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Injectable biomaterials for minimally invasive orthopedic treatments

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Abstract Biodegradable and injectable hydroxy terminated-poly propylene fumarate (HT-PPF) bone cement was developed. The injectable formulation consisting HT-PPF and comonomer, *n*-vinyl pyrrolidone, calcium phosphate filler, free radical catalyst, accelerator and radiopaque agent sets rapidly to hard mass with low exothermic temperature. The candidate bone cement attains mechanical strength more than the required compressive strength of 5 MPa and compressive modulus 50 MPa. The candidate bone cement resin elicits cell adhesion and cytoplasmic spreading of osteoblast cells. The cured bone cement does not induce intracutaneous irritation and skin sensitization. The candidate bone cement is tissue compatible without eliciting any adverse tissue reactions. The candidate bone cement is osteoconductive and inductive and allow osteointegration and bone remodeling. HT-PPF bone cement is candidate bone cement for minimally invasive radiological procedures for the treatment of bone diseases and spinal compression fractures.

1 Introduction

Treatment of orthopedic bone disease originated from osseous tumors, trauma, disease, congenital defects, etc., is carried out with allograft, autograft and synthetic bone cement materials. However, allograft, autograft and synthetic bone cement materials are associated with major drawbacks. Human allograft bone is difficult to mould into the shape of bone defect and also carries the possibility of pathogen transfer from the donor. In the case of autograft, donor site morbidity and limited supply of bone graft has restricted the use of autograft.

There are a number of drawbacks associated with the invasive surgical procedures employed in the treatment of bone disease and fracture repair in orthopedic surgery viz long hospitalization, arthrotomy involving resecting tissue through skin, vessels, muscles, ligaments, tendons, and/or joint capsules, need for general or spinal anesthesia and blood transfusions and prolonged physical therapy. In order to avoid the problems associated with the invasive surgical procedures, the minimally-invasive radiological procedures can be adopted with bone cement.

Treatment of orthopedic bone disease and fractures is carried out successfully with minimally-invasive radiological procedures using bone cement. Fracture repair in osteoporosis patients with compression fractures in the spine and also the fracture repair in pelvis and hip are the major challenges in orthopedic surgery. Primary and secondary osteoporosis results in vertebral and intervertebral disc compression fractures. Percutaneous vertebroplasty, has been used for the treatment of osteoporotic fractures and stabilization of osteoporotic vertebral bodies in spine. This technique prevents the vertebral area from further collapse by augmenting strength in the vertebral bodies of the spine.

Non-biodegradable and radiopaque cement, consisting powdered polymethyl methacrylate polymer component and liquid methyl methacrylate monomer was developed for orthopedic applications. Various investigators [1–3] have fabricated the apparatus to mix powdered polymethyl methacrylate and liquid methyl methacrylate monomer and

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other ingredients and to deliver the bone cement. Fibre and particulate-reinforced bone cements were also developed by some investigators for the improvement of mechanical properties [4–6]. However, synthetic bone cement based on PMMA is associated with major drawbacks [7–10]. High incidence of radiographic loosening of the components and accumulation of fatigue damage lead to loosening at the bone cement–bone interface. A complete radiolucent line of $\sim$2 mm in width appears at the bone–cement/prosthesis–bone interface with Intervening soft-tissue layer. Such condition leads to accumulation of fatigue damage. PMMA is also vulnerable to bone lysis secondary to fragmentation of the cement, thermal necrosis and monomer toxicity and adverse host reactions. Moreover PMMA bone cement, being biologically inert, and acts as a barrier to fracture healing and does not permit direct bonding by host bone.

Currently non-biodegradable bone cement based on PMMA is used for percutaneous vertebroplasty and treatment of vertebral haemangioma. Mendec Spine Acrylic resin[@] by M/S Tecres S.p.A Spineplex Radiopaue bone cement (K032945) by M/S Stryker are marketed. Drawbacks of PMMA in percutaneous vertebroplasty are extravasation of PMMA cement in epidural or foraminal region which leads to nerve root compression and radiculopathy. Extravasation of PMMA cement in perivertebral veins leads to embolism to the lungs and deaths. Balloon Kyphoplasty has been introduced with Kyphx HV-R bone cement (K033801 and K041584) and balloon kyhoplasty kit by M/S Kyphon Inc., Sunnyvale, CA. Drawbacks of PMMA in balloon Kyphoplasty procedure are tissue necrosis and inflammation due to exothermic reaction (60–70°C) and unreacted toxic monomer. Moreover secondary osteoporotic patients are at increased risk for subsequent vertebral compression fractures compared to primary osteoporotic patients. Calcium phosphate cements were experimented by some entrepreneurs [11, 12]. Coral-derived calcium phosphate cements and mouldable calcium phosphate putty has been prepared and experimented. However these cements are more appropriate as a filler to augment the allograft tissue rather than as a stand-alone bone substitute. A putty of demineralised bone matrix, calcium sulphate and plasticising agent has been prepared and experimented. However this material has the drawbacks such as difficult in processing of demineralised bone matrix from donor bone under stringent screening conditions and immune responses.

