone cement was assayed using 3T3 mouse fibroblasts and compared with PMMA-based bone cement without modification. The acrylic bone cements formulated using 8.15 wt% of MSN exhibited a 96% of cell viability rate, while the PMMA bone cement without MSN in its formulation shows a 98% cell viability rate. In summarize, bone cements formulated with MSN exhibited low cytotoxicity to 3T3 fibroblast cells as well as a sustained and enhanced antibacterial effect, which suggested its suitability to be considered for preclinical investigations.

CONCLUSION

The present review intended to summarize recent advances in acrylic bone cements towards an increased osteointegration and mechanical behavior control. Certainly, nanotechnology is the best tool available in order to be able to develop a new generation of PMMA bone cements. By using different nanoparticles it is possible to tune the mechanical behavior of the cement in order to fulfill the patient's requirements. Additionally, while bioactive nanoparticles enhance osteointegration, drug-loaded nanoparticles are used to prevent postsurgical infections. The long-term stability of implants fixation and vertebral augmentation depends highly on the cements ability to bond to bone tissue. Even if these results are highly promising several difficulties, as nanoparticles agglometarion or catalyst toxicity, must be overcome before been tried in patients. Future research must be focused on overcoming these technological complications as well as considerably enhance the osteogenic nature of these materials in order to gain control over its mechanical behavior.

ABBREVIATIONS

PMMA, polymethyl methacrylate
MMA, methyl methacrylate
BPO, benzoyl peroxide
DMPT, dimethyl-*p*-toluidine
MA, methyl acrylate
PHB, poly(3-hydroxybutyrate)
PHBV, poly(3-hydroxybutyrate-co-valerate)
MTT, Cell viability/proliferation
ALP, Alkaline phosphatase
EHA, Ethyl hexylacrylate
HPMC, Hydroxypropylmethylcellulose
CS, Chitosan
HACC, Chloride chitosan
CSO, Chitosan oligosaccharides
SPNR, Sulphur prevulcanized natural rubber
NR, Natural rubber
PAA, Polyacrylic acid
PAM, Polyacrylamide
DMPT, *N*-*N*-dimethyl-*p*-toluidine
DEAEA, 2-(diethylamino)ethyl-acrylate
DMAEM, 2-(dimethylamino)ethyl-methacrylate
DEAEM, 2-(diethylamino)ethylmethacrylate
TMS, 3-(trimethoxysilyl)propyl methacrylate
ZM, ZrO_2 micron particles
ZN, Unfunctionalized ZrO_2 nanoparticles
ZNFT, ZrO_2 nanoparticles functionalized with TMS
BM, $BaSO_4$ micron particles
ZN, Unfunctionalized ZrO_2 nanoparticles
BN, Unfunctionalized $BaSO_4$ nanoparticles
BNFT, $BaSO_4$ nanoparticles functionalized with TMS
BMD, Bone mineral density
CNT, Carbon nanotube
CNTs, Carbon nanotubes
SWCNTs, Single wall carbon nanotubes
MWCNTs, Multiwall carbon nanotubes
SEM, Scanning electronic microcopy
MSNs, Mesoporous silica nanoparticles
PMMA/HA, Hydroxyapatite-reinforced PMMA
RCO, Rat calvarias osteoblast
GTMC, Gentamicin.

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