(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 October 2009 (29.10.2009)

PCT

(10) International Publication Number
WO 2009/131829 A2

(51) International Patent Classification:
A61L 27/14 (2006.01) *A61C 8/00* (2006.01)

(21) International Application Number:
PCT/US2009/039718

(22) International Filing Date:
7 April 2009 (07.04.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/107,273 22 April 2008 (22.04.2008) US

(71) Applicant *(for all designated States except US)*: **KYPHON SARL** [CH/CH]; Pierre-a-Bot 97, CH-2000 Neuchatel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MEYER, Jorg** [US/DE]; Im Sommerfield 66, 63150 Heusenstamm (DE). **WENZ, Robert** [US/DE]; Frankfurter Strasse 11, D-61206 Wollstadt (DE). **LEE, Samuel** [US/US]; 2342 California Street #16, Mountain View, CA 94040 (US).

(74) Agents: **DORLAND, Gregory, S.** et al.; 710 Medtronic Parkway MS LC340, Minneapolis, MN 55432 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: BONE CEMENT COMPOSITION AND METHOD

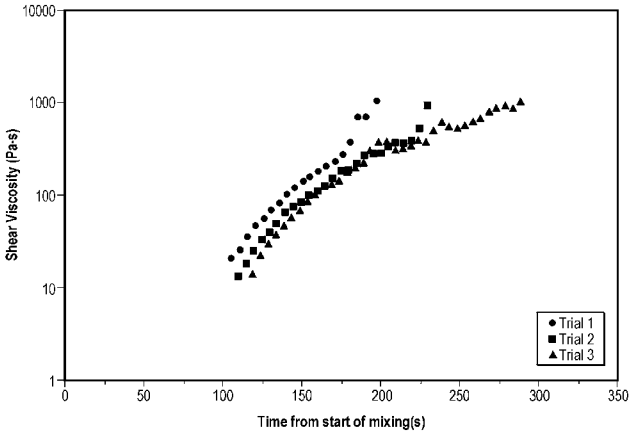


FIG. 1

(57) **Abstract**: The disclosure is directed to a composition includes a first component and a second component. The first component includes a poly(methyl methacrylate) (PMMA), a contrast agent, and a radical donor. The second component includes methyl methacrylate (MMA), a radical scavenger, and a polymerization accelerator. The composition has an average setting time of about 13 minutes. The disclosure is further directed to a kit and a method of making the above-mentioned composition.

WO 2009/131829 A2

BONE CEMENT COMPOSITION AND METHOD

BACKGROUND

Bone cement compositions are useful in applications such as dental and medical procedures. In particular, they are used in bonding or affixing an implant material to natural bone and to repair damaged natural bone. Although bone cement compositions enjoy wide use in the medical arts, these compositions need to be carefully designed depending on the surgical site at which they will be used. For example, compositions suitable for use in repairing a damaged bone in a limb may not be ideally suited for use in repairing damaged teeth. Similarly, compositions useful in repairing a limb or a tooth may not be ideally suited for surgically repairing the spinal column.

Typically, current bone cement compositions are sold in two-part preparations containing a powder (or dry) part and a liquid (or wet) part, which, when combined, polymerize to form a hardened substance mimicking many of the physical properties of natural bone. The powder part typically includes a polymeric material, such as acrylate polymers, while the liquid part includes a reactive monomer, such as methylmethacrylate. Recent developments have focused on modifying the bone cement composition for particular medical procedures.

For example, to attach prostheses to bone, Faccioli et al. (U.S. Patent No. 5,004,501) discloses a bone cement composition having a polymer with submicron particle size, i.e. less than 0.9 microns. As stated in Faccioli et al., the function of the submicron particles is to fill any voids left in the bone cement composition to produce stronger bone cement. The patent further discloses the use of fluoride salts to produce a stronger bond between the bone cement and the bone of the patient.

For particular medical applications such as vertebroplasty, manufacturers have turned to producing bone cement compositions having radiopacity and longer setting times. For example, Lavergne et al. (U.S. Patent Application No. 2005/0256220) describes a bone cement composition having setting times greater than 15 minutes. In particular, the bone cement is a polymethyl methacrylate (PMMA)-based composition. Lavergne et al. achieves a longer setting time using a PMMA-based composition that includes hydroxyapatite and barium sulfate.