Biodegradable polymers and composites have more advantages over the non-biodegradables. Polyglycolide and polylactide have been used for several biomedical applications viz bone fixation [13], surgical suture [14], scaffold for tissue engineering [15, 16], matrix for controlled drug release [17] and as bone substitution material [18–20]. FDA has approved PLA and PLGA based bone fixation devices (anchor system, Inion ANCHRON^{TM}), PDS/PGA Staple (Mitek) and pins and screws (ReFIX^{TM} Xtremi-T, LLC). However the success of polyglycolide and polylactide implants largely depends on the mechanical properties and biological lifetime. Biological lifetime depends on the degree of polymerization and crystallinity and control of inflammatory process in the vicinity of the implant. PLA and PLGA undergo excessive biodegradation and liberation of acidic components at the vicinity of degradation site leading to tissue necrosis. Moreover, these polymers can not be used as an injectable system for minimally-invasive surgical procedures.

Biodegradable and injectable polymeric bone cements are new developments for the treatment of bone diseases and fracture repair in bone. The advantages of degradable materials are (i) they do not have to be removed after use by secondary surgery because degradation products formed can be excreted from the body through natural pathways, (ii) progressive loss of degradable implant material will lead to regeneration of bone by osteoblasts. Injectable bone cement is more capable of penetrating the trabeculae of bones leading to better fixation of bones under the minimally invasive surgical technique. Biodegradable bone cement polymers could be designed to degrade in vivo in a controlled manner over a predetermined period.

Unsaturated polyester poly(propylene fumarate) (PPF) has been considered as one of the potential biodegradable polymers for bone cement. Jayabalan et al. [21–23] has prepared poly(propylene fumarate-co-ethylene glycol) and evaluated for the use as scaffold for correcting the bone defects. For the success of the repairs of bone disease, complete restoration of function with growth of new bone has to be established. Therefore it is important to design dispensable and biodegradable polymeric bone cement using appropriate monomers to achieve optimum mechanical properties, bioactivity and biodegradability. For better penetration of bone cement, the bone cement having viscosity in the range of 1000–2000 poise and good setting characteristics is required. Injectable bone cement based on hydroxy terminated-polypropylene fumarate was developed using a new method of synthesis for polypropylene fumarate. The paper deals with the salient features of the novel biodegradable and injectable bone cement.

2 Materials and methods

2.1 Preparation of hydroxy terminated-poly(propylene fumarate) resin

Hydroxy terminated-poly(propylene fumarate) (HT-PPF) was synthesized by reacting maleic anhydride with 1–2, propylene glycol under high temperature, 200°C and

vacuum conditions for 2 h. The reaction was catalyzed by sodium acetate and morpholine. The reaction product was dissolved in acetone and then washed with 25% aqueous methanol to remove unreacted reactants. The polymer was reprecipitated in petroleum ether, filtered and dried under vacuum. A highly viscous, yellowish brown and transparent resin was obtained.

Spectral analysis of HT-PPF was carried out using FTIR spectrometer of 6300 type A by NaCl window. The viscosity of the resin was determined in by Brookfield Viscometer at 27°C. The molecular weight and polydispersity of HT-PPF resin were determined using waters HPLC system. Styragel-HR-5E/4E/2/0.5 columns in series with mobile phase tetrahydrofuran were used.

2.2 Preparation and evaluation of physico-chemical and mechanical properties of HT-PPF bone cement

Sterile injectable HT-PPF bone cement was prepared by blending with sterile HT-PPF and biocompatible comonomer *n*-vinyl pyrrolidone, calcium phosphate filler, free radical catalyst, accelerator and radiopaque agent under room temperature. Physico-chemical properties of the bone cement viz setting and polymerization time and crosslink density was determined. Setting time, exothermic temperature and hardening time were determined as per ISO 5833/1-1999 E Standard. For setting experiments, HT-PPF bone cement mixture was prepared by blending with all above mentioned ingredients under room temperature and allowed to set. While setting, the initial temperature, T_0, and maximum exothermic temperature, T_{max}, were noted. The average temperature was determined by taking half the sum of T_0 and T_{max}. The time taken to reach the average temperature was considered as setting time. Setting time, exothermic temperature and final hardening time were recorded.

