


Cite this: *RSC Adv.*, 2025, 15, 26959

Material properties and progress in modification of hydrogel-based self-expandable poly(methyl methacrylate) bone cement

Haochang He,^{†a} Yuanbiao Liu,^{ID†a} Yukai Dong,^a Wenjie Zhao,^b Keyuan Wang,^a Kai Guo,^a Enxiang Jiao,^a Shanshan Xu,^a Guannan Ju,^a Peng Wang,^a Duanhong Ma,^a Gaopeng Shi^c and Haijun Zhang^{*a}

Although traditional poly(methyl methacrylate) (PMMA) bone cements have been widely used in clinical practice, they are beset with many inherent drawbacks such as high polymerization heat, weak osteoinductive and osteoconductive ability, low bioactivity, volumetric shrinkage upon solidification, etc., which significantly limit its clinical application prospects. Chemical or physical modification of PMMA matrix to regulate its material properties has become a research hotspot in the field of bone tissue repair. Self-expandable PMMA bone cement (SBC) is a novel bone cement developed by copolymerizing PMMA matrix with hydrophilic monomers such as acrylic acid, hydroxyethyl acrylate, etc. They are of high bioactivity and adjustable mechanical properties, along with excellent volumetric swelling capability due to the spontaneous water absorption in body fluids. Moreover, with the addition of appropriate antibiotics and fillers, SBC can effectively prevent/heal tissue infection around the implant, and exhibit versatile biomechanical properties required for *in vivo* implantation, making SBC one of the best alternatives to replace commercially available bone cements. In this paper, the material properties and progress in modification of SBC will be reviewed, the influence of functional monomers and fillers on the biomechanical properties of SBC will be discussed, and the future research direction of SBC will be proposed.

Received 25th January 2025

Accepted 13th June 2025

DOI: 10.1039/d5ra00592b

rsc.li/rsc-advances

1. Introduction

With the accelerating aging of society and an upsurge in body-building activities, an increasing number of both aged and young people are suffering from orthopedic diseases, leading to an increasing demand for bone repair surgeries (such as artificial joint replacement and percutaneous vertebroplasty).¹ Bone cement is widely used in clinical practice to fill and repair bone loss, playing a vital role in fixing prostheses, bearing loads, reinforcing injured bones, and transferring stress from prostheses to bones.^{2–4} So far, poly(methyl methacrylate) (PMMA) bone cement has been the most widely used polymer-based bone substitute because of its excellent biocompatibility, high mechanical strength, and good chemical stability.^{5,6} The historical background and main development stages of PMMA bone cement is depicted in Fig. 1. All of them are composed of two phases. The solid is mainly composed of PMMA powders,

initiator (benzoyl peroxide, BPO), and an opacifier (ZrO₂ or BaSO₄); the liquid component is mainly MMA monomer, activator (dimethyl-*p*-toluidine, DMT), and a stabilizer to avoid premature polymerization. Particularly, ambient temperature is sufficient to solidify PMMA bone cement by mixing the solid and liquid components, and the uncured cement can be manually molded to match the contour of bone defect.^{7–9} All those properties make PMMA bone cement a desirable orthopedic implant in fields of bone (or tooth) defect repair, pedicle screw channel augmentation, and treatment of chronic osteomyelitis and spinal metastasis, etc.

However, bioinert PMMA bone cement is not gifted with osteoconductivity and osteoinductivity, so only mechanical interlocking is formed between PMMA bone cement and bone tissues.^{11,12} Here, osteoconductivity refers to the ability of bone cement to promote the adhesion, proliferation and differentiation of osteoblasts on the cement scaffold, while osteoinductivity refers to the capability of bone cement to directly induce mesenchymal stem cells to differentiate into osteoprogenitor cells and osteoblasts. Once the mechanical interlock fails, the gap between PMMA matrix and bone tissues will be broadened, friction and interfacial wear will occur. The production of PMMA debris will not only promote macrophages to differentiate into pro-inflammatory M1 phenotypes, triggering tissue

^aSchool of Materials Science & Engineering, Shandong University of Technology, Zibo 255000, China. E-mail: zhanghj@sdu.edu.cn

^bNo. 1 Middle School of Zhangdian, Zibo 255000, China

^cCollege of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, China

[†] The first two authors contribute equally to this paper.

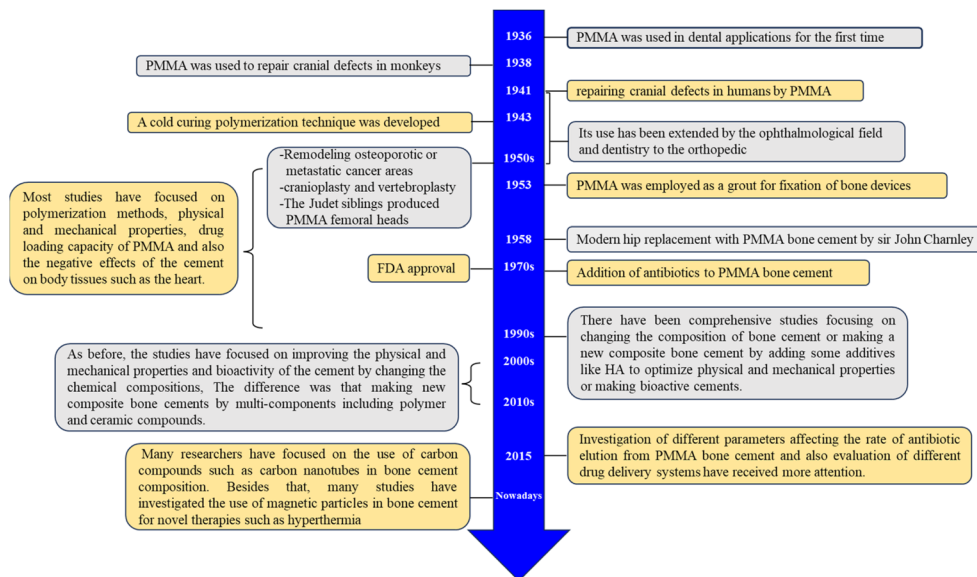



Fig. 1 Historical background of PMMA bone cement. Reprinted with the permission from ref. 10. Copyright 2020 John Wiley and Sons.

inflammatory responses, but also induce macrophages to differentiate into osteoclasts, causing osteolysis and ultimate aseptic loosening.^{13,14} Moreover, PMMA bone cement upon solidification behaves like a fragile glass with a Young's modulus of about 3 GPa, much higher than that of human trabecular bone (20–500 MPa).^{15,16} The huge difference in modulus typically causes “stress-shielding” effect, which may trigger bone resorption and aseptic loosening of the implant.¹⁷ Notably, the volume of PMMA shrinks (by about 5–7%) upon solidification,¹⁸ giving rise to a simultaneous increase in the internal stress at bone–bone cement interface. This generally reduces the interfacial shear strength and leads to interfacial micro-cracks, thus resulting in aseptic loosening and failure of PMMA implants.¹⁹

Notably, the polymeric heat is up to 57 kJ mol^{−1} for MMA monomers during the free radical polymerization.²⁰ Sometimes, the surface temperature of newly formed PMMA bone cement can be even higher than 100 °C *in vitro* due to the dramatic heat release in the dough and curing stage. Despite that the prosthesis surface and blood circulation can help dissipate polymerization heat to some extent, the surface temperature of PMMA bone cement can still reach up to 45–50 °C when placed in human body.^{21,22} In fact, bone tissue necrosis occurs at 50 °C, collagen denaturation happens at 56 °C, while 43 °C is sufficient to damage the temperature-sensitive neural tissues.^{23,24} Therefore, the implantation of PMMA bone cement inevitably brings about thermal damage to the surrounding living tissues. Fukushima *et al.*²⁵ explored the temperature changes at the bone cement interface during total knee arthroplasty. Results revealed that the setting temperature of a 3 mm thick PMMA bone cement layer is as high as 65 °C, then it drops to 56 °C at bone–bone cement interface, and an approximate 2 mm-thick osteonecrosis appeared near the bone cement. Urrutia *et al.*²⁶ injected PMMA bone cement into the vertebral cavity of New

Zealand rabbits and found that about 50% of rabbits showed early focal osteonecrosis.

From a clinical perspective, those inherent drawbacks, such as high polymerization heat, low bioactivity, weak osteoconductive and osteoinductive ability, and volume shrinkage upon solidification, *etc.*, severely limit the application prospect of traditional PMMA bone cements. An effective and feasible solution to modify the biomechanical properties of PMMA bone cement is by blending with functional additives, such that the material properties of both the constituting components can be combined, and the diverse clinical needs can be satisfied. For example, the addition of 12 wt% castor oil leads to a reduction in Young's modulus of PMMA bone cement from 1.5 GPa to 446 MPa, and maximum exothermic temperature from 41.3 to 25.6 °C.²⁷ However, castor oil seemed to interfere with the polymerization reaction, giving a negative effect on cell viability. Due to the plastic deformation and energy-dissipative ability of metal fibers (such as stainless steel, and titanium alloys), the addition of malleable metals can apparently enhance the fracture strength and toughness of PMMA matrix while maintaining good biocompatibility.^{28–30} Silver nanoparticles, as an antibacterial agent, can penetrate into the bacteria, inactivate enzymes and destroy DNA replication.³¹ The addition of 1 wt% nanosilver is sufficient to endow PMMA bone cement with excellent antibacterial ability against Gram-negative bacteria. However, those inert metals will inevitably be etched by body fluids, and the release of metal ions may cause toxic effects on cells and trigger inflammation or rejection responses of tissues.^{32,33} Bioactive ceramics^{34,35} (including degradable ones such as calcium phosphate and hydroxyapatite, and non-degradable ones like silica) have excellent biocompatibility with human tissues, and typically cause no adverse reactions *in vivo* such as inflammation, allergies, and rejection. Among them, nano-hydroxyapatite (HA, Ca/P ratio of 1.55–2.20) has a similar morphology, structure, and composition to that of human bones, and is capable of



bonding directly with bone tissues due to the excellent osteoinductivity and osteoconductivity.^{36–38} Besides that, HA powders can dissipate heat and reduce the maximum polymerization temperature of PMMA matrix.¹⁰ However, the addition of rigid bioceramics typically increases the tendency of the PMMA matrix toward stiffness and brittleness, and consequently, PMMA matrix usually exhibits an enhanced elastic modulus together with reduced flexural and tensile strengths.¹⁰

The “ideal” bone cement should satisfy the following requirements: (1) noncytotoxic, biocompatible; (2) trabecular bone-mimic 3D porous scaffold, osteoinductive, and osteoconductive; (3) easily-prepared under surgical conditions, low cost, and functionally stable; (5) biodegradable, easily drug-loaded, and free from the potential risk of disease transmission. Despite many blending modification trials as mentioned, so far there is no modified PMMA bone cement that can fully meet all these clinical requirements, and the enhancement in one material property is usually accompanied by the deterioration of the others. This has led researchers to gradually realize that adding additives alone may be inadequate to overcome the inherent drawbacks of PMMA bone cement, a structural modification of the bone cement matrix should be pivotal and indispensable for addressing those drawbacks.

2. Hydrogel-based self-expandable PMMA bone cement (SBC)

For PMMA bone cement, the weak molecular polarity is a major reason for the low equilibrium water-adsorbing ratio (below 2–3%) and apparent volume shrinkage (by about 5–7%)³⁹ upon solidification. As proposed by Orr *et al.*,⁴⁰ the residual stresses caused by volume shrinkage may be responsible for the crack initiation in the cement mantle, and cracks are likely to propagate by the mechanism of fatigue under cyclic loading. The formation of gap and voids at bone cement interface will further reduce the interfacial shear strength, enhance the interfacial wear, and permit distal migration of abraded particles.^{41,42} Those factors are important in the failure of implants by aseptic loosening, a most commonly used indicator for implant revision.

To prevent the shrinkage of PMMA matrix upon solidification, hydrogel-based self-expandable PMMA bone cements (SBC) were developed using hydrophilic functional monomers as a liquid phase to mix with the cement powders.^{43–45} Different from PMMA bone cement, the hydrophilized matrix structure of SBC allows for the adsorption of body fluid and swelling *in vivo* to compensate for shrinkage, thus getting the bone cavities completely filled.^{46,47} At present, hydroxyl group (–OH) containing monomers (such as acrylic acid (AA), hydroxyethyl methacrylate (HEMA)) and ester/ether bond-based monomers (such as 4-methacryloyloxylethyl trimellitate anhydride (META), ethoxytriethyleneglycol monomethacrylate (TEG)), with excellent hydrophilicity and bioactivity, are the most commonly used functional comonomers for preparing SBCs. The synthesis of self-expandable P(MMA-AA) bone cement, and the mechanism for water-adsorption and swelling in P(MMA-AA) matrix are

schematically illustrated in Fig. 2a. It is not unexpected that the wettability of hydroxyl groups or ester/ether bonds in comonomers is the key to improving the absorptive and expansive capability of PMMA matrix. With the solvation of those functional groups or bonds by water molecules, the mobility and dynamic response of polymer molecular chains can be enhanced, beneficial for a rapid conformation extension and expansion of polymer matrix (Fig. 2a). Meanwhile, the solvation effect also leads to water-adsorbing pathways in bone cement network, enabling the inward transfer of water molecules within the matrix, and the contact probability between simulated body fluid (SBF) and internal molecular chains can be enhanced. The swelling associated with the water uptake is expected to compensate for the volume shrinkage upon polymerization, press-fitting the implant and improving the bone-cement interfacial strength.

Due to the bioactivity and hydrophilicity of functional monomers, many studies found that the novel SBCs can well balance many of its material properties (including biocompatibility, osteogenic activity, biomechanical properties), and exhibit versatile biomechanical properties required for *in vivo* implantation in the presence of appropriate antibiotics and fillers. The relatively “ideal” biomechanical properties make SBC one of the best alternatives to replace commercially available bone cements, with a great application potential in orthopedic fields, including but not limited to artificial joint replacement, bone defect reconstruction, and pedicular screw fixation. The following text will review the material properties and progress in modification of hydrogel-based SBC, discuss in detail the influence of functional monomers and fillers on the biomechanical properties of SBC, and propose the future research directions in this area.