In another example of bone cements for vertebroplasty procedures, Voellmicke et al. (U.S. Patent No. 7,008,433 and U.S. Patent Application No. 2003/0032964) describe a PMMA-based composition to provide radiopacity and further increase the setting time of the bone cement. Specifically, the bone cement composition has a setting time that is at least greater than 18 minutes. To produce a bone cement with a higher setting time and increased radiopacity, Voellmicke et al. use barium sulfate at amounts of 20% by weight to 40% by weight. The barium sulfate particles have D_{50} sizes of greater than 3 microns and require 50% of the barium sulfate particles to be unbound (i.e. free) from the PMMA particles.

Other applications have focused on increasing the viscosity of the bone cement composition at an accelerated rate to infiltrate the medical site and prevent any migration of the cement during medical procedures. In particular, Beyar et al. (U.S. Patent Application Nos. 2007/0027230 and 2007/0032567), focus on a viscosity greater than 500 Pascal-second at 2 minutes after the initiation of mixing the two components of the bone cement composition. The U.S. Patent Applications of Beyar et al. achieve a high viscosity at an expedited rate by using one or more sub-population PMMA beads with a molecular weight that is significantly different than a main population of PMMA beads.

Bone cement compositions have been modified to have properties such as longer setting times and high viscosity produced at accelerated speeds. However, these properties are not beneficial for all medical application. Hence, it would be desirable to provide an improved bone cement composition.

SUMMARY

In a particular embodiment, a composition includes a first component and a second component. The first component includes a poly(methyl methacrylate) (PMMA), a contrast agent, and a radical donor. The second component includes methyl methacrylate (MMA), a radical scavenger, and a polymerization accelerator. The composition has an average setting time of about 13 minutes.

In another embodiment, a kit includes a packaged first component and a packaged second component. The packaged first component includes a poly(methyl methacrylate) (PMMA), a radical donor and a contrast agent. The second packaged component includes methyl methacrylate (MMA), a radical scavenger, and a polymerization accelerator. The

mixed first component and second component have an average setting time of about 13 minutes.

In another exemplary embodiment, a method is provided. The method includes mixing a first component and a second component. The first component includes a poly(methyl methacrylate) (PMMA), a radical donor and a contrast agent. The second component includes methyl methacrylate (MMA), a radical scavenger, and a polymerization accelerator. The method further includes providing a set bone cement composition after an average time of about 13 minutes.

BRIEF DESCRIPTION OF THE DRAWINGS

The present disclosure may be better understood, and its numerous features and advantages made apparent to those skilled in the art by referencing the accompanying drawings.

FIG. 1 includes graphical illustration of data representing the viscosity of exemplary bone cement compositions.

DESCRIPTION OF THE DRAWINGS

In a particular embodiment, a bone cement composition includes a first component and a second component. The first component includes a pre-polymerized vinyl polymer, a contrast agent, and a radical donor. The second component includes a reactive monomer, a radical scavenger, and a polymerization accelerator. The composition is a bone cement that has an average setting time of about 13 minutes. The bone cement composition is typically prepared by homogeneously mixing the first component with the second component using any suitable mixing method.

The first component of the bone cement composition is referred to as a dry or powder component. In an exemplary embodiment, the first component includes a pre-polymerized vinyl polymer. Pre-polymerized vinyl polymers include, for example, any medically suitable pre-polymerized polymers containing vinyl groups. Exemplary medically suitable pre-polymers include pre-polymerized acrylate polymers such as poly(methyl methacrylate) (PMMA), pre-polymerized styrene acrylates, poly-methacrylate, poly-ethacrylate, poly-butylmethacrylate, copolymers, and mixtures thereof.

In an exemplary embodiment, the pre-polymerized vinyl polymer is poly(methyl methacrylate) (PMMA).

Typically, the pre-polymerized vinyl polymer has a molecular weight of about 200,000 grams/mole to about 500,000 grams/mole. In an embodiment, the pre-polymerized vinyl polymer has an average particle size up to about 100.0 microns. In an embodiment, the pre-polymerized vinyl polymer has an average particle size of about 1.0 micron to about 100.0 microns. In a particular embodiment, the pre-polymerized vinyl polymer has an average particle size of about 35 microns to about 60 microns. In an embodiment, greater than 99.0% of the particles of the pre-polymerized vinyl polymer have a particle size of greater than about 1.0 micron.

The pre-polymerized polymer is typically present in the bone cement composition at about 60.0% by weight to about 75.0% by weight of total weight of the first component. In a particular embodiment, the pre-polymerized polymer is present in the bone cement composition at about 65.5% by weight to about 70.5% by weight, such as about 67.5% to about 68.5% by weight of the total weight of the first component.