Crosslink density of cured HT-PPF bone cement was determined by swelling experiments. The cured sample was immersed in solvents, dimethyl acetamide, dimethyl formamide, toluene, tetrahydrofuran, and water and their swelling property was evaluated. The swelling coefficient of crosslinked product, effective crosslink density (γ) and the molecular weight between the successive crosslinks (Mc) were determined using the procedure published elsewhere [24]. The compressive properties of the cured bone cement was determined using an Instron model series IX automated materials testing system 7.43.00 at crosshead speed of 5 mm/min. The shore-A hardness was determined for the cured bone cement as per ASTM standard D 2240-81.

2.3 In vitro studies on biodegradation of bone cement

The degradation of the candidate bone cement cured material was studied by in vitro aging at 37°C in various simulated biological and oxidative media as per ISO standard ISO 10993/13 in a tablet disintegration test apparatus. The media selected were Ringers solution, phosphate buffered saline (PBS), 0.1 M silver nitrate/sodium lactate solution and 5% hydrogen peroxide solution. The degree of degradation was assessed by evaluating the weight loss, pH and mechanical properties.

2.4 Studies on in vitro biomechanical evaluation of bone cement

The candidate cured bone cement material was subjected to in vitro biomechanical test under compression mode in simulated physiological fluids, Ringer's solution and PBS solution using a Universal Testing Machine to evaluate the biomechanical stability at body temperature of 37°C. The compression properties were evaluated.

2.5 Studies on osteogenic activity of HT-PPF of the bone cement

The adhesion and growth of osteogenic cells on the HT-PPF of the bone cement was investigated using human osteosarcoma cell line (MG-63). MG-63 cell was cultured using appropriate media. The cell attachment was monitored by exposing MG-63 cells to the substrate. The number of attached cells to the surface of the substrate was determined. Cell morphology was studied.

2.6 Toxicological screening and biocompatibility of bone cement

The candidate bone cement was subjected to routine toxicological screening as per standard protocols. The bone cement was prepared using sterile-filtered resin and other ingredients. Intracutaneous irritation was carried out as per the method USP 28NF 23(88), 2005—biological reactivity tests in vivo—intracutaneous test. Extracts of the test materials were prepared with physiological sodium chloride solution and cotton seed oil as per the ISO standard. The extract of the test material was injected into five sites (0.2 ml/site) in rabbits. Blank sodium chloride solution and cotton seed oil were also injected as control. Skin irritation, erythema and edema were graded for test and blank sites at 24, 48 and 72 h to assess the intracutaneous irritation potential.

Maximisation test for delayed hypersensitivity was carried out as per the method ISO-10993-10, 2994(E)-Tests for irritation and delayed type hypersensitivity-clause 7.4 to assess the potential for skin sensitization in guinea pigs. Extract of the test material was prepared with physiological sodium chloride solution as per the ISO standard. Three injection media, (i) extract of the test material/control alone, (ii) mixture (50:50 v/v) of Freund's complete

adjuvant with physiological sodium chloride solution and (iii) extract of the test material/control alone emulsified in (50:50 v/v) Freund's adjuvant mixture were used for the investigation. A pair of intradermal injection (0.1 ml) of the above media was made at thee respective sites in the intrascapular region of G. pigs. Seven days after intradermal injection, the test and control extracts were topically applied (topical induction phase). 46 h later, the dressings and patches were removed. Seven days after topical application, the test and control sites were challenged with test and control extracts, respectively (challenge phase). Twenty-four hours later, the dressings and patches were removed. The appearance of the challenge phase skin sites of the test and control animals were observed at 24, 48 and 72 h after the removal of dressings and patches. Skin reactions for erythema and edema were scored and graded to assess the skin sensitization potential.

In vivo soft-tissue biocompatibility was evaluated as per the ISO standard ISO 10993/6 Tests for local effects after implantation-clause 5.0. The test material was implanted intra muscularly in the dorsal paravertebral muscle of healthy adult Albino rabbits with body weight not less than 2.0 kg, whose fur can be clipped closely on both sides of spinal column. Test and negative control (RMCAC007) samples were implanted on left and right side of spine, respectively. Implantation was carried out with three animals per implantation period under clean and aseptic condition using sterile needle. The period of implantation was 1, 4 and 12 weeks. During the period of implantation the animals were observed for edema, erythema etc. Animals were sacrificed after the post implantation period of 1, 4 and 12 weeks. The sites of implantation were examined macroscopically for hemorrhage, necrosis, discoloration and infections. The test and control samples with the tissue surrounding the material were harvested, fixed in 10% buffered formalin. The tissues surrounding the material were processed for histopathological investigation.