3. Material properties of hydrogel-based SBCs

3.1 Water-adsorbing and volume-expansion capability

To adjust the swelling properties of SBC, many efforts have been put on tuning the liquid or solid components of a typical bone cement formulation. Tang *et al.*⁴⁸ prepared a solid phase-modified P(MMA-AA) bone cement (denoted as SMBC) by combining liquid MMA monomers with solid powders containing P(MMA-AA) and PMMA microparticles (the weight ratio of P(MMA-AA) to PMMA is 1 : 1, and the liquid and solid phases are at a ratio of 2 g : 1 mL), and studied the dependence of water adsorption and volume expansion on AA contents. It was found that SMBC typically adsorbs more SBF at higher AA content in P(MMA-AA) copolymers. When AA content is up to 50 mol%, the equilibrium absorption ratio and expansion ratio of SMBC is 27.5% and 26% (Fig. 2b and c), respectively, much higher than the adsorption ($\approx 2\%$) and expansion ($\approx -5\%$, or a volumetric contraction of 5%) of PMMA bone cement just mentioned. In general, the adsorption behavior can be separated into two stages, *i.e.*, the adsorption ratio increases rapidly prior to solidification and then gradually reaches equilibrium adsorption after curing. This is consistent with the proposal of Long



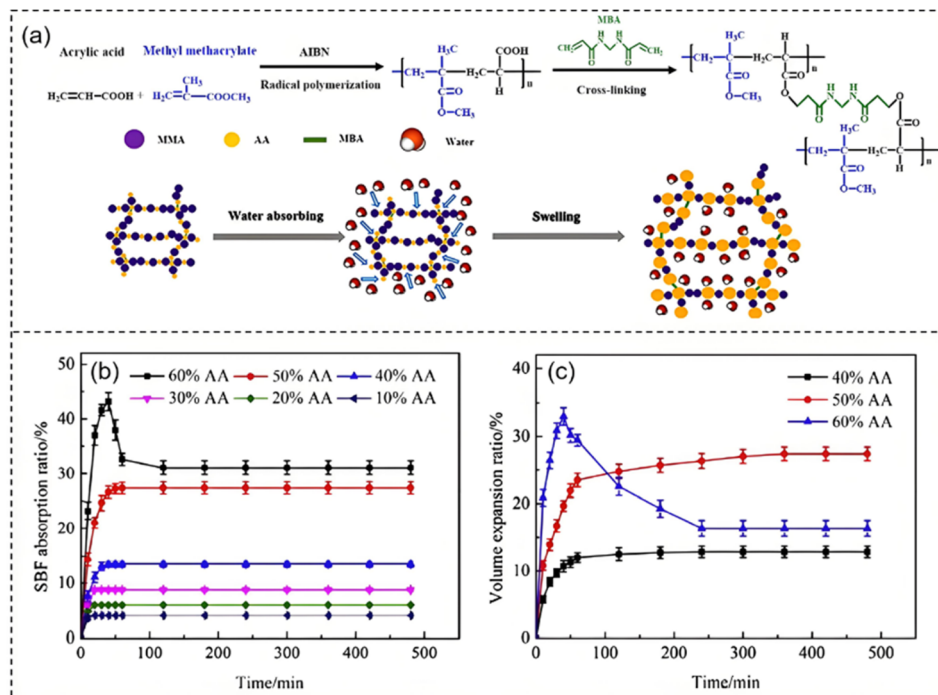


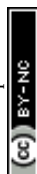
Fig. 2 (a) Mechanism for water-adsorption and swelling in self-expandable P(MMA-AA) matrix. Reprinted with the permission from ref. 53. Copyright 2017 American Chemical Society; time dependence of (b) SBF absorption ratio and (c) volume expansion ratio for SMBC (liquid phase of MMA monomers, solid phase of P(MMA-AA)/PMMA powder mixtures) containing different AA content in P(MMA-AA) powders. Reprinted with the permission from ref. 48. Copyright 2020 Elsevier.

and Richman^{49,50} from the viewpoint of molecular relaxation, that the diffusion process should involve an initial stage of molecular rearrangements that can occur almost instantaneously, and the second stage of slower process associated with penetrant transport due to the time dependence of the surface concentration. For 60% AA system, the adsorption and expansion ratio climbed initially and then decreased to an equilibrium plateau (Fig. 2b and c), and this phenomenon can be ascribed to the detachment and scatter of the partial matrix due to the weak interaction between P(MMA-AA) and the PMMA components.

By introducing HEMA comonomers into liquid MMA monomers and blending the monomer mixture with the solid phase of SMBC (liquid and solid phases are at a ratio of 1.5 g : 1 mL), a HEMA-modified P(MMA-AA) bone cement (labeled as HMBC)⁵¹ was prepared and compared with the SMBC control group. It turned out that the incorporation of hydrophilic HEMA could further enhance the adsorptive and expansive properties of P(MMA-AA) bone cement. With the incorporation of 50% (v/v) HEMA in liquid phase, HMBC exhibits an equilibrium adsorption ratio of 88.5%, together with an expansion ratio of 97.4%, much higher than the adsorption (60%) and expansion (61%) of SMBC control group. Interestingly, HMBC with a HEMA content higher than 20% even swelled after the solidification of the HMBC, contrary to previous findings that the swelling of expandable bone cement mainly occurs before solidification. Tang *et al.*⁵² also fabricated a composite bone cement by physically mixing sodium polyacrylate short fibers

(PAAS_f) with PMMA bone cement. It was found that the volume expansion ratio of PMMA/PAAS_f bone cements containing 10% and 20% (v/v) PAAS_f was 1.6% and 7.4%, respectively, while the expansion ratio rapidly increased to 25.7% when PAAS_f content reaches 30%, a phenomenon related to the enhanced probability of exposure of PAAS_f on bone cement surface and increased contact between SBF and PAAS_f. These studies show that the introduction of hydrophilic functional monomers/fillers by either physical blending or chemical copolymerization can significantly improve the adsorptive and expansive capability of PMMA matrix.

The *in vitro* test for the surface contact angle measured the hydrophilic ability of the materials tested. Cheng *et al.*⁵⁴ fabricated three kinds of SBC by mixing PMMA spherical powders with different forms of liquid MMA monomers (*i.e.*, MMA with 20% (v/v) HEMA, MMA with 20% (v/v) AA, and MMA with 10% (v/v) HEMA and 10% (v/v) AA). Changes in contact angle indicated that the incorporation of AA or HEMA monomers induced a hydrophilic transformation of PMMA bone cement, which is essential for enhancing the affinity of cements with surrounding bones. For example, P(MMA-HEMA), P(MMA-AA-HEMA), and P(MMA-AA) bone cements showed a contact angle of about 63.8°, 63.2°, and 54.0°, respectively, which are smaller than that of PMMA control group (72.2°). Notably, the smaller contact angle found in AA containing cements compared to HEMA containing ones should suggest that AA monomers may have a stronger hydrophilic capacity or water-adsorbing ability than HEMA monomers. The same feature



was already proved by the water uptake results of a SBC specimen whose liquid phase is a mixture of MMA monomers with AA or HEMA comonomers, that 27 wt% AA in liquid phase is sufficient to provide the SBC with equivalent or higher water adsorption than the SBC counterpart containing 100 wt% HEMA in liquid phase.⁴⁵ Ogawa *et al.*⁵⁵ added META comonomers to MMA monomers to render it hydrophilic, and then blended META/MMA mixtures with PMMA powders to prepare a hydrophilic P(MMA-META) bone cement. Contact angle on P(MMA-META) surface was found to remain below 60° for up to 1 h under wet conditions and gradually approach an equilibrium value of 68° after 1 day. However, the sustained hydrophilicity under wet conditions was not observed for PMMA system, which remained hydrophobic (~75°) regardless of condition and time observed.

Compared with SMBC with only one water-adsorbing P(MMA-AA) network dispersed in hydrophobic PMMA matrix, HMBC not only retains the effective adsorbent component P(MMA-AA), but also partially replaces the PMMA with P(MMA-HEMA) in the bulk,⁵¹ which enables the previously non-adsorbent parts to transfer SBF. Therefore, the promoted hydrophilicity together with the presence of dual water-adsorbing networks synergistically result in a higher equilibrium SBF adsorption ratio of HMBC compared to the SMBC control group. Compared to hydroxyl-based hydrophilic cements, a smaller water adsorption ratio can be found in ester/ether bond-containing ones. Goñi *et al.*⁵⁶ fabricated a hydrophilized PMMA bone cement by mixing PMMA powders with 40% (v/v) TEG-containing MMA monomers. As is found, the P(MMA-TEG) cement shows an equilibrium water adsorption of 6%, much lower than that in SBCs with equivalent AA or HEMA contents. This can be ascribed to the weaker hydrophilic capability of ester/ether bond compared to hydroxyl groups. The difference in hydrophilic capability may also be reflected by the water diffusion behavior within cement matrix. As evidenced by the typical plots of the water adsorption *versus* $t^{1/2}$, all P(MMA-TEG) bone cements containing 0% to 40% hydrophilic TEG monomers exhibit a Fickian diffusion behavior,⁵⁶ indicating a diffusion-controlled penetration process of water molecules. By contrast, diffusion of water in the AA- or HEMA-modified SBCs typically followed the non-Fickian diffusion mechanism,^{51,57,58} suggesting that the relaxation of internal molecular chains is more dominant than the diffusion of water. This may be caused by the stronger coupling of water with hydrophilic AA or HEMA-containing chains, together with the magnified fluctuations in free volumes and osmotic pressures due to the clustering of the adsorbed huge amount of water.⁵⁹

3.2 Polymerization temperature

The curing process of PMMA bone cement, during which the free radical polymerization of MMA monomers proceeds, is usually accompanied by the release of a huge amount of heat and a significant increase in polymerization temperature. This can easily cause irreversible thermal damage or necrosis to the surrounding bone tissues, and induce many intraoperative/postoperative complications to human body (including

intraoperative hypotension, shock, cardiac arrest, postoperative local infection, neurological dysfunction, aseptic osteolysis and prosthesis loosening), potentially weakening the long-term therapeutic effect of the implant.^{60–62} In fact, the exothermic phenomenon is a complex one that depends on the interplay of several factors including total polymerization heat, polymerization kinetics, and heat transport phenomenon.⁶³ Compositional changes of liquid or solid phases can alter one or more of these factors. Compared with MMA monomer, TEG monomer has a lower reactivity but a higher molecular weight. Therefore, replacing MMA with TEG not only slows down the rate of polymerization,⁵⁶ but also reduces the total mols of monomers participating in the reacting process (while keeping the same total reaction volume), giving rise to a reduced maximum peak temperature. As TEG monomers substitute for 0% to 60% (v/v) of MMA monomers in liquid phase, the peak temperature of P(MMA-TEG) bone cement linearly decreased from 84 to 45 °C, accompanied by a prolonged setting time from 6 to 14 min (Fig. 3). These results are encouraging since a lower exothermic temperature is beneficial for alleviating the thermal damage to surrounding tissues, and a longer curing process can ensure a good injectability of the bone cement and provide more flexible operation time for surgeons during surgery.

Interestingly, SMBC also exhibits a reduced polymerization temperature with increasing AA content.⁴⁸ As AA molar fraction in P(MMA-AA) powders increases from 0% to 60%, the maximum temperature of SMBC decreases from 103.6 to 45.8 °C, and the setting time increases from 14 to 45 min. For PMMA/PAAS_f bone cement,⁵² a substitution of PMMA powders with up to 30% (v/v) PAAS_f leads to a reduction of maximum temperature by 28 °C, together with an increase of setting time by 5.8 min. The reduced peak temperature in the two bone cements is easy to understand since P(MMA-AA) powders and PAAS_f fillers, acting as a diluting component, do not participate in the polymerization reaction, so the reduced MMA content in the solid phase slows down the polymerization process and decreases the heat release.⁵² Moreover, AA-containing particles/fillers have a higher thermal conductivity than PMMA matrix,⁶⁴ so the addition of P(MMA-AA) particles or PAAS_f fillers allows the polymerization heat of MMA monomers to be quickly transferred outward, beneficial for a rapid removal of generated heat from PMMA matrix.

By contrast, HMBC exhibits an increased peak temperature with the addition of HEMA comonomers. As the HEMA content in liquid phase increases from 0% to 60%, the maximum exothermic temperature of HMBC increases from 69.9 to 100.4 °C, and the setting time decreases from 29.4 to 17.5 min, while both the maximum temperature and setting time were between that of PMMA bone cement and SMBC control group.⁵¹ This phenomenon can be rationalized by the fact that HEMA monomers, with a greater reactivity and a higher polymerization enthalpy than MMA monomers,^{65,66} are added to the liquid phase of the cement formulation, and they participate in copolymerization with MMA monomers. Unlike other monomers that need to diffuse into the PMMA particles to initiate the polymerization,⁶⁷ the polymerization and dramatic heat release of HEMA monomers can be achieved rapidly with low resistance



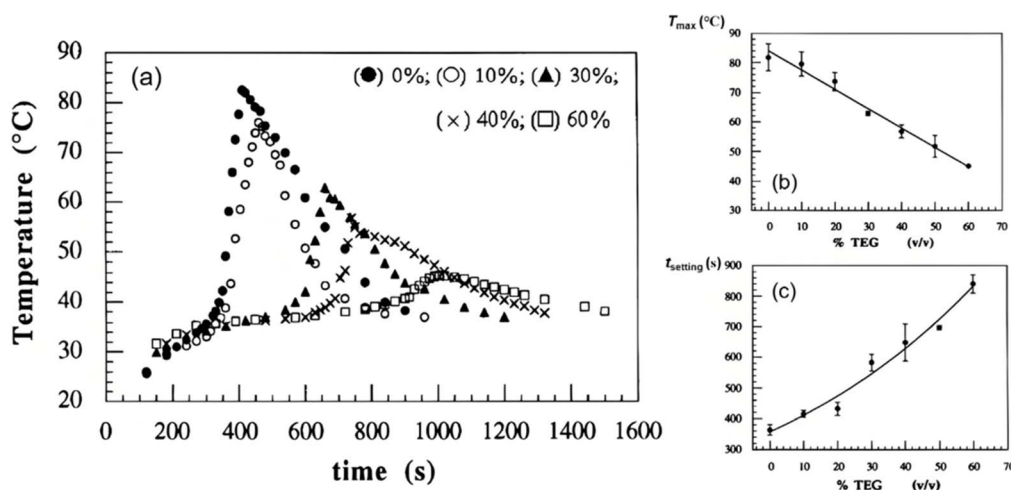


Fig. 3 (a) Polymerization exotherm of P(MMA-TEG) bone cements (solid component of PMMA powders, liquid component of META/MMA monomer mixtures) containing 0% to 60% (v/v) TEG in liquid phase; maximum temperature (b) and setting time (c) as a function of TEG content (v/v) in liquid phase of cement formulation. Reprinted with the permission from ref. 56. Copyright 1999 Elsevier.

before they diffuse into the particles. Nonetheless, one advantage of adding more reactive AA or HEMA monomers is that it can increase the conversion degree of polymerization, beneficial for alleviating the cytotoxicity caused by residual unreacted monomers.⁶⁸ When unreacted acrylic monomers are leached into blood or body fluid, they can trigger adverse responses at the cell, tissue, and organ levels such as allergies, endothelial cell segregation, cartilage tissue congestion/edema/necrosis, cardiac arrest, and even individual death.^{69,70}

3.3 Mechanical performance

PMMA bone cement, as an adhesive between prosthesis and bones, is generally subjected to complex stress conditions and has to function in the relatively aggressive environment due to the intense body activities. For example, forces transmitted through the hip joint are high, about 3 times body weight when walking, which rises to 8 times body weight when stumbling. According to ISO-5833,⁷¹ there are three requirements for set and cured cement: compressive strength (minimum of 70 MPa), bending modulus (minimum of 1800 MPa) and bending strength (minimum of 50 MPa). Commercial PMMA bone cement is generally weak in tension (tensile strength of 35.3 MPa), strong in compression (compression strength of 93.0 MPa), and has a low bending resistance (bending strength of 64.2 MPa, bending modulus of 2552 MPa). As such, glassy PMMA bone cement may fracture in a brittle way when functioning under overloaded tensile or flexural stress, although it is compression resistant. Nonetheless, bone cement is typically supported by cortical bone to allow the compression to be generated and to restrict tensile stresses, such that it is subjected to compression whenever possible. So far, most concerns have been concentrated on the variation of compression strength with compositional modifications of the bone cement.