The first component of the bone cement composition further includes a radical donor. The radical donor is typically used to initiate a polymerization reaction with the reactive monomer present in the second component. In an embodiment, any known radical donor may be used. In an exemplary embodiment, the radical donor may be benzoyl peroxide (BPO), azo-bis-isobutyrylnitrile (AIBN), and mixtures thereof. In a particular embodiment, the radical donor is benzoyl peroxide (BPO). Typically, the radical donor is present at not greater than about 3.0% by weight of the total weight of the first component. In an embodiment, the radical donor is present at about 0.5% by weight to about 3.0% by weight, such as about 0.8% by weight to about 3.0% by weight, such as about 0.8% by weight to about 2.0% by weight, such as about 1.5% by weight to about 2.0% by weight of the total weight of the first component.

The first component of the bone cement composition further includes a contrast agent. The contrast agent may be selected depending on the medical instrumentation used to view the contrast agent. Suitable contrast agents include, for example, barium sulfate ($BaSO_4$), zirconium dioxide, CHI_3, Na_2FPO_3, and CaF_2. In an exemplary embodiment, the contrast agent is barium sulfate. Typically, the barium sulfate contrast agent may be imaged by fluoroscopy. In an embodiment, the barium sulfate is present at an amount

sufficient to allow continuous imaging by fluoroscopy during the medical procedure, such as the injection of the bone cement in a patient, without impacting the mechanical properties or the desired setting time of the bone cement. The contrast agent is typically present at not less than about 20% by weight of the total weight of the first component. In an embodiment, the contrast agent is present at about 25% by weight to about 35% by weight, such as about 28% by weight to about 35% by weight, such as about 30% by weight to about 35% by weight, or even 30% by weight to about 32% by weight of the total weight of the first component.

In a particular embodiment, the contrast agent has an average particle size of about 0.3 microns to about 10.0 microns, such as about 0.3 microns to about 2 microns, such as about 2.0 microns. In an embodiment, the contrast agent has an average particle size of about 1.0 micron to about 5.0 microns. In an embodiment, greater than 99.0% of particles of the contrast agent have a size of less than about 10.0 microns. In an embodiment, when viewed under scanning electron microscopy (SEM), the particles of the contrast agent typically are spherical in shape and appear as amorphous agglomerates. In particular, the contrast agent as present in the first component typically appears as amorphous agglomerates distributed on the surface of the pre-polymerized vinyl polymer particles. In an embodiment, at least about 60%, such as at least about 70%, such as at least about 80% of the particles of the contrast agent are distributed on the surface of the pre-polymerized vinyl polymer particles. In other words, there are less than about 40%, such as less than about 30%, such as less than about 20% "freely floating" contrast agent particles that are not distributed on the surface of the pre-polymerized vinyl polymer.

The first component can further include optional ingredients. Optional ingredients include, for example, antibiotics, cytostatis agents, analgesic agents, disinfectants, preservatives, growth factors, proliferative factors, proteins, peptides, biopolymers, dyes, and mixtures thereof. In an exemplary embodiment, the optional ingredient includes gentamycine, tobramycine, clindamycine, vancomycine, β-TGF or an analog thereof, a bone morphogenic protein series compound, and mixtures thereof. Additionally, the bone cement composition is substantially free of hydroxyapatite. Further, the bone cement composition is substantially free of fluoride salt. "Substantially free" as used herein refers to a less than 99.99% by weight of the total composition.

The second component of the bone cement composition is generally referred to as a liquid component. The second component includes a reactive monomer, which reacts with the radical donor and polymerizes. In an embodiment, the reactive monomer is a methyl methacrylate (MMA), PEG monoacrylates, PEG diacrylates, PEG monomethylacrylates, PEG dimethyacrylates, PEG-mono/di-acrylates/methyacrylate, butanediol methacrylates, polyolefin-acrylates, urethaneacrylates, methacrylates, and mixtures thereof. Among the PEG-based reactive monomers, they typically have a molecular weight of about 200 Daltons (D) to about 1500 D. In an exemplary embodiment, the reactive monomer is methyl methacrylate (MMA).

The second component typically includes about 10.0% by weight to about 99.9% by weight of the reactive monomer, based on the total weight of the second component. In an embodiment, the reactive monomer is present at about 80% by weight to about 99.9% by weight, such as about 95.0% by weight to about 99.9% by weight, such as about 98.5% by weight to about 99.9% by weight of the total weight of the second component.

In an embodiment, the second component includes a polymerization accelerator. Typically, the polymerization accelerator is selected such that the polymerization reaction occurs at or below normal body temperatures so as not to cause thermal damage to the surgical site or surrounding areas. In an embodiment, the polymerization accelerator is a tertiary amine. In an exemplary embodiment, the tertiary amine includes, but is not limited to, dimethylparatoluidine (DMPT) and dihydroxyethylorthotoluidine.