2.7 Studies on in vivo femural bone repair in animal model

The studies on in vivo femural bone repair were carried out in rabbit animal model as per the ISO standard ISO 10993/6. The bone cement prepared by mixing with sterile-filtered resin and other ingredients. The mixed ingredient was delivered at the site of bilateral femural proximal cylindrical defects 2 mm interior to the epiphysis and 4-mm from the femural tubercle. The animal was scarified at the intervals of 12, 24 and 48 weeks. The femur was excised, blocks of bone with implant microsectioned and stained. The bone growth and progressive break down of bone cement was assessed by photomicrography.

3 Results and discussion

3.1 Synthesis of fast setting unsaturated polyester PPF resin

In order to get biodegradable, bioassimilable, easily dispensable and fast setting unsaturated polyester PPF for bone cement, a meticulous synthesis and process optimization protocols has to be used. Because, the synthesis (condensation reaction involving the acid/anhydride and alcohol) is interfered always with reverse reactions as well as side reactions at the double bonds. Several researchers have reported synthesis of poly(propylene fumarate) (PPF) polymer. Sanderson has prepared PPF as a powder by transesterification reaction [25]. Gerhart and Hayes [26] and Domb et al. [27] have also synthesized low molecular weight PPF (M_n = 500–1200) by a condensation reaction involving propylene glycol and fumaric acid. Yazemski [28] and Peter et al. [29] also have produced PPF by a two step process involving the synthesis of bis (2-hydroxy propyl fumarate). Jayabalan et al. [23, 30] has prepared poly(propylene fumarate)/phloroglucinol triglycidyl methacrylate and poly(propylene fumarate-*co*-ethylene glycol) oligomers were prepared and studied as an alternate biodegradable bone cement polymers.

The molecular weight of PPF is limited by the reversibility of polyesterification and transesterification reactions proceeding in temperatures above 180–200°C for several hours. More over, the condensation reaction at 190°C involves cyclization side reactions involving maleic anhydride and glycols which reduces the unsaturation (about 10–20%). In order to get low molecular weight PPF with less strained, highly reactive and more planar trans fumarate configuration a meticulous synthetic procedure is needed. The low molecular weight and highly reactive PPF resin is very much essential to obtain an injectable bone cement.

The present candidate hydroxy terminated-poly(propylene fumarate) (HT-PPF) oligomeric resin is obtained by esterification and isomerisation of maleate during the refluxing and vacuum condensation. The chemical structure of the HT-PPF resin is shown in Fig. 1. The chemical composition of HT-PPF resin was identified by IR analysis. The IR spectrum analysis reveals the presence of strong peak for ester (C=O) group at 1722 cm^{-1} and an intense peak for hydroxyl group (–OH) at 3517 cm^{-1}. The absence of broad band at 3400 cm^{-1} reveals that the end groups are hydroxyl groups instead of carboxyl groups. The peak around 2983 cm^{-1} is due to the aliphatic C–H group in the chain. The peak for unsaturated double bonds(C=C) between carbon atoms of fumarate linkage was observed at 1644 and 982 cm^{-1}.