For SBC, the introduction of flexible hydrophilic monomers generally deteriorates the mechanical strength of the matrix. As is revealed, when TEG monomers account for 0% to 50% (v/v) of

MMA monomers in liquid phase, the compressive strength of P(MMA-TEG) bone cement decreases from 90.8 to 46.3 MPa, together with tensile strength from 38 to 22 MPa. However, when less than 20% (v/v) MMA is substituted by TEG, the requirement for a minimum strength of 70 MPa can be satisfied. AA or HEMA-based bone cements also show a decreased compressive strength or elastic modulus with the enrichment of hydrophilic monomers (Fig. 4). As shown in Fig. 4a, HMBC modified by substitution of 50% (v/v) MMA with HEMA in liquid phase exhibits a compression strength of 58 MPa,⁵¹ much smaller than that of SMBC control group (75 MPa). However, HMBC containing less than 20% HEMA also showed a compressive strength higher than 70 MPa, satisfying the ISO standard. The reduced mechanical strength in those SBC can be rationalized by the fact that the partial replacement of rigid PMMA chains by flexible TEG, AA, or HEMA components can enhance the molecular flexibility of PMMA matrix, which weakens the mechanical robustness of the bone cement. Besides that, the poor surficial compatibility between strongly-polar hydrophilized microspheres and weakly-polar PMMA matrix may generate an interface between them, capable of inducing the propagation of cracks, which can also decrease the mechanical properties. The mechanical strength of SBC will be further deteriorated when SBC is immersed in SBF to ensure a saturated adsorption and expansion (Fig. 4), since water molecules typically act as plasticizers for polymers, and the construction of water-adsorbing pathways creates micropores in matrix.^{48,51} However, given the elastic restrictive forces developed in the network as opposing the swelling process, the reduction in mechanical strength may be compensated for to some extent by the great expansion stress upon swelling, and the expandable bone cement is expected to still provide stable support for bones.⁵⁹

The huge modulus difference between PMMA bone cement (1.7–3.7 GPa) and human cancellous bone (50–800 MPa) typically causes “stress-shielding” effect^{17,72} at the bone cement



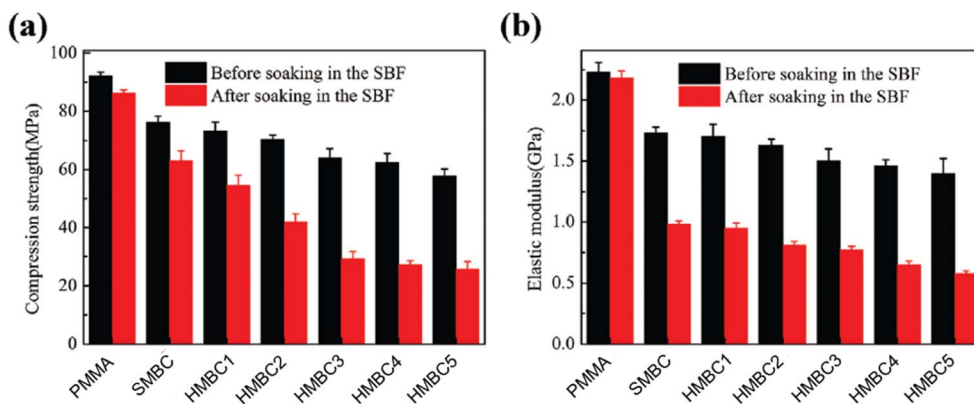


Fig. 4 Mechanical properties of PMMA, SMBC, and different components of HMBC before and after soaking in simulated body fluid (SBF). (a) Compressive strength; (b) elastic modulus. HMBC1, HMBC2, HMBC3, HMBC4, HMBC5 represent the components with 10%, 20%, 30%, 40%, 50% volume fraction of HEMA in the liquid phase of HMBC, respectively. Reprinted with the permission from ref. 51. Copyright 2020 John Wiley and Sons.

interface. As mechanical loads are transferred from the distal end of the prosthesis stem to the diaphyseal cortex, the proximal cancellous or cortical bones generally bear less load and will suffer more significant osteolysis and bone resorption according to the Wolff's law.^{73,74} As a result, the interfacial adhesion between bone and bone cement will be weakened, giving rise to an ultimate aseptic loosening of the implant. For osteoporosis-induced compression fractures, although injecting PMMA bone cement can effectively stabilize the injured vertebrae and rapidly relieve pain symptoms, the modulus of the strengthened vertebrae can be increased by 17%.⁷⁵ Consequently, the strengthened vertebrae will exert greater stress on surrounding vertebrae, which in turn increases the risk of fracture of the adjacent vertebrae.^{76,77} Those issues associated with the rigid nature of PMMA can be effectively addressed by the partial substitution of MMA monomers with hydrophilic TEG, AA or HEMA comonomers, since the modulus of the so-obtained SBC can be significantly reduced due to the combined effects of the flexibility of comonomers, the plasticizing effect of adsorbed water, and the micropore formation paralleling the construction of water pathways. Mechanical results showed that with an increase of AA content in P(MMA-AA) powders from 0% to 50 mol%, the elastic modulus of SMBC decreases from 2.2 to 1.5 GPa.⁴⁸ As HEMA accounts for 0% to 50% (v/v) of the liquid component, the elastic modulus of HMBC decreases from 1.7 to 1.4 GPa (Fig. 4b).⁵¹ PMMA/PAAS_f bone cement also exhibits a reduced elastic modulus from 0.57 to 0.28 GPa when PAAS_f content increases from 0% to 30% (v/v).⁵² Notably, the PAAS_f content should not exceed 30 vol%, otherwise the surface-exposed PAAS_f will detach from PMMA matrix due to their weak interactions.

Bone cements are always simultaneously subjected to cyclic and static loads. In the last case, the material will undergo a continuous, slow, and long-term deformation under the applied stress, usually called creep. Creep tests may provide information on the viscoelastic behavior of biomaterials, especially if the tests are performed in simulated physiological conditions. The typical creep behavior of polymers can be

described as an 'instantaneous' elastic response followed by a delayed elastic response. In general, commercial PMMA sample shows almost no creep due to its rigid nature and very low water-uptake. Comparatively, an enhanced immediate elastic deformation with more pronounced viscoelastic strain can be observed in AA-modified PMMA bone cements.^{44,58} A fraction of the creep strain does not completely recover for long times, and its magnitude seems proportional to AA content, indicating that an irreversible viscous component occurred in the whole process of creeping.^{44,58} This behavior could be assigned to the presence of water (viscous material) in the systems, and indicates that the plasticizing effect of water molecules drives more significant creep of acrylic matrix. During the *in vivo* service of bone cement, the occurrence of creep can not only quickly relax the cement stresses and create a more favorable stress distribution at the interfaces, but also allow the expansion of the cement mantle and subsequent prosthetic subsidence without causing cement fracture.

Due to the plasticizing effect of water, swelled SBC became ductile and tough and can deform to higher extents without fracturing. As is found by Boesel *et al.*,⁵⁸ P(MMA-AA) bone cements exhibit a brittle fracture at dry state, while they became very ductile after 7 days of immersion in isotonic saline solution, with a 4-fold increase in ductility and a 2-fold increase in the total energy at break. An appreciable increase in the fracture strain can also be found in TEG-modified cements⁵⁶ after immersion in saline solution until equilibrium adsorption. The 50% (v/v) TEG-modified cement showed a strain to failure of 5.5%, almost twice that of conventional PMMA bone cement (2.8%). The brittle-ductile transformation can be reflected by the SEM morphologies of fractured surfaces (Fig. 5).^{44,56} P(MMA-TEG) bone cement with less than 20% TEG exhibits a brittle fracture with a smooth fracture surface, on which PMMA beads can be distinguished from the matrix formed by the copolymerization of the liquid phase (Fig. 5a). By contrast, a rough fracture surface is found in 50% TEG-modified cements, which is uneven with appreciable matrix deformation, and PMMA beads are integrated perfectly into the matrix formed by the

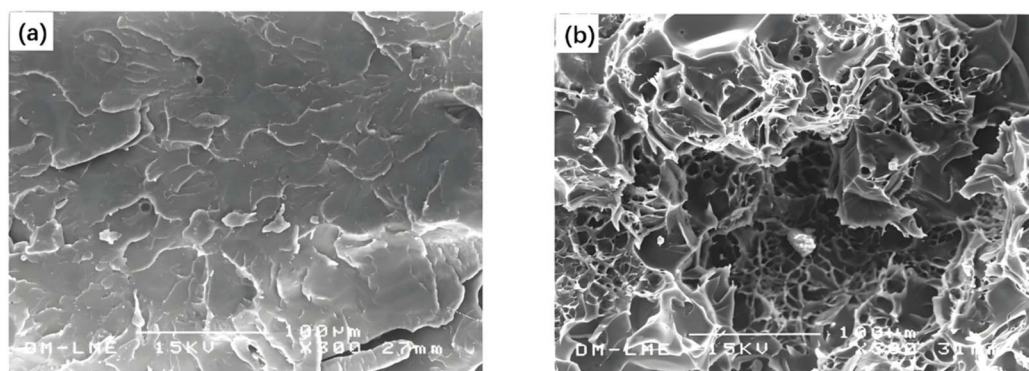


Fig. 5 SEM photographs demonstrating the brittle–ductile transformation for P(MMA–TEG) bone cements (solid component of PMMA powders, liquid component of META/MMA monomer mixtures) containing (a) 20% (v/v) and (b) 50% (v/v) TEG in liquid phase. Reprinted with the permission from ref. 56. Copyright 1999 Elsevier.

polymerization of liquid phase (Fig. 5b). The propagating crack cuts through the beads, reflecting good adhesion between the two phases. Notably, incorporation of hydrophilic monomers also has the advantage of enhancing the damping properties of the cement matrix, as evidenced by the enhancement in loss factor $\tan \delta$.⁴⁴ This can allow for the dissipation of a fraction of the mechanical energy imposed to the material at relevant frequencies of body motion, essential for damping the vibrations in clinical orthopedic practice.

3.4 Biological properties

Despite the biocompatibility with human tissues, PMMA bone cements are bioinert in nature, and they can neither induce the natural growth of bone tissues nor form a direct bonding with human bones.^{78,79} Hydroxyl groups are common in biological molecules and can participate in metabolism processes or biocatalytic reactions in living organisms.⁸⁰ Their bonding patterns at the surface of molecules are commonly used to drive molecular specificity, giving hydroxyl groups excellent bioactivity. So far, hydroxyl-based materials have been widely used in the preparation of biomedical materials such as wound dressings, drug delivery systems, artificial cartilage and blood vessels.^{81–83} As such, the introduction of hydroxyl-containing functional monomers in PMMA matrix could significantly improve the biological properties of PMMA bone cement.

3.4.1 Bioactivity. To compare the cytotoxicity of PMMA bone cement and SMBC, Tang *et al.*⁴⁸ co-cultured the primary osteoblasts of Sprague–Dawley (SD) rats with the extracts of the two bone cements, and assessed the optical density (OD) value by the CCK-8 method. The α -modified Eagle's medium (α -MEM) without extracts was used as the control. The cell viability was evaluated by the ratio of OD value in cement extracts to that in control group. As is revealed, at each incubation time (1, 4 and 7 days), the viability of osteoblasts in P(MMA-AA) extracts was always higher than that in PMMA extracts, indicating a lower cytotoxicity of the former. Both SMBC and PMMA bone cements showed a lower cell viability compared to the control group, which is related to the diffusion of the residual cytotoxic MMA monomers into the culture medium for the two systems. By

further comparing the cytotoxicity of PMMA bone cement, SMBC, and HBMC, it was found that at each incubation time of 1, 3 and 5 days, the cell viability in the three bone cement extracts can be ranked in a decreasing order as HBMC > SMBC > PMMA, once again verifying that the introduction of AA or HEMA monomers could effectively reduce the cytotoxicity of PMMA matrix.⁵¹ Moreover, HBMC presents a lower cytotoxicity than that of SMBC, suggesting that there may be a synergistic effect between HEMA and AA, and HBMC is more suitable for serving as *in vivo* implants. The survival rate of osteoblasts in HBMC extracts can reach up to 97.1% after 5 days of incubation.

By directly seeding the rat osteoblasts on the surface of PMMA bone cement, SMBC, and HBMC for 1, 3 and 5 days, the surface cell attachment was further investigated and compared. Results revealed that at each incubation time, the number of osteoblasts on the surface of the three bone cements can be ranked in a decreasing order as HBMC > SMBC > PMMA, indicating a faster cell proliferation rate in the presence of AA or HEMA monomers, consistent with the cell viability results just mentioned. SEM morphologies⁵¹ suggest that on the first day of incubation, osteoblasts preferentially anchored on the surface of HBMC, and they developed a typical polygon shape with filamentous pseudopodia as the incubation time reaches 3 days. After 5 days, the surface of HBMC was almost completely covered by osteoblasts with a multi-layered cellular structure. However, there are always less osteoblasts proliferating on the surface of PMMA bone cement compared to HBMC at different incubation times. These results prove that the introduction of AA or HEMA monomers can not only improve the biosafety of the bone cement, but also promote the adhesion and proliferation of osteoblasts on bone cement surfaces.

3.4.2 Osteogenic activities. One self-expandable P(MMA-AA-St) bone cement is fabricated by dispersion copolymerization of MMA, AA, and styrene (St) monomers. It has superior volumetric swelling (expansion ratio 87.5%) compared to P(MMA-AA) bone cement (expansion ratio 15.2%), while no significant difference in elastic modulus and compressive strength can be found for the two cements.⁵³ This characteristic is correlated with the fact that more crosslinking agents were



added to P(MMA-AA-St) bone cement than to P(MMA-AA) bone cement, such that the linear chains of P(MMA-AA-St) can be transformed to a better 3D crosslinking network with a higher water-storage capability. The efficacy of PMMA, P(MMA-AA), and P(MMA-AA-St) bone cements in filling defect and promoting repair was analyzed and compared by filling them into the medial femoral condyle cavity of New Zealand rabbits.⁵³ Fig. 6a shows the X-ray images of the rabbit femoral condyle cavity filled with different types of bone cements after 1 week of injection. Clearly, each cement sufficiently filled the femur cavity defect without fracture or cement leakage. However, significant differences in bone cement interfaces can be observed in the histological microphotographs of bone–cement contact stained with Ponceau S after 1, 4, and 12 weeks (Fig. 6b). Specifically, minor cracks appeared at the interface of PMMA bone cement at 1 and 4 weeks postimplantation, a natural result of the enhanced interfacial stresses due to the volume shrinkage of PMMA. On the contrary, direct and cohesive contact with bone can be found in P(MMA-AA) and P(MMA-AA-St) bone cements, revealing that the excellent volumetric swelling compensated for the shrinkage effectively. Furthermore, the bone began to grow into the self-expandable bone cements after 12 weeks and showed osteogenic capacity *in vivo*, which can be proved by the osteogenic positive staining in Fig. 6b. However, no evidence of osteogenic behavior can be found in PMMA bone cement. These results show that the P(MMA-AA) and P(MMA-AA-St) bone cements could be an interesting alternative in the clinical treatment for vertebral compression fractures.

For self-expandable PMMA bone cement, the enhancement in bioactivity and osteogenic activity accompanying the addition of AA or HEMA comonomers may be rationalized in terms of the following aspects of facts:

(1) In the body fluid, the surficial carboxyl (–COOH) and hydroxyl (–OH) groups of the bone cement are typically negatively charged after ionization, which can serve as recognition sites for living cells.⁸⁴ Kabaso *et al.*⁸⁵ studied the impact of

surface charge of titanium implant on adsorption of osteoblasts. Results showed that the negative potential (or negative surface charge density) on the titanium surface can promote the adhesion of osteoblasts, thus facilitating the formation of new bones. Actually, the strong electrostatic interaction between negatively charged osteoblasts and bone cements should be caused by the existence of some positively charged proteins (such as fibronectin) embedded in the surficial lipid layer of osteoblasts.^{86,87} Scotchford *et al.*⁸⁸ found that some proteins on the surface of osteoblasts do show a preferential adsorption for surface groups. For example, the adsorption preference of fibronectin in serum-containing cell medium was $-\text{COOH} > -\text{OH} > -\text{CH}_3$, which may correlate with the ionizable ability or ionic strength of those groups. These results once again demonstrate that surface groups and their charges can tune the adsorption selectivity of proteins. Of particular note, the adhesion of osteoblasts to bone cement surface is a prerequisite for further osteointegration (involving proliferation, growth and differentiation of osteoblasts) of the bone cement.^{89,90}

(2) Surficial –COOH and –OH groups may induce *in situ* mineralization of hydroxyapatite on the surface of bone cements, a viable approach mimicking the biological mineralization procedures with organic material acting as a template for hydroxyapatite generation.^{91–94} Matsuda *et al.*⁹⁵ analyzed the ability of apatite formation on self-assembled monolayers of alkanethiols having –CH₃, –COOH, and –OH terminal groups formed on a gold surface soaked in SBF. By tracing the concentration of Ca and P atoms, it was revealed that the growth rate of apatite follows a decreasing order as $-\text{COOH} > -\text{OH} > -\text{CH}_3$. This can be ascribed to the fact that –COOH is easily ionizable, and –OH is partially ionizable, while –CH₃ is non-ionizable group. Since Ca^{2+} complexation with nonionic group (–CH₃) proceeds *via* ionic-induced dipolar interaction, the weak interaction compared with electrostatic interaction between Ca^{2+} and negatively charged group (such as $-\text{COO}^-$) can be responsible for a low apatite formation capability. Spriano *et al.*^{96,97} proposed that the precipitation kinetics of