In an embodiment, an advantageously low level of polymerization accelerator is used. Although DMPT is believed to be toxic to humans, the bone cement composition of the present disclosure contains particularly low levels without adverse consequences to the patient or the mechanical properties and setting time of the bone cement composition. For instance, the polymerization accelerator is present at less than about 1.0% by weight, such as even less than about 0.5% by weight of the total weight of the second component. In an embodiment, the polymerization accelerator is present at about 0.2% by weight to about 1.0% by weight, such as about 0.2% by weight to about 0.5% by weight of the total weight of the second component.

In an embodiment, the second component further includes a radical scavenger. Typically, the radical scavenger is present to retard or arrest the ability of the reactive monomer to self-polymerize. In an exemplary embodiment, the reactive monomer does

not polymerize until the first component and the second component are mixed. In an embodiment, the radical scavenger is hydroquinone, hydroquinone monomethylether, vitamin E, and mixtures thereof. In an exemplary embodiment, the radical scavenger is hydroquinone monomethylether. The radical scavenger is typically present at an amount to prevent the reactive monomer from self-polymerizing. In an embodiment, the radical scavenger is present at an amount of about 30 ppm to about 400 ppm, such as about 50 ppm to about 200 ppm, or even about 20 ppm to about 100 ppm.

The second component may further include ingredients such as a diluent, a dye, an admixture of proteins, a chemotherapeutic, a drug, an antibiotic, and mixtures thereof. The admixture of proteins may include, for example, an admixture of heat sensitive/unsensitive proteins such as mitogenic growth factors, morphogenic growth factors, and mixtures thereof. An example of a suitable drug that can be included in the second component is bisphophonate.

In an embodiment, an optional diluent is added to the second component. Any suitable diluent may be used. Suitable diluents include, for example, polyethylene glycol (PEG), an ester of mellitic acid, and mixtures thereof. In an embodiment, the diluent is polyethylene glycol. An exemplary ester of mellitic acid is tri-octylmellitic ester. Generally, the diluent should have a molecular weight such that the diluent remains in liquid form at room temperature. For example, in an exemplary embodiment, the polyethylene glycol has a molecular weight of about 100 Daltons (D) to about 1000 D, such as about 400 D to about 800 D. When included, the diluent provides multiple benefits to the bone cement composition. For instance, the diluent desirably provides the ability to control the stiffness of the bone cement composition after curing/hardening. While not wishing to be bound by any particular theory, it is believed that lower stiffness is beneficial because it better simulates the actual properties of human bones. The presence of polyethylene glycol in the aforementioned weight range does not adversely affect the compressive strength and bending strength of the preparation. Thus, the stiffness can be more readily/easily controlled by the presence of polyethylene glycol, without compromising the compressive strength and the bending strength of the preparation relative to the previously known bone cement preparations. The compressive and bending strengths may be adversely affected when the amount of diluent exceeds 30% by weight, based on the total weight of the composition. In an embodiment, the diluent

may be present at about 1% by weight to about 90% by weight, such as 5% by weight to about 60% by weight, such as about 10% by weight to about 40% by weight of the total weight of the second component. Furthermore, the presence of the diluent rapidly destabilizes the radical donor (thus, resulting in a faster hardening of the preparation) and reduces the amount of polymerization accelerator needed.

When a dye is present in the first or second component, it does not impart any mechanical attributes to the composition. Typically, the dye is used as an aid to assist the user (for instance, the surgeon, medical technician, aid, or nurse). In an embodiment, the dye can be used to readily inform the surgeon of the type of composition he or she is using. For instance, a purple-colored dye may have become known in the field by users to be indicative of a bone cement composition suitable for use in the spine, whereas a different color material may be known in the art by users to be indicative of a bone cement composition suitable for another application. In an embodiment, the dye is present at about 1% by weight to about 10% by weight of the total weight of the first component or second component..

The bone cement composition is typically prepared by a method that includes mixing the first and second components under conditions suitable to form the reaction product. In an embodiment, the reaction product is curable under standard pressure and at a temperature of about 18°C to about 25°C, such as about 20°C to about 25°C. In an embodiment, the weight ratio of the first component to the second component is about 2.2:1 to about 3.3:1, such as about 2.5:1. Further, the mixing may be done by any suitable mixing device.

When the first and second components are combined, a polymerization reaction is initiated by the polymerization accelerator present in the second component and the radical donor present in the first component. In practice, the radical donor will decompose when it encounters the polymerization accelerator evolving a free radical that will attack the double bonds present in the monomer causing the monomer to polymerize and ultimately, harden. The reaction in the context of the composition will yield a cured composition.