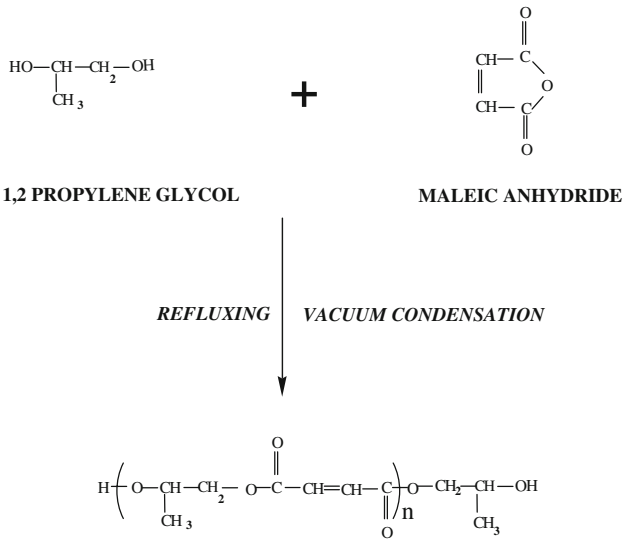

Fig. 1 Preparation of hydroxy terminated-poly(propylene fumarate) oligomer

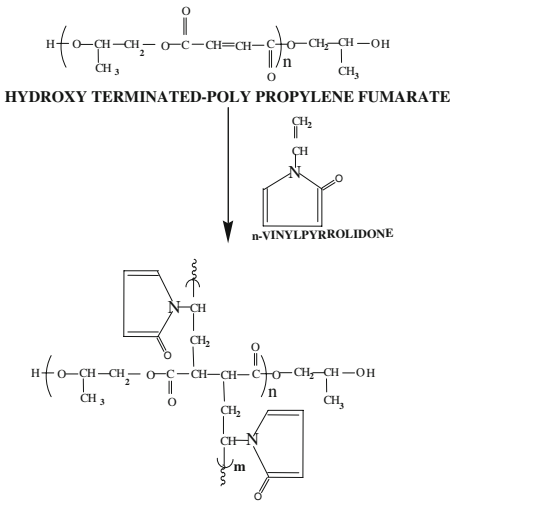

Fig. 2 Crosslinking of HT-PPF with comonomer

The molecular weight of the resin is 1814Mn, 2082Mw, 1814Mp, 2415Mz, and 2797Mz + 1 and poly dispersity of 1.148. The Brookfield viscosity of the resin determined at 50 RPM was 237.5 cp at 27°C. The low molecular weight of HT-PPF resin (Mn 1814 and Mw 2082) suggests that HT-PPF is an oligomeric free flowing liquid resin. This low molecular weight of the resin can also enable the flow nature of the additive-loaded HT-PPF cement. Therefore the cement consisting inorganic filler and comonomer can be dispensed with minimally invasive technique by injecting it into a bone void/defect of any shape and size.

3.2 Setting characteristics of bone cement

HT-PPF undergoes crosslinking with the comonomer, NVP through the unsaturated double bonds of the HT-PPF resin in the presence of initiator and accelerator by free radical mechanism. The crosslinking (setting) initiated at ambient temperature is accelerated with the accelerator. The reaction scheme for the crosslinking is shown in Fig. 2. Since the molecular weight of HT-PPF is very low, the propagation of crosslinking chain and growth lead to a highly crosslinked three dimensional structure.

The setting characteristics of the bone cement, setting time 5 min and exothermic temperature 42°C, which are within the acceptable limit of bone cement as per ISO Standard 5833/1-1999 E (Table 1). ISO Standard 5833/1-1999 E specifies the setting time range as 4–15 min and maximum exothermic temperature as 90°C for acrylic bone cements. The exothermic heat produced during the setting of this cement under the physiological conditions is low in comparison with PMMA cement. The crosslink density and molecular weight between crosslinks of the cured cement are 22.69×10^{-3} and 44.08 mol/cm^3, respectively. The crosslinked nature of the present bone cement reveals that the present cement can undergo slow degradation in vivo physiological conditions.

Table 1 Setting and mechanical properties of HT-PPF bone cement

Properties	Value
Setting properties	
Setting time (min)	5
Setting temperature (°C)	42.0
Mechanical properties of cured bone cement	
Shore D hardness	51
Compressive stress at max load (MPa)	76.62
Compressive modulus (Autyoung) (MPa)	723.23

3.3 Mechanical properties of bone cement

The formulation of the bone cement is tailor made to give optimum mechanical properties in vivo to the suit the

Table 2 Biodegradation of HT-PPF bone cement in simulated physiological media

Properties	Change of pH (original pH of medium)	Loss of weight (%)
PBS	6.78 (7.36)	18.51
Ringers solution	3.51 (7.72)	17.52
Silver nitrate/sodium lactate	4.53 (5.31)	15.58
5% H_2O_2	3.99 (4.50)	18.25

mechanical properties of bone. The compressive strength data are comparable with that of trabecular and vertebral bone (Table 1). The compressive strength and modulus of the candidate bone cement are 76.62 and 723.23 MPa, respectively. The trabecular bone has compressive strength 5 MPa and compressive modulus 50 MPa. Human wet vertebrae has ultimate compressive strength 5.3937 MPa (60–79 years).