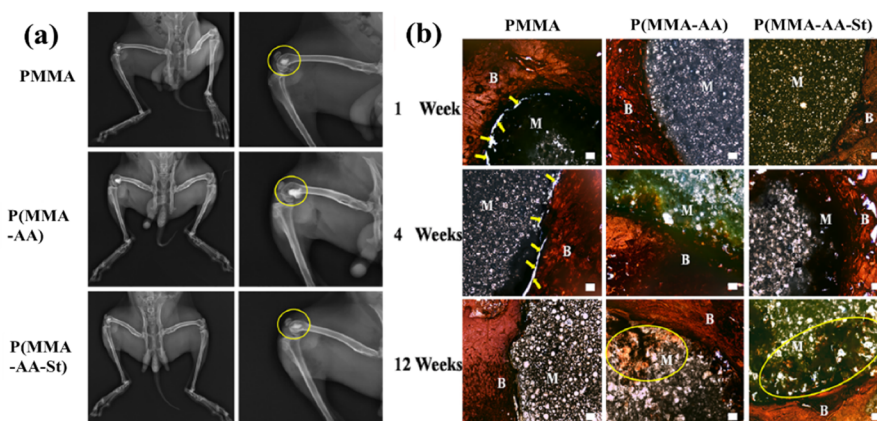


Fig. 6 (a) X-ray examination of the rabbit femoral condyle cavity after 1 week injection of PMMA, P(MMA-AA), and P(MMA-AA-St) bone cements (yellow circle: the femur cavity defect filled with cements); (b) Ponceau S staining of bone–cement contact (B: bone; M: bone cement; yellow arrows: minor crack; yellow circle: osteogenic positive staining) at 1, 4, and 12 weeks. Scale bars: 200 μm. Reprinted with the permission from ref. 53. Copyright 2017 American Chemical Society.

hydroxyapatite follows an ion exchange mechanism, involving the adsorption, nucleation, and crystallization of calcium ions and phosphate ions, and the total reaction formula can be described as:



Upon ionization, the negatively charged surficial $-\text{COOH}$ or $-\text{OH}$ groups can provide binding sites for Ca^{2+} cations present in the body fluid. This process may be followed by the attraction/complexation of PO_4^{3-} anions toward these uniformly distributed Ca^{2+} sites *via* electrostatic interactions, initiating the crystallization process of hydroxyapatite.⁹⁵ Such an electrostatic model for the hydroxyapatite formation can accelerate the deposition of bone-like Ca-P layer on the surface of bone cement, which may facilitate the subsequent new bone formation and growth. However, it should be noted that if AA undergoes incomplete polymerization, the leakage of AA monomers or oligomers in body fluid will not only damage cells or tissues, but also inhibit the apatite precipitation on polymer surfaces.^{45,67}

4. Progress in modification of hydrogel-based SBCs

4.1 Reinforcement in mechanical strength

Although the volumetric swelling of PMMA matrix is enhanced by adding hydrophilic comonomers/fillers, the water uptake generally weakens the mechanical strength of the cement. Many efforts have been made to solve this issue, for example, by adding crosslinking comonomers or reinforcing fibers to the cement. Puska *et al.*⁹⁸ fabricated a novel glass fibers-containing hydrophilic PMMA bone cement crosslinked by ethylene glycol dimethacrylate (EGDMA). Here, one amino acid-based oligomer with a mean molecular weight of 5000 g mol^{-1} is used as the hydrophilic filler, which allows for water diffusion through acrylic matrix, and causes swelling and dissolution of the filler. As is found, the crosslinked PMMA/oligomer filler (20 wt%) bone cement by replacing 5% MMA monomers with EGDMA in liquid phase shows a flexural strength of 45 MPa, much higher than that (37 MPa) of non-crosslinked PMMA/oligomer filler control group, and it further increases to 76 MPa by adding 6.2 wt% chopped glass fibers. After immersion in SBF for 7 days, the crosslinked PMMA/oligomer filler (20 wt%)/glass fiber (6.2 wt%) bone cement and the crosslinked PMMA/oligomer filler (20 wt%) bone cement exhibit a flexural strength of 33 MPa and 30 MPa, respectively, much higher than that (24 MPa) of non-crosslinked PMMA/oligomer filler control group. These findings suggest that the plasticizing effect arising from both the oligomer fillers and the adsorbed water can be compensated for by the reinforcement effect of glass fibers and crosslinking network. The mechanism can be rationalized by two aspects of facts. On the one hand, there is good adhesion between PMMA matrix and one-dimensional orientational glass fibers after surface silanization, which enables effective adsorption, transfer, and dispersion of external stresses,

beneficial for reducing the stress concentration in the system.⁹⁹ Based on the Krenchel's factor, the reinforcing effect is 20% in every direction even for isotropic chopped fiber-reinforced composites.⁹⁹ On the other hand, the presence of crosslinking monomers in bulk may possibly produce a semi-interpenetrating network structure (containing crosslinked, partially crosslinked, and linear chains), which topologically constrains the relative motion of molecular chains, thus enhancing the mechanical robustness of the matrix.

Graphene oxide (GO), a product of graphene after oxidation, is a one-atom-thick 2D sheet with distinct physicochemical features (including hydrophilicity, a honeycomb carbon lattice) and abundant surficial functional groups ($-\text{C}-\text{O}-\text{C}-$, $-\text{OH}$, $-\text{COOH}$).^{100–102} It owns excellent bioactivity, heat dissipation ability, high fracture strength and toughness, and is capable of forming strong interactions with matrix materials. All those features make GO modification a feasible and effective means for improving the biomechanical properties of PMMA bone cement.^{103,104} For P(MMA-AA-St) system,³⁹ regardless of the mechanical reinforcement by presence of mechanically strong St components, the cement is characterized by a low compression strength (58.9 MPa) due to remarkable water adsorption. Tang *et al.*³⁹ introduced GO sheets (0.5 wt% of the monomers) in P(MMA-AA-St) bone cement, and investigated the effect of GO doping methods on the biomechanical properties of the composite cement. As is revealed, whether GO was added into the reacting monomers during the synthesis of P(MMA-AA-St) powders or directly mixed with P(MMA-AA-St) powders, the compressive strength and elastic modulus of the so-obtained composite bone cement (labeled as PGBCs and PGBCm, respectively) were effectively improved. Specifically, the compressive strength of PGBCs and PGBCm reaches 99.2 and 74.0 MPa, respectively, satisfying the ISO requirement for bone cement (70 MPa). Meanwhile, the elastic modulus of PGBCs and PGBCm is 2.60 and 1.77 GPa, respectively, higher than that of a previously-synthesized P(MMA-AA-St) bone cement (1.47 GPa). These findings indicate that GO modification has a significant reinforcement effect on the mechanical properties of the matrix. The GO-induced mechanical reinforcement can be ascribed to three mechanisms: firstly, the wrinkled surface and high surface area facilitate a strong interlock between GO and the polymer matrix.¹⁰⁵ Secondly, the abundant superficial functional groups are capable of forming rich chemical interactions with P(MMA-AA-St) matrix (Fig. 7a), including $\pi-\pi$ interactions, hydrogen bonding, and ester bonding, thus enhancing the cohesive energy density of the bone cement. In addition, the crack propagation can be hindered by the so-called “bridging effect” originating from the strong interfacial adhesion or chemical linkage between GO and P(MMA-AA-St), which might be another reason for mechanical improvement.¹⁰⁶

With the addition of GO, one can observe a reduced exothermic temperature and prolonged setting time for the composite bone cement. This may be explained by the fact that GO sheets can hinder the contact between monomers, accelerators, and initiators, and annihilate the free radicals in the reacting system, which leads to retarded polymerization of MMA monomers.^{105,107} Besides that, the high thermal



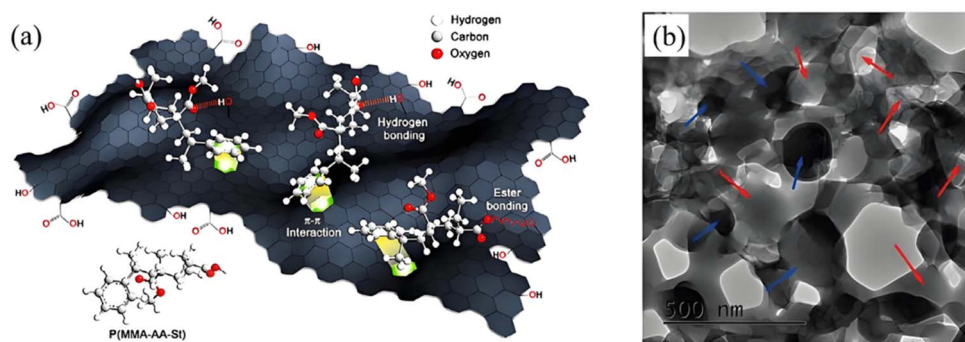


Fig. 7 (a) Schematic of the chemical interaction between the GO sheet and P(MMA-AA-St) indicating π - π interactions between St and GO, hydrogen bonds, and ester bonds between AA and GO. Reprinted with the permission from ref. 39. Copyright 2023 Elsevier; (b) TEM images of P(MMA-AA)/GO nano-units (red arrow indicates GO sheet and blue arrow indicates P(MMA-AA) microspheres). Reprinted with the permission from ref. 108. Copyright 2021 John Wiley and Sons.

conductivity of GO can enhance the heat dissipation capability of the cement, ensuring a quick transfer of the polymerization heat to surrounding environment. Interestingly, PGBCs exhibits a stronger water-adsorbing and swelling capability compared to PGBCm, and this phenomenon results naturally from the different dispersion morphology of GO sheets in the systems. When GO sheets were added in the reacting MMA monomers to synthesize P(MMA-AA-St) powders, they could participate in polymerization with MMA monomers at a hydrogen position *via* esterification. Consequently, GO sheets can evenly distribute around P(MMA-AA-St) particles, forming a unique “microsphere-lamellar” structure (Fig. 7b).^{39,57,108} The interlaced form of microspheres and sheets not only plays a role of collaborative water absorption, with a large surface area for water contact, but also increases the depth of water absorption and dimensional expansion of PGBCs. In contrast, direct mixing of GO with P(MMA-AA-St) nanoparticles may lead to self-aggregation of GO, and the reduced contact with water is unfavorable for enhancing the water-adsorbing capability.

Due to the hydrophilic nature and abundant functional groups, GO is of excellent biocompatibility and bioactivity, and the addition of GO can effectively improve the osteogenic capability of the cement matrix.^{107,109} At the gene level, the expression of some important osteogenic genes, such as the alkaline phosphatase (*Alp*, an osteogenic marker gene) and osteopontin (*Opn*, an osteogenic marker and regulator of the osteoblast adhesion), could be enhanced by adding bioactive GO additives.¹¹⁰ As demonstrated by the quantitative real-time polymerase chain reaction (qRT-PCR) data, PGBCs and PGBCm show a higher expression level of *Opn* and *Alp* than traditional PMMA bone cement in osteoblasts after 7 days of coculture,³⁹ suggesting an enhanced osteogenic capability induced by bioactive GO. At the protein level, due to the important role of GO's rich interactions (π - π interactions, electrostatic and hydrogen bonding) in protein preconcentration, GO can serve as a preconcentration platform for serum proteins, which can further induce osteoblast cell growth and osteogenic differentiation.^{111–113} Actually, the enhanced gene expression may also trigger a high-quality protein transcription, as evidenced by an enhanced expression in Smad5 (a

transcription factor transducing the bone morphogenetic protein signals into the nucleus to promote osteoblast maturation), which paves another way for promoting osteogenic differentiation.¹¹⁴

4.2 Alleviation of radical toxicity

For current PMMA bone cement products, the necessary production of free radicals from the peroxide initiator (often benzoyl peroxide, BPO) could induce oxidative stress at the cellular and tissue levels.^{115,116} As a result, the cemented prosthesis is at increased risk of triggering multiple adverse tissue reactions including impaired bone remodeling, necrosis, fibrosis, and histiocytosis, which may further evolve into a dire adverse systemic complication known as bone cement implantation syndrome, characterized by hypotension, hypoxemia, cardiac arrhythmias, cardiac arrest, or their combination.^{117–119} Indeed, osteoblasts exposed to BPO-containing PMMA resin show a high percentage of cell death and severely compromised proliferation and differentiation.^{120,121} In humans, antioxidant and detoxification capacities diminish with age. Circulating glutathione, a major oxidant scavenging mechanism in humans, is 17% lower in people aged 40–59 years and 45% lower in those aged 60–79 years than those aged 20–39 years,¹²² so the unique biological demand of an aging society necessitates more biocompatible bone cements. Compared with BPO, tri-*n*-butyl borane (TBB) can better promote polymerization, leaving less residual monomer while suppressing the production of free radicals.^{123,124} Moreover, TBB-initiated polymerization generates less heat than BPO.¹²⁵ Unlike BPO, TBB is also moisture resistant,^{126,127} and the addition of TBB may help promote polymerization under wet conditions, a valuable property for bone cement used in bone marrow cavities.

Ogawa *et al.*⁵⁵ used TBB as a polymerization initiator instead of BPO to reduce free radical production during the preparation of PMMA bone cement. Meanwhile, 4-methacryloyloxyethyl trimellitate anhydride (META) was added to MMA monomers to make a hydrophilic PMMA matrix, beneficial for increasing the cellular affinity. The structure and reaction formula during polymerization of META/MMA-TBB materials is shown in the



upper panel of Fig. 8. Electron spin resonance spectroscopy revealed that the free radical production for P(MMA-META)-TBB was approximately 1/25th that of PMMA-BPO 1 h post-mixing, 1/10th that of PMMA-BPO 1 day post-mixing, and 1/6th that of PMMA-BPO at the later stages of polymerization (*i.e.*, 10 days post-mixing). These results were further supported by the significant improvement in the biocompatibility of PMMA-BPO by mixing with anti-oxidant amino acid (NAC),¹²⁰ which can scavenge free radicals within resin materials during polymerization. Of great note, the number of osteoblasts attached on cement surfaces 24 h after seeding was considerably increased for PMMA-BPO with NAC compared to PMMA-BPO without NAC, while NAC did not significantly impact the osteoblasts number on P(MMA-META)-TBB, indicating that there were not much free radicals to scavenge in the material.

To examine the initial attachment and viability of osteoblasts, rat bone marrow-derived osteoblasts were cultured on the surfaces of PMMA-BPO and P(MMA-META)-TBB systems.⁵⁵ After 24 h of cultivation, the viability of osteoblasts on P(MMA-META)-TBB (80.1%) was higher than that (58.0%) on PMMA-BPO, and approximately 15 times more osteoblasts attached to P(MMA-META)-TBB. A schematic diagram of the enhanced

osteoblastic attachment and proliferation on P(MMA-META)-TBB is shown in the bottom panel of Fig. 8. High magnification confocal microscopy confirmed that at 24 h, osteoblasts on P(MMA-META)-TBB had a wider distribution and developed more intensive cytoskeletal actin along the cellular outline than that on PMMA-BPO, suggestive of advanced lamellipodia-like cytoplasmic projection development. Meanwhile, osteoblasts on P(MMA-META)-TBB also showed a higher expression of a focal adhesion protein (vinculin) and osteogenic gene (osteopontin and osteocalcin). MicroCT and histomorphometric analysis revealed that there was extensive and intimate bone formation along P(MMA-META)-TBB cement, with little fibrous tissue interposing between the bone cement and bone. In the later stage of culture (after 14 days), the mineralized area on P(MMA-META)-TBB was 20 times greater than that on PMMA-BPO. The bone-cement integration strength of P(MMA-META)-TBB after 4 weeks of healing, as evaluated by the biomechanical push-in test, was 5 times greater than that of PMMA-BPO. These results suggest that P(MMA-META)-TBB shows significantly enhanced osteoconductivity compared to PMMA-BPO due to the uniquely created hydrophilic and radical-free interface.