The bone cement component has desirable processing properties. In particular, once the bone cement composition is mixed, it has an average setting time of about 13 minutes. The setting time is the cumulative time it takes for the reaction product to form a

cured product once mixing of the first and second component has been initiated. "Cure" as used herein refers to a viscosity of at least greater than about 2000 Pa-s. In an embodiment, the setting time is about 8 minutes to about 14 minutes, such as about 9 minutes to about 13 minutes, such as about 10 minutes to about 12 minutes. In an embodiment, the setting time of the bone cement composition is about 9 minutes. In an embodiment, the median setting time of the bone cement composition is about 11 minutes. In a particular embodiment, setting of the bone cement composition occurs at standard temperature (about 22°C). In a further embodiment, the setting time of the composition is not greater than about 14 minutes. In certain medical applications, a shorter setting time is desired to decrease the surgeon's waiting time while the bone cement composition cures. Accordingly, a lower setting time is beneficial to the patient since it decreases the total time of the medical procedure.

Further, once mixing of the first component and the second component is initiated, the viscosity of the bone cement composition reaches a viscosity of about 200 Pascal-second (Pa-s) at a time of greater than about 2:30 minutes. In an embodiment, the viscosity of the bone cement composition reaches a viscosity of about 500 Pa-s at a time of greater than about 3:15 minutes (195 seconds). Typically, the bone cement composition reaches a viscosity of about 1000 Pa-s at a time of greater than about 4:00 minutes.

In an exemplary embodiment, the bone cement composition advantageously exhibits desirable mechanical properties when cured. For instance, the bone cement composition has advantageous compression strength when cured. In an embodiment, the compression strength of the bone cement composition after 6 days of storage and tested on a Zwick testing machine Z010, according to ASTM F451-99a and ISO 5833, is greater than about 75.0 MPa, such as greater than about 80.0 MPa, such as greater than about 100.0 MPa, such as even greater than about 105.0 MPa, providing a composition within medical strength regulations and guidelines usable for surgical implants.

In an exemplary embodiment, the components of the composition are capable of being readily injectable through a syringe-like device or other delivery mechanism to a surgical site, where they react to form the composition and cure to the hardened state. The composition is persistent at the surgical site, preferably adhering to the tissue and/or bone at the site. Furthermore, the composition is stable in that it generally does not undergo any significant changes *in situ*. When set/cured, the composition is also tough and elastic in

that it is capable of bearing loads without experiencing undue or permanent deformation. Still further, the composition is believed to be well tolerated by the body in that it produces, at most, tolerable levels of immune and inflammatory responses. It is to be appreciated, however, that in exemplary embodiments of the compositions, while satisfying at least some of these advantages, may not satisfy all of these advantages in every instance.

In an embodiment, the composition is sold and distributed to users in a kit where the first and second components are maintained apart (e.g., separately packaged or contained) until they are ready for use in forming the composition. The user may receive a mixer apparatus containing the components in separate compartments thereof. See generally, U.S. Patent No. 6,241,734, U.S. Patent No. 6,613,054, U.S. Patent No. 7,018,089, and U.S. Patent application publication No. 2002/0191487 A1. These publications generally describe suitable apparatus for mixing and delivering the composition's components and mixtures thereof to form the composition. The components likely will be mixed by the user immediately prior to the surgical procedure with a suitable mixing apparatus. In an embodiment, the composition may be formed by mixing the first and second components and the composition is transferred to an apparatus suitable to deliver the composition (or mixture of the components) to the surgical site before the composition (or mixture) sets and cures.

The composition may be applied using a variety of mechanisms such as, for example, those described in U.S. Patent Nos. 5,972,015 and 6,066,154. These patents generally describe a procedure referred to as "Kyphoplasty", which uses one or two balloons, similar to angioplasty balloons, to reduce the vertebrae bone fracture and restore vertebral height prior to injecting a bone cement composition. In an example, two balloons are introduced into the vertebra via bilateral transpedicular cannulae. The balloons are inflated to reduce the fracture, then deflated and removed, leaving a relatively empty cavity into which a bone cement composition is injected. The inflation of the balloons and subsequent injection of the composition helps restore vertebral height.