3.4 Biodegradability

The degradation of bone cement ought to start after a definite period of time and produce only bioassimillable byproducts. The studies on hydrolytic degradation of present cured bone cement in simulated biological fluids, Ringer's solution and PBS reveal degradation over a period of time. HT-PPF undergoes hydrolysis of ester in simulated

Table 3 In vitro biomechanical evaluation in simulated physiological media

Medium	Compression properties			
	Maximum percent strain (%)	Modulus (Autyoung) (MPa)	Stress at max load (MPa)	Strain at max load (%)
Ringers solution	20.83 (33.42)	405.22 (723.23)	25.72 (76.62)	14.42 (29.65)
PBS	25.67 (33.42)	219.26 (723.23)	18.61 (76.62)	16.78 (29.65)

Note: The mechanical properties of virgin sample are given in parenthesis

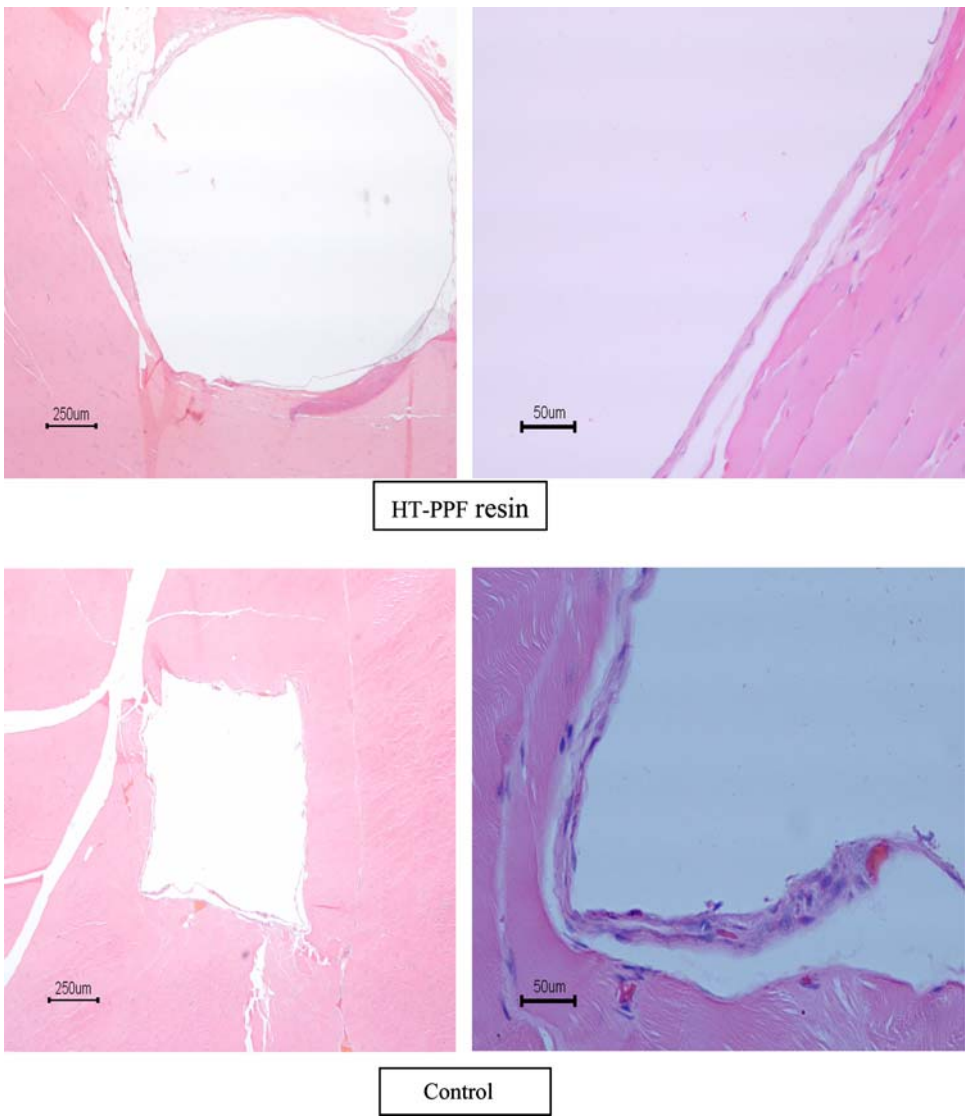

Fig. 3 Optical photomicrograph showing tissue compatibility of HT-PPF resin and after 3 months implantation in rabbit animal model