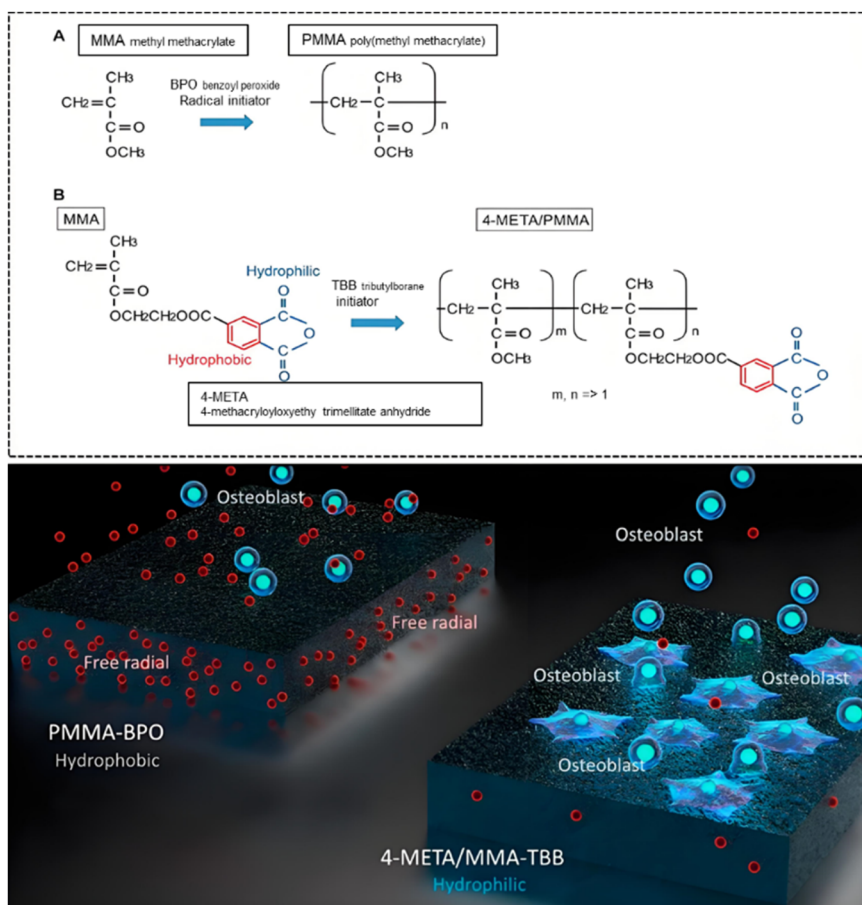
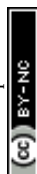


Fig. 8 (Upper panel) Structure and chemical formula during polymerization of MMA-BPO (A) and META/MMA-TBB (B) materials; (Bottom panel) schematic diagram of unique physicochemical property of META/MMA-TBB characterized by a hydrophilic surface and minimal free radical production during polymerization, which enhances osteoblastic attachment and subsequent osteogenic function. Reprinted with the permission from ref. 55. Open Access.



4.3 Drug-loading modifications

For drug-loaded PMMA bone cement, the continuous drug release is crucial for the long-term antibacterial ability of the bone cement.¹²⁸ Porosity, surface roughness, and wettability are the main factors affecting the drug release behavior of the bone cement.^{129,130} In general, the higher the porosity, the hydrophilicity, and the surface roughness, the greater the release rate and amount of loaded drugs. The drug-eluting characteristic of drug-loaded PMMA bone cement can be described as the sudden release of huge doses of antibiotics at the initial stage, followed by a subsequent decrease in release rate.^{131,132} The sudden drug release not only causes undesired toxic effects on surrounding cells or tissues, but also makes the drug-eluting process unsustainable with a short release equilibrium, thus impairing the long-term antibacterial activity of bone cement.¹³³ For PMMA bone cement, the unstable drug-elution can be ascribed to the dense/compact structure, which hinders the diffusion of internal drugs to the exterior of the bone cement, and only a small portion of the drugs on bone cement surface can be released.¹²⁹ By increasing the porosity of bone cement (for example, *via* introducing pore formers that create micropores within the matrix after degradation), the cumulative drug release was found to be significantly increased.¹³⁴

Nien *et al.*¹³⁰ developed a novel drug-loaded hydrophilic PMMA bone cement by mixing MMA monomers with solid PMMA powders which contained 5 wt% crosslinked poly(methylmethacrylate-acrylic acid sodium salt) particles (denoted as P(MMA-AAS-AMA)) and 4.22 wt% ketoprofen. Here, allyl-methacrylate (AMA) is used for cross-linking the swellable P(MMA-AAS-AMA) particles, and ketoprofen is a non-steroidal anti-inflammatory drug. The accumulated drug release ratio of hydrophilized PMMA/ketoprofen systems is shown in Fig. 9a. As revealed, after a high initial release of ketoprofen in PBS in the first 8 days, a reduced yet constant release of ketoprofen sustained until the end of the drug eluting test (60 days). Understandably, the initial prompt release was due to the elution of ketoprofen from the region near the surface of bone cement, while the following sustained release originates from the

dissolution and diffusion of ketoprofen inside the cement through the swollen P(MMA-AAS-AMA) particles. The equilibrium ketoprofen release rate (mg h^{-1}) by diffusion through the entire cement corresponds to the curve slope of the sustained drug-eluting period from 18 days to 60 days, and the initial ketoprofen release rate ($\mu\text{g cm}^{-2} \text{h}^{-1}$) can be calculated from the curve slope over the first 6 h of release. Results show that the initial and equilibrium release rates of P(MMA-AAS-AMA)/ketoprofen bone cement (MMA, AAS, and AMA are at a volume ratio of 80/20/10) is $23.8 \mu\text{g cm}^{-2} \text{h}^{-1}$ and $2 \times 10^{-5} \text{ mg h}^{-1}$, respectively, higher than that of conventional PMMA/ketoprofen bone control group ($18.1 \mu\text{g cm}^{-2} \text{h}^{-1}$, $8 \times 10^{-6} \text{ mg h}^{-1}$). These findings highlight the importance of hydrophilic P(MMA-AAS-AMA) particles, which can adsorb water and create continuous interconnected water pathways. Such pathways can not only allow the water molecules to penetrate into the bone cement, facilitating rapid dissolution of the drug, but also act as microchannels to deliver drug molecules outside of the cement, contributing to sustained drug elution (Fig. 9b). The compressive strength is tested after full immersion of the specimen in PBS at 37 °C for 107 days. Interestingly, the hydrophilized PMMA/ketoprofen bone cement exhibits a compressive strength of 80.8 MPa, even slightly higher than that of conventional PMMA/ketoprofen control group (75.8 MPa). This suggests that the mechanical strength of bone cement was trivially affected by the swelling of P(MMA-AAS-AMA) particles, essential for providing robust mechanical support for prosthesis.

Tang *et al.*¹³⁵ prepared P(MMA-AA) nanoparticles loaded with alendronate sodium (ALN) *via* solution polymerization, and introduced them in PMMA bone cement containing gentamicin sulfate (GS) to obtain a swelling and dual drug release bone cement (SDBC). Here, ALN is a bone resorption inhibitor that can effectively inhibit the activity of osteoclasts, and GS is an antibiotic with broad-spectrum antibacterial properties, excellent thermal stability, and low allergenicity. Both GS and ALN are the most commonly used drugs in orthopedic clinical practice. Results revealed that SDBC exhibits a rapid water

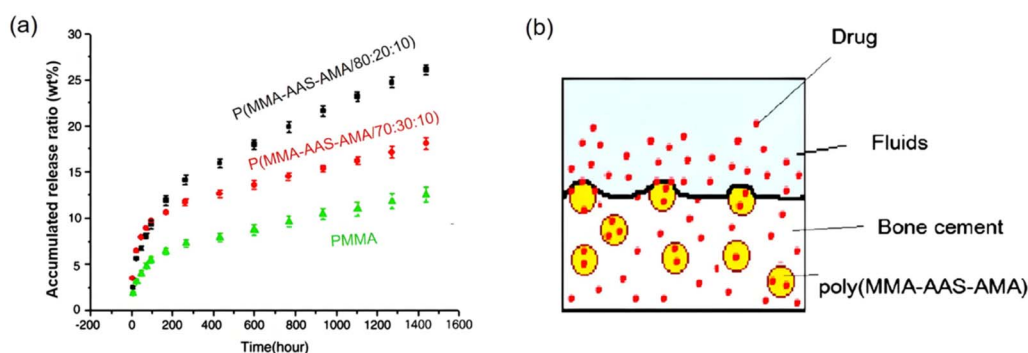


Fig. 9 (a) Accumulated drug release ratio of hydrophilized PMMA/ketoprofen systems, of which the liquid phase is MMA monomers, and solid phase is PMMA powders containing 5 wt% crosslinked P(MMA-AAS-AMA) particles and 4.22 wt% ketoprofen; black squares represent that P(MMA-AAS-AMA) is at a volume ratio of 80/20/10, red circles represent that P(MMA-AAS-AMA) is at a volume ratio of 70/30/10, and green triangles represent traditional PMMA/ketoprofen control group. (b) Schematic illustration of the releasing mechanism of ketoprofen in hydrophilized PMMA matrix. Reprinted with the permission from ref. 130. Copyright 2013 Elsevier.

adsorption in the initial 20 min, beneficial for a quick entry of water molecules into the matrix. This can also facilitate a rapid construction of water-adsorbing pathways composed of P(MMA-AA)/ALN, such that the dissolved GS and ALN molecules can be continuously transported outward.¹³⁵ The equilibrium release ratio of GS and ALN in SDBC soaked in PBS buffer (pH = 7.4) is 74.7% and 75.2%, respectively, much higher than that of GS and ALN in PMMA bone cement (4.4% and 4.8%, respectively). Besides, the release of GS and ALN reaches an equilibrium state after 4 and 15 weeks, respectively, much longer than their release cycle in PMMA bone cement (5 and 10 days, respectively). The sustained release of GS and ALN is believed to guarantee a long-term promotional effect on osteoblasts proliferation and long-lasting antibacterial activities for SDBC. Given that ALN is encapsulated by P(MMA-AA) nanoparticles buried in PMMA matrix, the release of ALN is expected to go through three stages:¹³⁵ in the first stage, the rapid water adsorption destroys the intermolecular forces and hydrogen bonding between ALN and the 3D network of P(MMA-AA), leading to dissolution of ALN in the absorbed water. In the second stage, the 3D network of the nanoparticles unfolds and results in swelling behavior of P(MMA-AA)/ALN, allowing the diffusion of ALN to the nanoparticle interfaces. In the third stage, the dissolution and release of GS around the P(MMA-AA)/ALN located on the bone cement surface generates pore structures, and ALN gradually diffused outward through both water pathways and pores. Since the migration of ALN through the cement matrix suffers great topological resistance from both P(MMA-AA)/ALN and PMMA matrix, the release cycle of ALN can be significantly extended to 15 weeks. By contrast, the outward diffusion of GS may experience less obstacles since it is only buried in PMMA matrix, consistent with a shorter release cycle (4 weeks) of GS.

The surficial adhesion of osteoblasts was compared by cultivating them on SDBC and PMMA bone cements. Fluorescence micrographs revealed that after 1 day of cultivation, osteoblasts attached and anchored to the surface of SDBC, forming a typical polygonal shape, and the filamentous pseudopodia gradually spread out from osteoblasts. After 5 days of cultivation, the number of osteoblast cells was significantly increased and the cells covered the SDBC surface.¹³⁵ Compared with PMMA cement, there were always more osteoblasts cells with better morphology on the surface of SDBC at the same incubation time, indicating that the introduction of P(MMA-AA)/ALN particles promoted the osteoblast adhesion and proliferation. Staining images of muscle tissues surrounding the bone cements showed that inflammatory cells appeared in the muscle tissue 2 weeks after implantation of SDBC and PMMA bone cement, indicating an early mild inflammatory response, which plays a positive role in tissue healing. The inflammatory response gradually diminished after 4 weeks of implantation, as evidenced by a decreased number of inflammatory cells. However, at various time points, the number of inflammatory cells in SDBC group was always lower than that in PMMA group, which can be attributed to the long-lasting antibacterial ability due to the sustained GS release in SDBC.

4.4 Porosity control

For traditional PMMA bone cement, only weak forces join the cement to the bone, as the cement can only form mechanical interlock with bones after penetrating into the trabecular spaces. The weakness of cement interfaces is regarded as a main cause of the most important problem found in these materials, *i.e.*, the aseptic loosening of the implant during long-term implantation, with a subsequent need of a revision surgery. To improve the cement–bone interaction, novel successful formulations should provide a means of inducing bones to grow inside the cement material. For this to occur, it is necessary for the material to be hydrophilic (to offer a high-affinity matrix and make the inner particles accessible), degradable (to create empty volume which would be filled by the bone), and highly bioactive (to induce the formation of calcium phosphate on the surfaces of the matrix). So far, degradable polymers (such as starch, collagen, chitosan, *etc.*) and bioactive glass–ceramics (borate glass, hydroxyapatite, *etc.*) have been widely incorporated into hydrophilized PMMA matrix, attempting to create a bioactive porous bone cement with the capability of establishing a direct bond to bone.^{66,68,136}

Boesel *et al.*^{137,138} prepared a hydrophilic, bioactive, and partially degradable composite bone cement by mixing the solid component (bioactive glasses and degradable corn starch/cellulose acetate particles) with the liquid component constituted by HEMA monomers. Here, corn starch-based polymers degrade in human body through a hydrolysis reaction, a process catalyzed by α -amylase, an enzyme that exists in low concentrations in human serum.¹³⁹ The degradation level can be evaluated by the changes in concentration of reducing sugars, percentage of weight loss, and morphologic evolution of the cement, and it can be easily controlled by the amount of α -amylase added to the cement. In general, high levels of degradation can be achieved if high enough quantities of enzyme are incorporated.¹³⁸ Notably, starch degradation undergoes a dramatic acceleration at a percolation concentration, *i.e.*, the minimum concentration of the dispersed medium that creates full connectivity through the matrix, such that the degraded starch can create a connected network of pores and voids that allows the transport of enzyme inside the material for enzymatic action. It seemed that the maximum degradation extent depends more on the total amount of starch present in the formulation than on the amount of enzyme added to it. SEM micrographs of the cross sections of the degraded specimen showed a heterogeneously distributed porosity after enzymatic action. As shown in Fig. 10a, the pores had a round shape and its size was limited by the particle size of degradable starch fillers, that is 125 μm , while the structure was kept by the inert acrylic matrix.

In Boesel's degradable formulations, Na_2O (or MgO)– SiO_2 – CaO – P_2O_5 glass–ceramics were used as bioactive fillers to render the composite bone cement bioactivity.^{137,138} Those bioactive ceramics typically release high amounts of Ca^{2+} and PO_4^{3-} when dissolved in SBF solution, beneficial for saturating the solution and expediting the apatite formation. SEM images showed that after 4 days of incubation in SBF, agglomerates



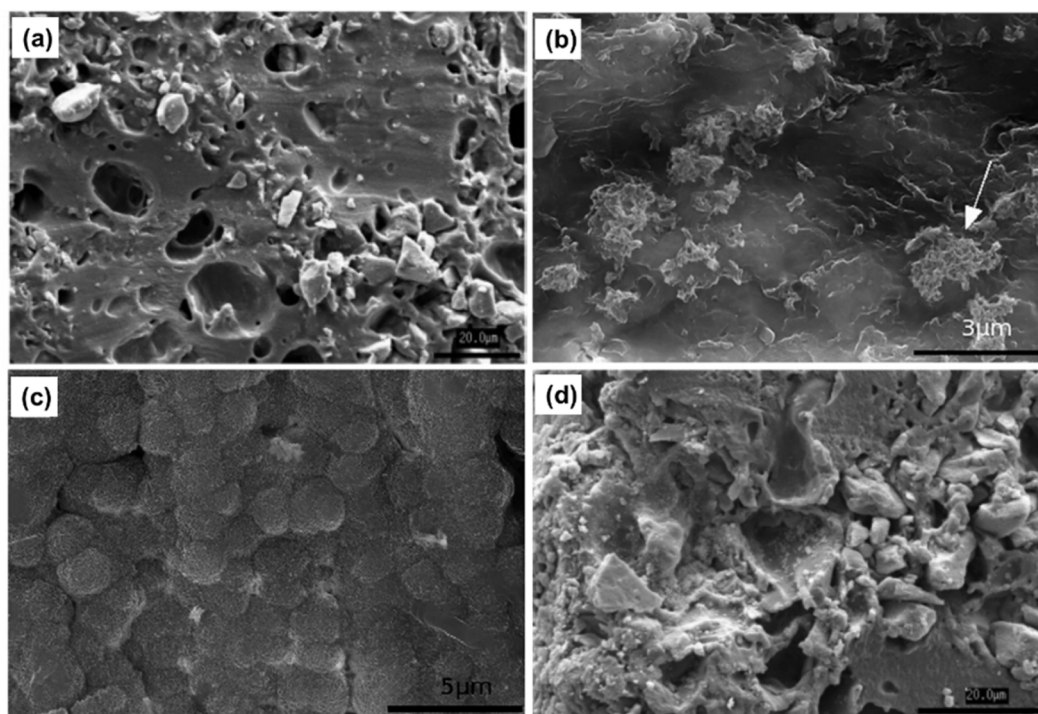


Fig. 10 SEM micrographs showing (a) the porosity formation after 16 weeks of immersion in SBF and (d) the spreading of calcium phosphate nuclei to inner pores near the surface after 2 weeks of immersion in SBF for one degradable cement specimen (liquid phase: HEMA and thermostable α -amylase; solid phase: corn starch/cellulose acetate powders and $\text{Na}_2\text{O}-\text{SiO}_2-\text{CaO}\cdot\text{P}_2\text{O}_5$ bioactive glass). Reprinted with the permission from ref. 138. Copyright 2006 American Chemical Society; SEM micrographs of the surface of cement specimens (liquid phase: HEMA; solid phase: corn starch/cellulose acetate powders and $\text{MgO}-\text{SiO}_2-\text{CaO}\cdot\text{P}_2\text{O}_5$ bioactive glass) immersed in SBF for (b) 4 and (c) 7 days. Reprinted with the permission from ref. 137. Copyright 2007 Elsevier.

containing Ca and P atoms appeared on the cement surface (Fig. 10b). After 7 days of immersion, a needle-like “cauliflower” morphology (Fig. 10c) was clearly visible, which evolved into a dense and thick apatite layer after 9 days. This gives a clear indication of apatite formation. After 2 weeks of immersion, calcium phosphate nuclei spread to the walls of inner pores near the surface (as well as on the glass particles themselves), indicating that apatite is nucleating inside the cements (Fig. 10d). The results of energy dispersive spectroscopy further supplemented the mechanism of apatite formation. It was found that a unique calcium phosphate precipitate phase, with a Ca/P ratio of 1.82, was initially formed on surfaces of SBCs, which was amorphous or crystalline. As the precipitates grew and formed a layer after 1 week, the Ca/P ratio approached and stabilized at 1.59, close to the Ca/P ratio (1.67) of HA. These results demonstrate that the developed composites with promoted degradation/bioactivity can induce the nucleation and growth of apatite layer on/inside the cements, beneficial for creating a stronger, more stable, and longer lasting interface between bone and cement.