EXAMPLE 1

Seven formulations are prepared for a performance study. Specifically, the setting time of the formulations are measured for three varying amounts of polymerization accelerator. A first component (i.e. a dry or powder component) is prepared by combining

(a) about 208.4 grams of polymethyl methacrylate polymer (PMMA) obtained from Roehm GmbH & Co. KG, Darmstadt, Germany, having a molecular weight of 200,000 g/mole to about 500,000 g/mole, (b) about 91.8 grams of barium sulfate obtained from Merck KGaA, Darmstadt, Germany, and (c) about 5.8 grams of benzoyl peroxide (BPO) obtained from Degussa Initiators GmbH, Pullach, Germany. These ingredients are mixed together in a ball mill rotating at a speed of about 200 rotations per minute with 405 grams of Stealit balls of 20.0mm diameter for 50 minutes. A second component (i.e. the wet component) is prepared and includes (a) about 8.97 grams of methyl methacrylate (MMA) obtained from

Roehm GmbH & Co. KG, Darmstadt, Germany, (b) about 0.027 grams to about 0.045 grams of N,N-dimethyl-p-toluidine (DMPT) obtained from Roehm GmbH & Co. KG, Darmstadt, Germany, (c) about 50 parts per million (ppm) of hydroquinone monomethylether obtained from Merck KGaA, Darmstadt, Germany. The first component (20.0 grams) and the second components (9.0 grams) are mixed together at standard temperature and pressure and are set to provide a hardened material. The handling characteristics are measured at standard temperature (about 22°C). Setting time measurements are conducted according to ASTM F451-99a and ISO 5833-92. Setting characteristics is illustrated in Table 1.

Table 1

	DMPT g/ % (by weight of second component)	Temperature (°C)	Setting Time (minute)
Formulation 1	0.045g / 0.5%	19.7 to 19.9	11:08
Formulation 2	0.027g / 0.3%	24.8 to 24.9	8:40
Formulation 3	0.027g / 0.3%	23.9	8:40
Formulation 4	0.027g / 0.3%	24.5	8:25
Formulation 5	0.0315g / 0.35%	20.6	13:55
Formulation 6	0.027g / 0.3%	20.6	13:50
Formulation 7	0.0315g / 0.35%	20.4 to 20.6	13:30
Formulation 8	0.0315g / 0.35%	20.3 to 20.7	12:22
Formulation 9	0.0315g / 0.35%	19.8 to 20.5	13:45

The nine formulations have setting times ranging from 8:25 minutes to 13:55 minutes. Results in Table 1 further demonstrate that the level of DMPT used in the bone cement composition can be advantageously low and less toxic to the patient and still have an advantageously low setting time.

The average setting time is measured for Formulation 2 using a single factor ANOVA analysis at an average ambient temperature of about 22.7°C. Four runs are conducted and the data is seen in Table 2.

Table 2

Run	Ambient Temperature (°C)	Setting Time (minute)
1	22.6	13.4
2	22.9	12.9
3	22.9	12.9
4	22.5	13.0
Average (Std. Dev.)	22.7 (0.2)	13.1 (0.3)
Range	22.5 – 22.9	12.9 – 13.4

As seen in Table 2, the average setting time is about 13 minutes at ambient temperature.

EXAMPLE 2

The mechanical properties of the several formulations are evaluated. The method for preparing the formulation and components of the formulation used are described in Example 1. There are variations in the amount of benzoyl peroxide (BPO), N, N-dimethyl-p-toluidine (DMPT), and hydroquinone monomethylether (HQME). The test slabs are compression molded at 23 +/- 1°C for one hour and post-cured at 23 +/- 1°C for 6 days. Compression strength measurements are carried out according to ASTM F451-99a and ISO 5833 on a Zwick testing machine Z010. The results are summarized in Table 3.

Table 3

BPO (% w/w)	DMPT (% w/w)	HQME (ppm)	Compression strength (MPa)
1.92	0.2	50	75.52 +/- 1.75

1.92	0.3	50	94.33 +/- 2.86
1.92	0.5	50	104.26 +/- 1.53
1.92	0.7	50	106.21 +/- 1.18
1.92	1.0	50	108.46 +/- 3.86
1.92	0.3	20	82.90 +/- 2.17
1.92	0.3	50	94.33 +/- 2.86
1.92	0.3	100	88.18 +/- 3.17
0.80	0.3	50	80.15 +/- 2.44
0.98	0.3	50	96.07 +/- 1.63
1.92	0.3	50	94.33 +/- 2.86
2.83	0.3	50	88.80 +/- 4.09
3.00	0.3	50	87.66 +/- 1.00

As seen in Table 3, a decrease in the level of DMPT does not have an adverse impact on the mechanical properties of the bone cement. Advantageously low levels of DMPT as well as BPO and HQME provide bone cement compositions that have desirable compression strength for medical applications.