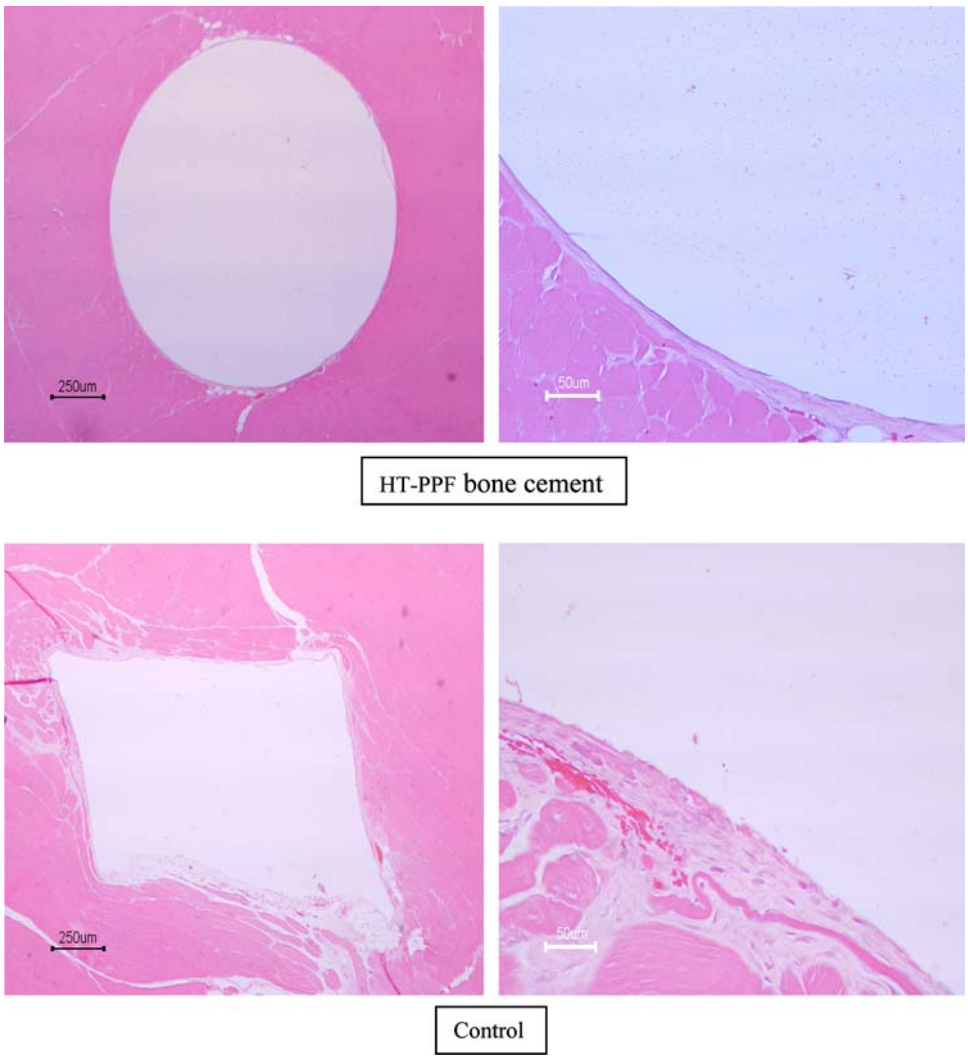

Fig. 4 Optical photomicrograph showing tissue compatibility of HT-PPF bone cement after 3 months implantation in rabbit animal model

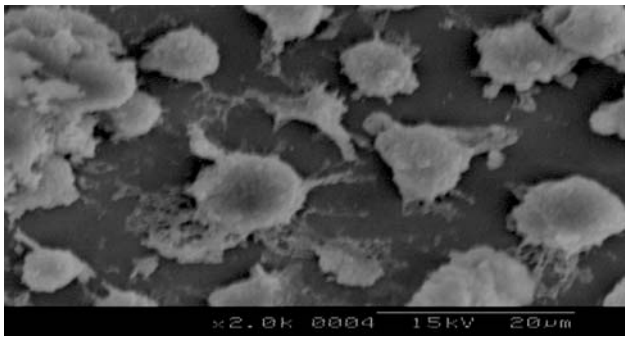

Fig. 5 SEM microphotograph of osteoblast cell interaction with cured HT-PPF resin of the bone cement

physiological media, PBS and Ringers solution, producing fumaric acid and propylene glycol which are non-toxic. The significant reduction of weight and pH in these media reveal the hydrolytic degradation (Table 2). The degraded fragments, fumaric acid and propylene glycol could be either metabolised or excreted from the body via natural pathways. HT-PPF also exhibits significant reduction of weight and pH in silver nitrate/sodium lactate and 5% hydrogen peroxide media which is attributed to the oxidative degradation at the uncrosslinked fumarate double bonds in HT-PPF.

The aging in simulated physiological media reveals reduction in compressive strength after 72 h (Table 3). The compressive stress and modulus of the aged bone cement in Ringers solution are 25.72 and 405.22 MPa, respectively. The compressive stress and modulus of the aged bone cement in PBS are 18.61 and 219.26 MPa, respectively. However the reduction lies above the required mechanical property of trabecular and vertebral bone (compressive stress 5 MPa and compressive modulus 50 MPa). The compressive properties of the cured sample confirm the suitability of the present bone cement for the indented orthopedic applications.