5. Summary and outlook

The SBCs represent a step forward in bone cement research and their conception is based on a study of the major drawbacks of commercially available PMMA bone cements (such as high

polymerization heat, low bioactivity, weak osteoconductive and osteoinductive ability, and volume shrinkage upon solidification, *etc.*) and on an attempt to overcome such drawbacks. They are not simply “one more” alternative to the conventional bone cements, since several modifications are combined in a synergistic way to achieve better results than any of them alone. By adjusting the composition and structure of the cement, multifunctional SBCs can achieve a good balance among many material properties (such as osteogenic activity, mechanical properties, Young’s modulus, *etc.*), making them one of the best alternatives.

Compared with traditional PMMA bone cements, the key advantages of SBCs can be assigned to the hydrophilicity (or self-expandability), bioactivity, and low heat release upon solidification. At present, hydrophilic monomers containing hydroxyl groups and ester/ether bonds have been widely used for preparing hydrogel-based SBCs. However, due to differences in biochemical properties, those monomers play different roles in determining the material properties of SBCs. For example, hydroxyl-based cements have a stronger water adsorption capability than ester/ether bond-based ones, since hydroxyls have a stronger hydrophilic capability or wettability than ester/ether bonds. In body fluid, the negatively-charged surficial carboxyl and hydroxyl groups may serve as recognition sites for living cells, which facilitates osteoblast adhesion to bone cement surface and favors further osteointegration of the

cement. Moreover, the ionized surficial carboxyl or hydroxyl groups may provide binding sites for Ca^{2+} present in body fluid and induce *in situ* mineralization of hydroxyapatite on cement surfaces, thus mimicking the biological mineralization procedures. The unique biochemical properties have made AA or HEMA-based SBCs a current research hotspot, and how the incorporation of AA or HEMA adjusts the biomechanical properties of the cement have attracted much attention. A schematic diagram describing the application principles of SBCs with innovated formulations and biomechanical properties is shown in Fig. 11.

The long-term stability of SBC *in vivo* depends on the combined effects of the degradation behavior, swelling properties, and interfacial mechanical integrity over time, which determines whether a revision surgery is needed. Unlike the traditional PMMA bone cement undergoing a volumetric contraction after solidification, the swelling of SBCs associated with the water uptake can get the bone defect completely filled, beneficial for enhancing the bone–cement interfacial strength. Constructing porous structure in bioactive ceramics-containing SBCs can induce the growth of apatite layer inside the cements, facilitating the ingrowth of bones and a direct bonding of bones to cement. During the *in vivo* service of the cement, the occurrence of creep in swelled SBC can create a more favorable stress distribution at the interfaces, allowing the expansion of the cement mantle and subsequent prosthetic subsidence without causing cement fracture. Those appealing results all suggest that SBCs can maintain a long-term stability after *in vivo* implantation, thus diminishing the need for a revision surgery. Those novel SBCs may have a great application potential in orthopedic fields, including but not limited to artificial joint replacement, bone defect reconstruction, and pedicular screw fixation (Fig. 11).

However, considering the diverse clinical needs for bone cement properties and functionalities (excellent bioactivity,

high porosity, bio-mimetic morphology, *etc.*), there are still many unresolved issues in the research field of SBCs: first of all, although biodegradable materials with regular shape were widely used as pore formers to convert the bone cement to a porous scaffold after biodegradation, which promotes the cell proliferation and ingrowth of blood vessels,^{72,136,140–142} few studies have paid intense attention to the mechanism of pore formation. Besides, constructing porosity within well swelled cement typically weakens the mechanical strength of the scaffold and diminishes the mechanical support. In view of this, future studies should seek an effective method that can accurately create pores and transform the SBC to a trabecular bone-like 3D porous structure, without sacrificing other biomechanical properties. Secondly, most SBCs are in the laboratory stage, and an evaluation of the *in vivo* stability/reliability of SBCs is still lacking. Therefore, there needs a long-term tracking of the *in vivo* stability of SBC after clinical implantation, and their pathological features should be fully confirmed by clinical evidence. To enhance the biosafety of those novel bone cements, more pathological evidence should be provided in future to elucidate how cement implantation affects the function and metabolism of human cells, tissues and organs. Preclinical and clinical studies on these innovations are also crucial for establishing new formulations in the market. In addition, the current research mainly concerns the formula design and biomechanical properties of the bone cements, while the preparation of novel bone cements based on tissue engineering is still rare. Many studies have found that the implantation of bone cement scaffolds with primary cells seeded on it can self-assemble to the desired bone tissues *in situ* to replace the diseased or damaged bone tissues.^{143,144} Therefore, future design of SBC should combine with cell/gene bioactive materials to achieve targeted induction of osteogenic differentiation for bone formation, thus strengthening the repair efficiency of SBC for bone defects.

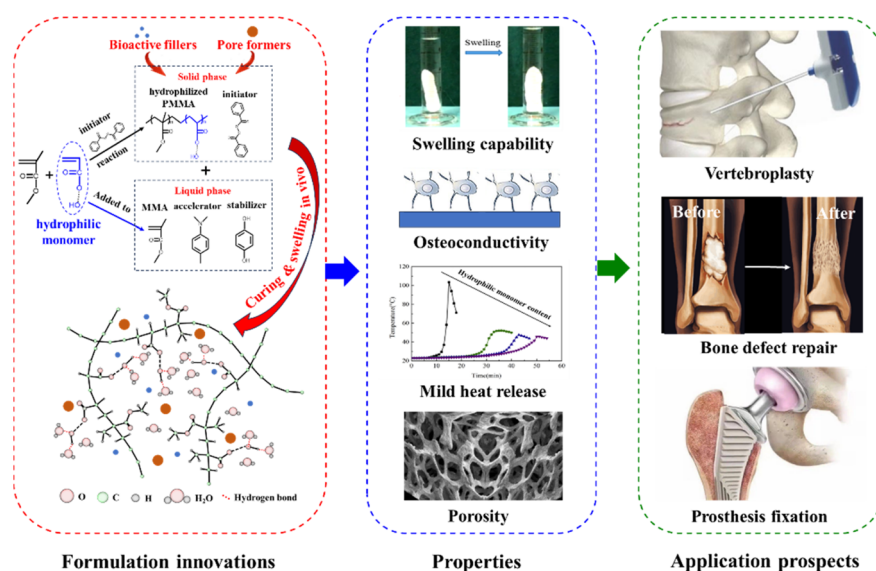


Fig. 11 Schematic diagram of the application principles of SBCs with innovated formulations and biomechanical properties.



Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Author contributions

Haochang He: conceptualization, methodology, resources; Yuanbiao Liu: data curation, writing – original draft preparation, writing – review & editing, visualization; Yukai Dong: resources, methodology; Wenjie Zhao: investigation, validation; Keyuan Wang: methodology; Kai Guo: investigation, resources; Enxiang Jiao: methodology; Shanshan Xu: investigation; Guannan Ju: methodology; Peng Wang: investigation, methodology; Duanhong Ma: investigation, methodology; Gaopeng Shi: methodology, data curation; Haijun Zhang: writing – reviewing and editing, supervision, project administration.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This research was supported by the Shandong Provincial Natural Science Foundation (grant number ZR2023QE032), the National Natural Science Foundation of China (grant number 82270535), the Shandong Provincial Key R&D Program (Major Scientific and Technological Innovation Project, No. 2024CXGC010607) and National Key R&D Program of China (grant number 2023YFC2411900).

References

- 1 D. K. Filippiadis, S. Marcia, S. Masala, F. Deschamps and A. Kelekis, Percutaneous vertebroplasty and kyphoplasty: Current status, new developments and old controversies, *Cardiovasc. Intervent. Radiol.*, 2017, **40**(12), 1815–1823.
- 2 J. S. Wang, J. Diaz, A. Sabokbar, N. Athanasou, F. Kjellson, K. E. Tanner, I. D. McCarthy and L. Lidgren, In vitro and *in vivo* biological responses to a novel radiopacifying agent for bone cement, *J. R. Soc. Interface*, 2005, **2**(2), 71–78.
- 3 Y. Liu, K. Guo, E. Jiao, S. Xu, J. Yang, W. Li, G. Liu, L. Zhao and H. Zhang, Material properties and progress in modification of PMMA bone cement, *Polym. Bull.*, 2023, **36**(12), 1610–1633.
- 4 B. Magnan, M. Bondi, T. Maluta, E. Samaila, L. Schirru and C. Dall'Oca, Acrylic bone cement: Current concept review, *Muscle. Surg.*, 2013, **97**(2), 93–100.
- 5 X. Yu, X. Tang, S. V. Gohil and C. T. Laurencin, Biomaterials for bone regenerative engineering, *Adv. Healthcare Mater.*, 2015, **4**(9), 1268–1285.
- 6 S. Yadav and S. Gangwar, An overview on recent progresses and future perspective of biomaterials, *IOP Conf. Ser.:Mater. Sci. Eng.*, 2018, **404**(1), 012013.
- 7 C. Mounika, T. Tadge, M. Keerthana, R. Velyutham and G. Kapusetti, Advancements in poly (methyl Methacrylate) bone cement for enhanced osteoconductivity and mechanical properties in vertebroplasty: A comprehensive review, *Med. Eng. Phys.*, 2023, **120**, 104049.
- 8 V. S. Seesala, L. Sheikh, B. Basu and S. Mukherjee, Mechanical and bioactive properties of PMMA bone cement: A review, *ACS Biomater. Sci. Eng.*, 2024, **10**(10), 5939–5959.
- 9 G. Lewis, Emerging modified poly (Methyl Methacrylate)(PMMA) bone cements for augmentation of osteoporosis-induced compression fractures of vertebral bodies: Present status and future prospects, *J. Mater. Sci. Res. Rev.*, 2024, **7**(3), 441–467.
- 10 S. Soleymani Eil Bakhtiari, H. R. Bakhsheshi-Rad, S. Karbasi, M. Tavakoli, S. A. Hassanzadeh Tabrizi, A. F. Ismail, A. Seifalian, S. RamaKrishna and F. Berto, Poly(methyl methacrylate) bone cement, its rise, growth, downfall and future, *Polym. Int.*, 2021, **70**(9), 1182–1201.
- 11 T. Albrektsson and C. Johansson, Osteoinduction, osteoconduction and osseointegration, *Eur. Spine J.*, 2001, **10**(2), S96–S101.
- 12 M. Arora, E. K. Chan, S. Gupta and A. D. Diwan, Polymethylmethacrylate bone cements and additives: A review of the literature, *World J. Orthod.*, 2013, **4**(2), 67–74.
- 13 D. Rentería-Zamarrón, D. A. Cortés-Hernández, L. Bretado-Aragón and W. Ortega-Lara, Mechanical properties and apatite-forming ability of PMMA bone cements, *Mater. Des.*, 2009, **30**(8), 3318–3324.
- 14 T. W. Bauer and J. Schils, The pathology of total joint arthroplasty: II. Mechanisms of implant failure, *Skelet. Radiol.*, 1999, **28**(9), 483–497.
- 15 N. R. Patel and P. P. Gohil, A review on biomaterials: Scope, applications & human anatomy significance, *Int. J. Emerg. Technol. Adv. Eng.*, 2012, **2**(4), 91–101.
- 16 A. Boger, A. Bisig, M. Böhner, P. Heini and E. Schneider, Variation of the mechanical properties of PMMA to suit osteoporotic cancellous bone, *J. Biomater. Sci., Polym. Ed.*, 2008, **19**(9), 1125–1142.
- 17 Q. Zhang, A. Cossey and J. Tong, Stress shielding in bone of a bone-cement interface, *Med. Eng. Phys.*, 2016, **38**(4), 423–426.
- 18 J. L. Gilbert, J. M. Hasenwinkel, R. L. Wixson and E. P. Lautenschlager, A theoretical and experimental analysis of polymerization shrinkage of bone cement: A potential major source of porosity, *J. Biomed. Mater. Res.*, 2000, **52**(1), 210–218.
- 19 P. E. Sinnett-Jones, M. Browne, W. Ludwig, J. Y. Buffière and I. Sinclair, Microtomography assessment of failure in acrylic bone cement, *Biomaterials*, 2005, **26**(33), 6460–6466.
- 20 K. D. Kuehn, W. Ege and U. Gopp, Acrylic bone cements: Composition and properties, *Orthop. Clin.*, 2005, **36**(1), 17–28.
- 21 G. Lewis, Properties of nanofiller-loaded poly (methyl methacrylate) bone cement composites for orthopedic applications: A review, *J. Biomed. Mater. Res., Part B*, 2017, **105**(5), 1260–1284.