EXAMPLE 3

Viscosity of a bone cement formulation is measured. The viscosity prior to setting of the bone cement is evaluated. The method for preparing the formulation and components of the formulation used are described in Example 1. DMPT is present at

about 0.3% by weight and HMQE at 50 ppm. Viscosity measurements are performed on a rotating shear rheometer. The parameters are as follows: TA Instruments AR 1000 Controlled Stress Rheometer having a 4 cm stainless steel parallel plate. Gap: 1000 μm; Temperature: 23°C; Shear rate: 0.5 s^{-1}; Sampling rate: 0.5Hz.

The cements are hand mixed in air and loaded into the rheometer. After the sample is loaded, the excess cement is wiped away, leaving a uniform edge at the upper geometry. A timer is started at the onset of mixing and the rheology test start time is recorded. Shearing characterization begins at less than three minutes after the start of mixing. All data is reported as time from the start of mixing. Data collection stops when the viscosity reaches 1000 Pa-s to allow the cement to be removed from the rheometer before it completely hardens.

Results can be seen in FIG. 1. The viscosity of the bone cement formulation is measured in triplicate and follows the same trend with good reproducibility. The deviation from a linear trend, as seen in FIG. 1 is the result of slippage as the edges of the cement exposed to the atmosphere cure faster than the cement at the center of the plate. The viscosity of the bone cement composition reaches a viscosity of about 200 Pascal-second (Pa-s) at a time of greater than about 2:30 minutes (150 seconds). In an embodiment, the viscosity of the bone cement composition reaches a viscosity of about 500 Pa-s at a time of greater than about 3:15 (195 seconds) minutes. Typically, the bone cement composition reaches a viscosity of about 1000 Pa-s at a time of greater than about 4:00 minutes.

The above-disclosed subject matter is to be considered illustrative, and not restrictive, and the appended claims are intended to cover all such modifications, enhancements, and other embodiments, which fall within the true scope of the present invention. Thus, to the maximum extent allowed by law, the scope of the present invention is to be determined by the broadest permissible interpretation of the following claims and their equivalents, and shall not be restricted or limited by the foregoing detailed description.

WHAT IS CLAIMED IS:

1. A composition comprising:

a) a first component comprising a poly(methyl methacrylate) (PMMA), a contrast agent, and a radical donor; and

b) a second component comprising methyl methacrylate (MMA), a radical scavenger, and a polymerization accelerator;

wherein the composition has an average setting time of about 13 minutes.

2. The composition of claim 1, wherein the composition is substantially free of hydroxyapatite.

3. The composition of claim 1 or claim 2, wherein the PMMA has an average particle size of about 35 microns to about 60 microns.

4. The composition of claim 1, claim 2 or claim 3, wherein the PMMA has a molecular weight of about 200,000 grams/mole to about 500,000 grams/mole.

5. The composition of any one of claims 1 to 4, wherein the contrast agent is present at not less than about 20% by weight of the total weight of the first component, preferably about 35% by weight of the total weight of the first component.

6. The composition of any one of claims 1 to 5, wherein the contrast agent is selected from the group consisting of barium sulfate ($BaSO_4$), zirconium dioxide, CHI_3, Na_2FPO_3, and CaF_2, and mixtures thereof.

7. The composition of any one of claims 1 to 6, wherein the contrast agent has an average particle size of about 0.3 microns to about 10 microns.

8. The composition of any one of claims 1 to 7, wherein the radical donor is selected from the group consisting of benzoyl peroxide (BPO), azo-bis-isobutyrylnitrile (AIBN), and mixtures thereof.

9. The composition of any one of claims 1 to 8, wherein the radical donor is present at about 1.5% by weight to about 2.0% by weight of the total weight of the second component.

10. The composition of any one of claims 1 to 9, wherein the radical scavenger is selected from the group consisting of hydroquinone monomethylether, hydroquinone, vitamin E, and mixtures thereof.

11. The composition of any one of claims 1 to 10, wherein the polymerization accelerator is selected from the group consisting of dimethylparatoluidine (DMPT), dihydroxyethylorthotoluidine, and mixtures thereof.

12. The composition of any one of claims 1 to 11, wherein the polymerization accelerator is present at about 0.2% by weight to about 1.0% by weight of the total weight of the second component, preferably at about 0.2% by weight to about 0.5% by weight of the total weight of the second component.

13. The composition of any one of claims 1 to 12, wherein the composition has a setting time of about 9 minutes or having a viscosity of about 500 Pascal-second at a time of greater than about 3:15 minutes.

14. The composition of any one of claims 1 to 13, further comprising an optional ingredient selected from the group consisting of an antibiotic, a cytostatic agent, an analgesic agent, a disinfectant, a preservative, a growth factor, a proliferative factor, a protein, a peptide, a biopolymer, a dye, a chemotherapeutic, a drug, and mixtures thereof.