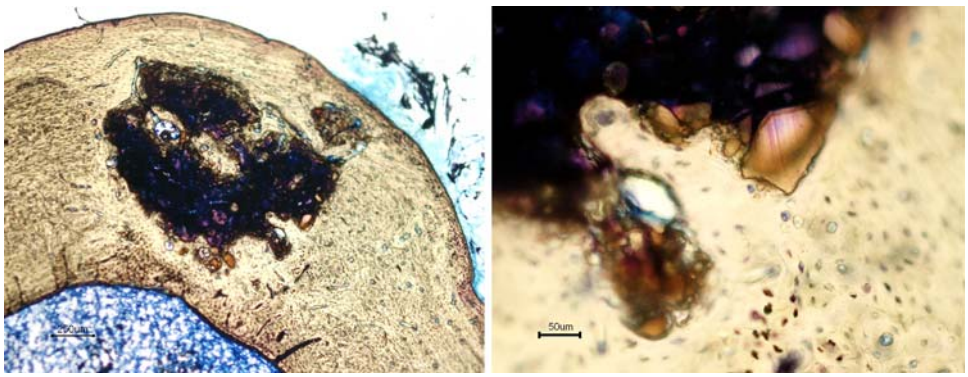

Fig. 6 Optical photomicrograph showing bone growth over HT-PPF bone cement after 12 months implantation in rabbit animal model

3.5 Biocompatibility

The bone cement has passed routine toxicological tests, intracutaneous irritation test (USP 28 NF (88) 2005), and maximisation test for delayed hypersensitivity (ISO-10993-10, 2994 E). Intracutaneous irritation test on cured HT-PPF resin and the bone cement reveal no significant irritation following intracutaneous injection of sodium chloride and cotton seed oil extract of the test materials. Intracutaneous irritation test reveals that the material posses no leachant that can cause allergic responses in vivo. The test for delayed hypersensitivity in guinea pigs has revealed no adverse skin reaction for the cured HT-PPF bone cement during the induction and challenge period. The extract of the test material induced a numerical grading of '0' for erythema and edema. Hence the cured HT-PPF bone cement does not induce skin sensitization.

In vivo intramuscular implantation of the candidate cured HT-PPF resin and bone cement in rabbit model and histopathological analyses of the tissues surrounding the implant confirmed the in vivo biocompatibility. The photomicrographs of tissue sites for negative control and cured HT-PPF resin for post-implantation period of 12 weeks are given in Fig. 3. The photomicrographs of tissue sites for negative control and cured HT-PPF bone cement for post-implantation period of 12 weeks are given in Fig. 4. The histopathological studies reveal no encapsulation, hemorrhage, infection or necrosis around the test materials. The absence of polymorphonuclear leucocytes (PMNs), neutrophils and macrophages shows the absence of inflammatory reaction after 3 months. Plasma cells and giant cells were absent. The absence of foreign body giant cells excluded the chance for the uncontrolled degradation. The histopathological analysis with test materials also reveals repair around the implant site with a thin layer of collagenous tissue with occasional of fibrocytes around the implant sites. This suggest the optimum tissue reactivity of the present bone cement. There is no evidence of chronic inflammatory responses from the test materials.

3.6 Osteo integration and bone growth

Poly(propylene fumarate)-based bone cement is an osteoconductive and inductive material which provide a frame work or scaffolding for vascular ingress by gradual degradation of the polymer, cellular infiltration and attachment, cartilage formation and calcified tissue deposition. This enables fast bone healing in defective bone site. The osteogenic potential of the HT-PPF resin was studied. The cured resin enables adhesion and cytoplasmic spreading of osteoblast cells as shown in Fig. 5.

The histopathological investigation of bone–bone cement after the implantation of bone cement in femural bone of rabbit for 12 months have revealed formation of new woven bone. The histopathological investigation after the implantation of bone cement in femural bone of rabbit for 12 months have revealed new woven bone on endosteal and periosteal aspect and Haversian canals in the new bone inside and around the implant. Material is in direct contact with new woven and laminar bone on all sides as well as inside the implant (Fig. 6).

4 Conclusion

The candidate HT-PPF bone cement is more advantageous in terms of dispensability, fast setting, low setting temperature, balanced mechanical properties, excellent biocompatibility, controlled biodegradability and excellent osteointegration and bone remodeling. The candidate HT-PPF bone cement is more promising bone cement for minimally invasive radiological procedures for the treatment of bone diseases and spinal compression fractures.

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