- 22 R. Vaishya, M. Chauhan and A. Vaish, Bone cement, *J. Clin. Orthop. Trauma*, 2013, **4**(4), 157–163.
- 23 T. Udiljak, D. Ciglar and S. Skoric, Investigation into bone drilling and thermal bone necrosis, *Adv. Prod. Eng. Manag.*, 2007, **2**(3), 103–112.
- 24 J. Carlander, C. Koch, L. Brudin, C. Nordborg, O. Gimm and K. Johansson, Heat production, nerve function, and morphology following nerve close dissection with surgical instruments, *World J. Surg.*, 2012, **36**(6), 1361–1367.
- 25 H. Fukushima, Y. Hashimoto, S. Yoshiya, M. Kurosaka, M. Matsuda, S. Kawamura and T. Iwatsubo, Conduction analysis of cement interface temperature in total knee arthroplasty, *Kobe J. Med. Sci.*, 2002, **48**, 63–72.
- 26 J. Urrutia, C. M. Bono, P. Mery and C. Rojas, Early histologic changes following polymethylmethacrylate injection (vertebroplasty) in rabbit lumbar vertebrae, *Spine*, 2008, **33**(8), 877–882.
- 27 A. López, A. Hoess, T. Thersleff, M. Ott, H. Engqvist and C. Persson, Low-modulus PMMA bone cement modified with castor oil, *Bio-Med. Mater. Eng.*, 2011, **21**, 323–332.
- 28 J. R. Frigstad and J. B. Park, Reinforcement of PMMA bone cement with a continuous wire coil-A 3D finite element study, *Bio-Med. Mater. Eng.*, 1996, **6**(6), 429–439.
- 29 S. P. Kotha, C. Li, S. R. Schmid and J. J. Mason, Fracture toughness of steel-fiber-reinforced bone cement, *J. Biomed. Mater. Res., Part A*, 2004, **70A**(3), 514–521.
- 30 L. D. T. Topoleski, P. Ducheyne and J. M. Cuckler, The fracture toughness of titanium-fiber-reinforced bone cement, *J. Biomed. Mater. Res.*, 1992, **26**(12), 1599–1617.
- 31 S. Gulati, S. Kumar, A. Diwan, P. Singh, and A. Mongia, “Nanosilver”: A versatile and new-generation nanoparticle in biomedical applications, in *Handbook of Consumer Nanoproducts*, ed. S. Mallakpour and C. M. Hussain, Springer Nature Singapore, Singapore, 2022, pp. 575–594.
- 32 R. Parai and S. Bandyopadhyay-Ghosh, Engineered bio-nanocomposite magnesium scaffold for bone tissue regeneration, *J. Mech. Behav. Biomed. Mater.*, 2019, **96**, 45–52.
- 33 J. Zhang, Y. Feng, X. Zhou, Y. Shi and L. Wang, Research status of artificial bone materials, *Int. J. Polym. Mater.*, 2021, **70**(1), 37–53.
- 34 J. A. Juhasz and S. M. Best, Bioactive ceramics: Processing, structures and properties, *J. Mater. Sci.*, 2012, **47**(2), 610–624.
- 35 A. J. Salinas and M. Vallet-Regí, Bioactive ceramics: From bone grafts to tissue engineering, *RSC Adv.*, 2013, **3**(28), 11116–11131.
- 36 H. Li, L. Yang, X. Dong, Y. Gu, G. Lv and Y. Yan, Composite scaffolds of nano calcium deficient hydroxyapatite/multi-(amino acid) copolymer for bone tissue regeneration, *J. Mater. Sci.: Mater. Med.*, 2014, **25**(5), 1257–1265.
- 37 J. Venkatesan and S. K. Kim, Nano-hydroxyapatite composite biomaterials for bone tissue engineering-A review, *J. Biomed. Nanotechnol.*, 2014, **10**(10), 3124–3140.
- 38 C. B. Danoux, D. Barbieri, H. Yuan, J. D. de Bruijn, C. A. van Blitterswijk and P. Habibovic, In vitro and *in vivo* bioactivity assessment of a polylactic acid/hydroxyapatite composite for bone regeneration, *Biomater.*, 2014, **4**(1), e27664.
- 39 Q. Tan, X. Jiang, L. Chen, J. Huang, Q. Zhou, J. Wang, Y. Zhao, B. Zhang, Y. Sun, M. Wei, X. Zhao, Z. Yang, W. Lei, Y. Tang and Z. Wu, Bioactive graphene oxide-functionalized self-expandable hydrophilic and osteogenic nanocomposite for orthopaedic applications, *Mater. Today Bio*, 2023, **18**, 100500.
- 40 J. Orr and N. J. Dunne, Measurement of shrinkage stresses in PMMA bone cement, *Appl. Mech. Mater.*, 2004, **1**, 127–132.
- 41 A. B. Lennon and P. J. Prendergast, Residual stress due to curing can initiate damage in porous bone cement: experimental and theoretical evidence, *J. Biomech.*, 2002, **35**(3), 311–321.
- 42 R. T. Müller and N. Schürmann, Shear strength of the cement metal interface-an experimental study, *Arch. Orthop. Unfall-Chir.*, 1999, **119**(3), 133–138.
- 43 A. R. Greenberg and I. Kamel, Polymer-ceramic composite for tooth-root implant, *J. Biomed. Mater. Res.*, 1976, **10**(5), 777–788.
- 44 L. F. Boesel, J. F. Mano and R. L. Reis, Optimization of the formulation and mechanical properties of starch based partially degradable bone cements, *J. Mater. Sci.: Mater. Med.*, 2004, **15**(1), 73–83.
- 45 L. F. Boesel and R. L. Reis, Hydrophilic matrices to be used as bioactive and degradable bone cements, *J. Mater. Sci.: Mater. Med.*, 2004, **15**(4), 503–506.
- 46 L. Chen, S. Zhang, B. Zhang, Q. Liang, D. Luo, X. Yu, B. Yao, K. Zhao, Z. Yang, Y. Tang and Z. Wu, Study on the poly(methyl methacrylate-acrylic acid)/calcium phosphate cement composite bound by chelation with enhanced water absorption and biomechanical properties, *J. Mech. Behav. Biomed. Mater.*, 2023, **147**, 106149.
- 47 Y. Nien and J. Chen, Studies of the mechanical and thermal properties of cross-linked poly(methylmethacrylate-acrylic acid-allylmethacrylate)-modified bone cement, *J. Appl. Polym. Sci.*, 2006, **100**(5), 3727–3732.
- 48 L. Chen, Y. Tang, K. Zhao, J. Liu, H. Bai and Z. Wu, Absorptive and expansive behaviors of poly (methyl methacrylate-co-acrylic acid) bone cement, *Colloids Surf., B*, 2020, **189**, 110848.
- 49 F. A. Long and D. Richman, Concentration gradients for diffusion of vapors in glassy polymers and their relation to time dependent diffusion phenomena^{1,2}, *J. Am. Chem. Soc.*, 1960, **82**(3), 513–519.
- 50 D. Richman and F. A. Long, Measurement of concentration gradients for diffusion of vapors in polymers^{1,2}, *J. Am. Chem. Soc.*, 1960, **82**(3), 509–513.
- 51 L. Chen, Y. Tang, K. Zhao, J. Liu, M. Jiao, H. Bai and Z. Wu, HEMA-modified expandable P(MMA-AA) bone cement with dual water absorption networks, *Macromol. Mater. Eng.*, 2020, **305**(3), 1900752.
- 52 Y. Tang, L. Chen, Z. Wu, K. Zhao and Q. Tan, Fabrication of injectable and expandable PMMA/PAASf bone cements, *Compos. Sci. Technol.*, 2017, **146**, 203–209.



- 53 Z. Yang, L. Chen, Y. Hao, Y. Zang, X. Zhao, L. Shi, Y. Zhang, Y. Feng, C. Xu, F. Wang, X. Wang, B. Wang, C. Liu, Y. Tang, Z. Wu and W. Lei, Synthesis and characterization of an injectable and hydrophilous expandable bone cement based on poly(methyl methacrylate), *ACS Appl. Mater. Interfaces*, 2017, **9**(46), 40846–40856.
- 54 Y. Ma, R. Wang, X. Cheng, Z. Liu and Y. Zhang, The behavior of new hydrophilic composite bone cements for immediate loading of dental implant, *J. Wuhan Univ. Technol., Mater. Sci. Ed.*, 2013, **28**(3), 627–633.
- 55 Y. Sugita, T. Okubo, M. Saita, M. Ishijima, Y. Torii, M. Tanaka, C. Iwasaki, T. Sekiya, M. Tabuchi, N. M. Rezaei, T. Taniyama, N. Sato, J. Saruta, M. Hasegawa, M. Hirota, W. Park, M. C.-I. Lee, H. Maeda and T. Ogawa, Novel osteogenic behaviors around hydrophilic and radical-free 4-META/MMA-TBB: Implications of an osseointegrating bone cement, *Int. J. Mol. Sci.*, 2020, **21**(7), 2405.
- 56 B. Pascual, M. Gurruchaga, M. P. Ginebra, F. J. Gil, J. A. Planell, B. Vázquez, J. San Román and I. Goñi, Modified acrylic bone cement with high amounts of ethoxytriethyleneglycol methacrylate, *Biomaterials*, 1999, **20**(5), 453–463.
- 57 L. Chen, Y. Tang, K. Zhao, J. Liu, X. Jiang, Y. Sun, Y. Zhao, Q. Tan, Z. Yang and Z. Wu, High water-absorbent and fast-expanding PMMA bone cement with double-bridged structure, *J. Appl. Polym. Sci.*, 2021, **138**(21), 50464.
- 58 L. F. Boesel, J. F. Mano, C. Elvira, J. San Roman, and R. L. Reis, in *Hydrogels and Hydrophilic Partially Degradable Bone Cements Based on Biodegradable Blends Incorporating Starch*, ed. E. Chiellini and R. Solaro, Biodegradable Polymers and Plastics, Springer, Boston, MA, 2003.
- 59 D. De Kee, Q. Liu and J. Hinestroza, Viscoelastic (Non-Fickian) Diffusion, *Can. J. Chem. Eng.*, 2005, **83**(6), 913–929.
- 60 R. Razuin, O. Effat, M. Shahidan, D. Shama and M. Miswan, Bone cement implantation syndrome, *Malays. J. Pathol.*, 2013, **35**(1), 87.
- 61 J. A. Hidalgo, C. G. Reddy, G. D. Schmit and R. J. Spinner, Sciatic neuropathy after extruded cement from cementoplasty, *Spine*, 2012, **12**(6), 532–533.
- 62 P. Lai, C. Tai, L. Chen and N. Nien, Cement leakage causes potential thermal injury in vertebroplasty, *BMC Musculoskeletal Disord.*, 2011, **12**(1), 116.
- 63 C. D. Jefferiss, A. J. C. Lee and R. S. M. Ling, Thermal aspects of self-curing polymethylmethacrylate, *J. Bone Jt. Surg., Br. Vol.*, 1975, **57-B**(4), 511–518.
- 64 X. Xie, D. Li, T. Tsai, J. Liu, P. V. Braun and D. G. Cahill, Thermal conductivity, heat capacity, and elastic constants of water-soluble polymers and polymer blends, *Macromolecules*, 2016, **49**(3), 972–978.
- 65 J. Yang, Study of polymerization of acrylic bone cement: Effect of HEMA and EGDMA, *J. Biomed. Mater. Res.*, 1998, **43**(1), 54–61.
- 66 L. F. Boesel and R. L. Reis, A review on the polymer properties of hydrophilic, partially degradable and bioactive acrylic cements (HDBC), *Prog. Polym. Sci.*, 2008, **33**(2), 180–190.
- 67 L. F. Boesel, M. H. V. Fernandes and R. L. Reis, The behavior of novel hydrophilic composite bone cements in simulated body fluids, *J. Biomed. Mater. Res., Part B*, 2004, **70B**(2), 368–377.
- 68 K. MacDonald, R. B. Price and D. Boyd, The feasibility and functional performance of ternary borate-filled hydrophilic bone cements: targeting therapeutic release thresholds for strontium, *J. Funct. Biomater.*, 2017, **8**(3), 28.
- 69 P. A. Leggat and U. Kedjarune, Toxicity of methyl methacrylate in dentistry, *Int. Dent. J.*, 2003, **53**(3), 126–131.
- 70 M. Kostic, A. Pejic, M. Igic and N. Gligorijevic, Adverse reactions to denture resin materials, *Eur. Rev. Med. Pharmacol. Sci.*, 2017, **21**(23), 5298–5305.
- 71 T. M. Hamdy, Modification of polymethylmethacrylate bone cement with halloysite clay nanotubes, *BMC Oral Health*, 2024, **24**(1), 893.
- 72 A. Boger, M. Bohner, P. Heini, S. Verrier and E. Schneider, Properties of an injectable low modulus PMMA bone cement for osteoporotic bone, *J. Biomed. Mater. Res., Part B*, 2008, **86B**(2), 474–482.
- 73 S. A. Naghavi, C. Lin, C. Sun, M. Tamaddon, M. Basiouny, P. Garcia-Souto, S. Taylor, J. Hua, D. Li and L. Wang, Stress shielding and bone resorption of press-fit polyether-ether-ketone (PEEK) hip prosthesis: A sawbone model study, *Polymers*, 2022, **14**(21), 4600.
- 74 C. H. Turner, On Wolff's law of trabecular architecture, *J. Biomech.*, 1992, **25**(1), 1–9.
- 75 H. Jiang, J. Xu, Z. Qiu, X. Ma, Z. Zhang, X. Tan, Y. Cui and F. Cui, Mechanical properties and cytocompatibility improvement of vertebroplasty PMMA bone cements by incorporating mineralized collagen, *Materials*, 2015, **8**(5), 2616–2634.
- 76 G. Baroud, J. Nemes, P. Heini and T. Steffen, Load shift of the intervertebral disc after a vertebroplasty: A finite-element study, *Eur. Spine J.*, 2003, **12**(4), 421–426.
- 77 G. Baroud and M. Bohner, Biomechanical impact of vertebroplasty, *Jt., Bone, Spine*, 2006, **73**(2), 144–150.
- 78 D. Xu, W. Song, J. Zhang, Y. Liu, Y. Lu, X. Zhang, Q. Liu, T. Yuan and R. Liu, Osteogenic effect of polymethyl methacrylate bone cement with surface modification of lactoferrin, *J. Biosci. Bioeng.*, 2021, **132**(2), 132–139.
- 79 F. Ghasemi, A. Jahani, A. Moradi, M. H. Ebrahimzadeh and N. Jirofti, Different modification methods of poly methyl methacrylate (PMMA) bone cement for orthopedic surgery applications, *Arch. Bone Jt. Surg.*, 2023, **11**(8), 485–492.
- 80 J. S. Weinger and S. A. Strobel, Participation of the tRNA A76 hydroxyl groups throughout translation, *Biochemistry*, 2006, **45**(19), 5939–5948.
- 81 B. Singh and A. Dhiman, Designing bio-mimetic moxifloxacin loaded hydrogel wound dressing to improve antioxidant and pharmacology properties, *RSC Adv.*, 2015, **5**(55), 44666–44678.
- 82 K. Şarkaya, G. Akıncioğlu and S. Akıncioğlu, Investigation of tribological properties of HEMA-based cryogels as