15. A kit comprising a composition according to any one of claims 1 to 14, wherein the first component is in a first package and the second component is in a second package within the kit.

16. A method of making a bone cement composition according to any one of claims 1 to 14, the method comprising:

mixing the first component and the second component and providing a set bone cement composition after an average time of about 13 minutes.

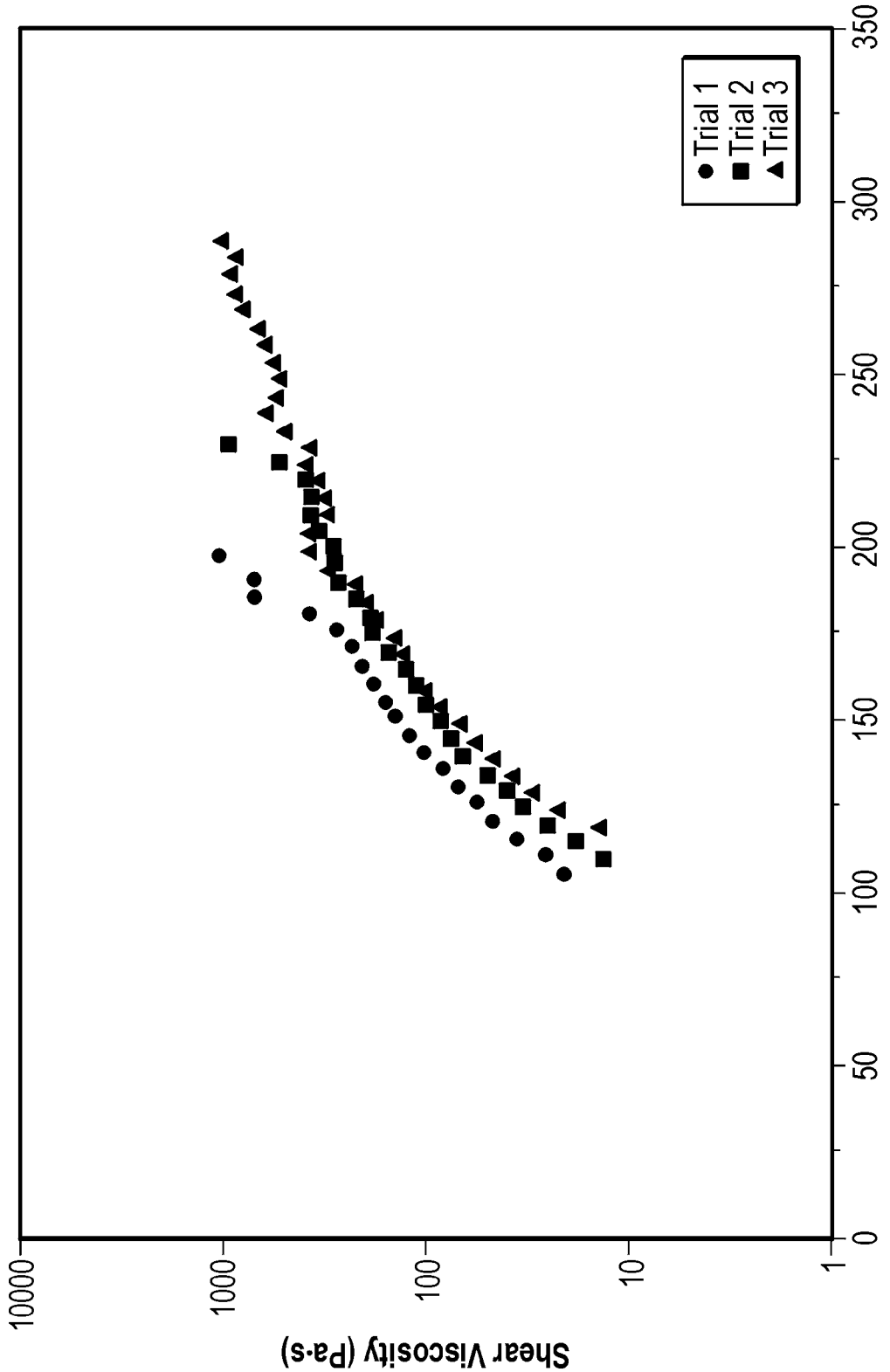

Shear Viscosity (Pa·s)
10000
1000
100
10
1
0
50
100
150
200
250
300
350
Time from start of mixing(s)
Trial 1
Trial 2
Trial 3

FIG. 1