- potential articular cartilage biomaterials, *Polym.-Plast. Technol. Mater.*, 2022, **61**(11), 1174–1190.
- 83 A. Hejčl, J. Růžicka, K. Kekulová, B. Svobodová, V. Proks, H. Macková, K. Jiráňková, K. Kárová, L. Machová Urdziková, Š. Kubinová, J. Cihlář, D. Horák and P. Jendelová, Modified methacrylate hydrogels improve tissue repair after spinal cord injury, *Int. J. Mol. Sci.*, 2018, **19**(9), 2481.
 - 84 A. Sugino, C. Ohtsuki and T. Miyazaki, In vivo response of bioactive PMMA-based bone cement modified with alkoxysilane and calcium acetate, *J. Biomater. Appl.*, 2008, **23**(3), 213–228.
 - 85 D. Kabaso, E. Gongadze, Š. Perutková, C. Matschegewski, V. Kralj-Iglič, U. Beck, U. van Rienen and A. Iglič, Mechanics and electrostatics of the interactions between osteoblasts and titanium surface, *Comput. Methods Biomech. Biomed. Eng.*, 2011, **14**(5), 469–482.
 - 86 L. Chen, J. M. Mccrate, J. C. Lee and H. Li, The role of surface charge on the uptake and biocompatibility of hydroxyapatite nanoparticles with osteoblast cells, *Nanotechnology*, 2011, **22**(10), 105708.
 - 87 M. Fernández-Yagüe, R. P. Antónanzas, J. J. Roa, M. Biggs, F. J. Gil and M. Pegueroles, Enhanced osteoconductivity on electrically charged titanium implants treated by physicochemical surface modifications methods, *J. Nanomed. Nanotechnol.*, 2019, **18**, 1–10.
 - 88 C. A. Scotchford, C. P. Gilmore, E. Cooper, G. J. Leggett and S. Downes, Protein adsorption and human osteoblast-like cell attachment and growth on alkylthiol on gold self-assembled monolayers, *J. Biomed. Mater. Res.*, 2002, **59**(1), 84–99.
 - 89 R. L. Sammons, N. Lumbikanonda, M. Gross and P. Cantzler, Comparison of osteoblast spreading on microstructured dental implant surfaces and cell behaviour in an explant model of osseointegration, *Clin. Oral Implants Res.*, 2005, **16**(6), 657–666.
 - 90 R. Fraioli, F. Rechenmacher, S. Neubauer, J. M. Manero, J. Gil, H. Kessler and C. Mas-Moruno, Mimicking bone extracellular matrix: Integrin-binding peptidomimetics enhance osteoblast-like cells adhesion, proliferation, and differentiation on titanium, *Colloids Surf., B*, 2015, **128**, 191–200.
 - 91 S. Mollazadeh, J. Javadpour and A. Khavandi, In situ synthesis and characterization of nano-size hydroxyapatite in poly(vinyl alcohol) matrix, *Ceram. Int.*, 2007, **33**(8), 1579–1583.
 - 92 S. Zhang, X. Ma, D. Sha, J. Qian, Y. Yuan and C. Liu, A novel strategy for tumor therapy: Targeted, PAA-functionalized nano-hydroxyapatite nanomedicine, *J. Mater. Chem. B*, 2020, **8**(41), 9589–9600.
 - 93 T. Miyazaki, C. Ohtsuki, M. Kyomoto, M. Tanihara, A. Mori and K. i. Kuramoto, Bioactive PMMA bone cement prepared by modification with methacryloxypropyltrimethoxysilane and calcium chloride, *J. Biomed. Mater. Res., Part A*, 2003, **67A**(4), 1417–1423.
 - 94 P. Feng, S. Peng, C. Shuai, C. Gao, W. Yang, S. Bin and A. Min, In situ generation of hydroxyapatite on biopolymer particles for fabrication of bone scaffolds owning bioactivity, *ACS Appl. Mater. Interfaces*, 2020, **12**(41), 46743–46755.
 - 95 M. Tanahashi and T. Matsuda, Surface functional group dependence on apatite formation on self-assembled monolayers in a simulated body fluid, *J. Biomed. Mater. Res.*, 1997, **34**(3), 305–315.
 - 96 S. Ferraris, S. Yamaguchi, N. Barbani, M. Cazzola, C. Cristallini, M. Miola, E. Vernè and S. Spriano, Bioactive materials: *In vitro* investigation of different mechanisms of hydroxyapatite precipitation, *Acta Biomater.*, 2020, **102**, 468–480.
 - 97 W. P. Inskeep and J. C. Silvertooth, Kinetics of hydroxyapatite precipitation at pH 7.4 to 8.4, *Geochim. Cosmochim. Acta*, 1988, **52**(7), 1883–1893.
 - 98 M. A. Puska, T. O. Närhi, A. J. Aho, A. Yli-Urpo and P. K. Vallittu, Flexural properties of crosslinked and oligomer-modified glass-fibre reinforced acrylic bone cement, *J. Mater. Sci.: Mater. Med.*, 2004, **15**(9), 1037–1043.
 - 99 M. A. Puska, L. V. Lassila, T. O. Närhi, A. U. O. Yli-Urpo and P. K. Vallittu, Improvement of mechanical properties of oligomer-modified acrylic bone cement with glass-fibers, *Appl. Compos. Mater.*, 2004, **11**(1), 17–31.
 - 100 S. Priyadarsini, S. Mohanty, S. Mukherjee, S. Basu and M. Mishra, Graphene and graphene oxide as nanomaterials for medicine and biology application, *J. Nanostruct. Chem.*, 2018, **8**(2), 123–137.
 - 101 X. Ma, Y. Li, W. Wang, Q. Ji and Y. Xia, Temperature-sensitive poly(N-isopropylacrylamide)/graphene oxide nanocomposite hydrogels by *in situ* polymerization with improved swelling capability and mechanical behavior, *Eur. Polym. J.*, 2013, **49**(2), 389–396.
 - 102 R. Eivazzadeh-Keihan, A. Maleki, M. De La Guardia, M. S. Bani, K. K. Chenab, P. Pashazadeh-Panahi, B. Baradaran, A. Mokhtarzadeh and M. R. Hamblin, Carbon based nanomaterials for tissue engineering of bone: Building new bone on small black scaffolds: A review, *J. Adv. Res.*, 2019, **18**, 185–201.
 - 103 H. Ma, W. Su, Z. Tai, D. Sun, X. Yan, B. Liu and Q. Xue, Preparation and cytocompatibility of polylactic acid/hydroxyapatite/graphene oxide nanocomposite fibrous membrane, *Chin. Sci. Bull.*, 2012, **57**(23), 3051–3058.
 - 104 G. Gonçalves, S. M. A. Cruz, A. Ramalho, J. Grácio and P. A. A. P. Marques, Graphene oxide *versus* functionalized carbon nanotubes as a reinforcing agent in a PMMA/HA bone cement, *Nanoscale*, 2012, **4**(9), 2937–2945.
 - 105 E. Paz, F. Forriol, J. C. del Real and N. Dunne, Graphene oxide *versus* graphene for optimisation of PMMA bone cement for orthopaedic applications, *Mater. Sci. Eng., C*, 2017, **77**, 1003–1011.
 - 106 F. Pahlevanzadeh, H. R. Bakhsheshi-Rad, M. Kharaziha, M. Kasiri-Asgarani, M. Omidi, M. Razzaghi, A. F. Ismail, S. Sharif, S. RamaKrishna and F. Berto, CNT and rGO reinforced PMMA based bone cement for fixation of load bearing implants: Mechanical property and biological response, *J. Mech. Behav. Biomed. Mater.*, 2021, **116**, 104320.



- 107 S. Soleymani Eil Bakhtiari, H. R. Bakhsheshi-Rad, S. Karbasi, M. Tavakoli, M. Razzaghi, A. F. Ismail, S. RamaKrishna and F. Berto, Polymethyl methacrylate-based bone cements containing carbon nanotubes and graphene oxide: An overview of physical, mechanical, and biological properties, *Polymers*, 2020, **12**(7), 1469.
- 108 L. Chen, Y. Tang, K. Zhao, J. Liu, X. Jiang, Y. Sun and Z. Wu, Rapid self-expansion behavior of the PMMA-based bone cement with P(MMA-AA)-GO nano-units, *Macromol. Mater. Eng.*, 2021, **306**(4), 2000749.
- 109 E. Paz, Y. Ballesteros, J. Abenojar, J. Del Real and N. J. Dunne, Graphene oxide and graphene reinforced PMMA bone cements: Evaluation of thermal properties and biocompatibility, *Materials*, 2019, **12**(19), 3146.
- 110 E. H. Mirza, A. A. Khan, A. A. Al-Khureif, S. A. Saadaldin, B. A. Mohamed, F. Fareedi, M. M. Khan, M. Alfayez, R. Al-Fotawi, P. K. Vallittu and A. Mahmood, Characterization of osteogenic cells grown over modified graphene-oxide-biostable polymers, *Biomed. Mater.*, 2019, **14**(6), 065004.
- 111 W. C. Lee, C. H. Y. X. Lim, H. Shi, L. A. L. Tang, Y. Wang, C. T. Lim and K. P. Loh, Origin of enhanced stem cell growth and differentiation on graphene and graphene oxide, *ACS Nano*, 2011, **5**(9), 7334–7341.
- 112 L. Wang, J. Qiu, J. Guo, D. Wang, S. Qian, H. Cao and X. Liu, Regulating the behavior of human gingival fibroblasts by sp² domains in reduced graphene oxide, *ACS Biomater. Sci. Eng.*, 2019, **5**(12), 6414–6424.
- 113 J. Yang, K. Y. Hsieh, P. V. Kumar, S. J. Cheng, Y. Lin, Y. C. Shen and G. Y. Chen, Enhanced osteogenic differentiation of stem cells on phase-engineered graphene oxide, *ACS Appl. Mater. Interfaces*, 2018, **10**(15), 12497–12503.
- 114 Z. Li, S. Xiang, Z. Lin, E. N. Li, H. Yagi, G. Cao, L. Yocum, L. Li, T. Hao, K. K. Bruce, M. R. Fritch, H. Hu, B. Wang, P. G. Alexander, K. A. Khor, R. S. Tuan and H. Lin, Graphene oxide-functionalized nanocomposites promote osteogenesis of human mesenchymal stem cells *via* enhancement of BMP-SMAD1/5 signaling pathway, *Biomaterials*, 2021, **277**, 121082.
- 115 S. Ratanasathien, J. C. Wataha, C. T. Hanks and J. B. Dennison, Cytotoxic interactive effects of dentin bonding components on mouse fibroblasts, *J. Dent. Res.*, 1995, **74**(9), 1602–1606.
- 116 F. Huang and Y. Chang, Prevention of the epoxy resin-based root canal sealers-induced cyclooxygenase-2 expression and cytotoxicity of human osteoblastic cells by various antioxidants, *Biomaterials*, 2005, **26**(14), 1849–1855.
- 117 S. B. Goodman, J. Schatzker, G. Sumner-Smith, V. L. Fornasier, N. Goften and C. Hunt, The effect of polymethylmethacrylate on bone: An experimental study, *Arch. Orthop. Trauma. Surg.*, 1985, **104**(3), 150–154.
- 118 N. A. Johanson, P. G. Bullough, P. D. J. Wilson, E. A. Salvati and C. S. Ranawat, The microscopic anatomy of the bone-cement interface in failed total hip arthroplasties, *Clin. Orthop.*, 1987, **218**, 123–135.
- 119 M. Bhandari, H. Koo, L. Saunders, S. G. Shaughnessy, R. B. Dunlop and E. H. Schemitsch, Predictors of in-hospital mortality following operative management of hip fractures, *Int. J. Surg. Invest.*, 1999, **1**(4), 319–326.
- 120 N. Tsukimura, M. Yamada, H. Aita, N. Hori, F. Yoshino, M. Chang-Il Lee, K. Kimoto, A. Jewett and T. Ogawa, N-acetyl cysteine (NAC)-mediated detoxification and functionalization of poly(methyl methacrylate) bone cement, *Biomaterials*, 2009, **30**(20), 3378–3389.
- 121 H. Aita, N. Tsukimura, M. Yamada, N. Hori, K. Kubo, N. Sato, H. Maeda, K. Kimoto and T. Ogawa, N-acetyl cysteine prevents polymethyl methacrylate bone cement extract-induced cell death and functional suppression of rat primary osteoblasts, *J. Biomed. Mater. Res., Part A*, 2010, **92A**(1), 285–296.
- 122 C. A. Lang, S. Naryshkin, D. L. Schneider, B. J. Mills and R. D. Lindeman, Low blood glutathione levels in healthy aging adults, *J. Lab. Clin. Med.*, 1992, **120**(5), 720–725.
- 123 C. Hirabayashi, Y. Imai and I. Studies on MMA-TBB resin, Comparison of TBB and other initiators in the polymerization of PMMA/MMA resin, *Dent. Mater. J.*, 2002, **21**(4), 314–321.
- 124 K. Nakagawa, M. Saita, T. Ikeda, M. Hirota, W. Park, M. Chang-Il Lee and T. Ogawa, Biocompatibility of 4-META/MMA-TBB resin used as a dental luting agent, *J. Prosthet. Dent.*, 2015, **114**(1), 114–121.
- 125 H. Kitagawa, K. Takeda, R. Tsuboi, M. Hayashi, J. i. Sasaki and S. Imazato, Influence of polymerization properties of 4-META/MMA-based resin on the activity of fibroblast growth factor-2, *Dent. Mater. J.*, 2017, **36**(6), 724–730.
- 126 S. Tanaka, T. Sugaya, M. Kawanami, Y. Nodasaka, T. Yamamoto, H. Noguchi, Y. Tanaka, T. Ikeda, H. Sano and S. K. Sidhu, Hybrid layer seals the cementum/4-META/MMA-TBB resin interface, *J. Biomed. Mater. Res., Part B*, 2007, **80B**(1), 140–145.
- 127 N. Nakabayashi, A. Watanabe and N. J. Gendusa, Dentin adhesion of “modified” 4-META/MMA-TBB resin: function of HEMA, *Dent. Mater.*, 1992, **8**(4), 259–264.
- 128 E. J. Oh, S. H. Oh, I. S. Lee, O. S. Kwon and J. H. Lee, Antibiotic-eluting hydrophilized PMMA bone cement with prolonged bactericidal effect for the treatment of osteomyelitis, *J. Biomater. Appl.*, 2016, **30**(10), 1534–1544.
- 129 L. Chen, Y. Tang, K. Zhao, X. Zha, J. Liu, H. Bai and Z. Wu, Fabrication of the antibiotic-releasing gelatin/PMMA bone cement, *Colloids Surf., B*, 2019, **183**, 110448.
- 130 Y. Nien, S. Lin and Y. Hsu, Preparation and characterization of acrylic bone cement with high drug release, *Mater. Sci. Eng., C*, 2013, **33**(2), 974–978.
- 131 G. T. Ensing, J. R. van Horn, H. C. van der Mei, H. J. Busscher and D. Neut, Copal bone cement is more effective in preventing biofilm formation than Palacos RG, *Clin. Orthop.*, 2008, **466**, 1492–1498.
- 132 K. Anagnostakos and J. Kelm, Enhancement of antibiotic elution from acrylic bone cement, *J. Biomed. Mater. Res., Part B*, 2009, **90**(1), 467–475.
- 133 V. Wall, T. H. Nguyen, N. Nguyen and P. A. Tran, Controlling antibiotic release from polymethylmethacrylate bone cement, *Biomedicines*, 2021, **9**(1), 26.



- 134 M. Shi, J. D. Kretlow, P. P. Spicer, Y. Tabata, N. Demian, M. E. Wong, F. K. Kasper and A. G. Mikos, Antibiotic-releasing porous polymethylmethacrylate/gelatin/antibiotic constructs for craniofacial tissue engineering, *J. Controlled Release*, 2011, **152**(1), 196–205.
- 135 L. Chen, Y. Tang, K. Zhao, X. Yu, B. Yao, X. Li, X. Zha, B. Zhang, Q. Tan, Z. Yang and Z. Wu, Self-expanding PMMA composite bone cement with sustained release of gentamicin sulfate and alendronate using water absorption pathways, *Mater. Des.*, 2022, **222**, 111081.
- 136 X. Zhao, J. Gao, H. Han, X. Lou, H. Ma, X. Su, L. Zhang, J. Tian, B. Lei and Y. Zhang, Bioactive strong biodegradable bone cement for rapid osteointegration and osteogenesis, *Chem. Eng. J.*, 2023, **474**, 145609.
- 137 L. F. Boesel, S. C. P. Cachinho, M. H. V. Fernandes and R. L. Reis, The *in vitro* bioactivity of two novel hydrophilic, partially degradable bone cements, *Acta Biomater.*, 2007, **3**(2), 175–182.
- 138 L. F. Boesel, H. S. Azevedo and R. L. Reis, Incorporation of α -amylase enzyme and a bioactive filler into hydrophilic, partially degradable, and bioactive cements (HDBC)s as a new approach to tailor simultaneously their degradation and bioactive behavior, *Biomacromolecules*, 2006, **7**(9), 2600–2609.
- 139 A. C. Mendes, L. F. Boesel and R. L. Reis, Degradation studies of hydrophilic, partially degradable and bioactive cements (HDBC)s incorporating chemically modified starch, *J. Mater. Sci.: Mater. Med.*, 2012, **23**(3), 667–676.
- 140 B. Liu, M. Li, B. Yin, J. Zou, W. Zhang and S. Wang, Effects of incorporating carboxymethyl chitosan into PMMA bone cement containing methotrexate, *PLoS One*, 2015, **10**(12), e0144407.
- 141 T. Li, X. Weng, Y. Bian, L. Zhou, F. Cui and Z. Qiu, Influence of nano-HA coated bone collagen to acrylic (polymethylmethacrylate) bone cement on mechanical properties and bioactivity, *PLoS One*, 2015, **10**(6), e0129018.
- 142 S. B. Kim, Y. J. Kim, T. L. Yoon, S. A. Park, I. H. Cho, E. J. Kim, I. A. Kim and J. W. Shin, The characteristics of a hydroxyapatite-chitosan-PMMA bone cement, *Biomaterials*, 2004, **25**(26), 5715–5723.
- 143 L. L. Hench and J. M. Polak, Third-generation biomedical materials, *Science*, 2002, **295**(5557), 1014–1017.
- 144 C. Ning, L. Zhou and G. Tan, Fourth-generation biomedical materials, *Mater. Today*, 2016, **19**(1), 2–3.

