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(71) Applicant: **ABYRX, INC.** [US/US]; 1 Bridge Street, Ste. 121, Irvington, New York 10533 (US).

(72) Inventors: **KRONENTHAL, Richard L.**; 1 Bridge Street, Ste. 121, Irvington, New York 10533 (US). **DARR, Aniq**; 1 Bridge Street, Ste. 121, Irvington, New York 10533 (US). **PACIFICO, John**; 1 Bridge Street, Ste. 121, Irvington, New York 10533 (US).

(74) Agent: **ELRIFI, Ivor** et al.; Cooley LLP, 1299 Pennsylvania Avenue, NW, Suite 700, Washington, District of Columbia 20004-2400 (US).

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Declarations under Rule 4.17:

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(54) Title: THERAPEUTIC PUTTIES CONTAINING ADDITIVES INCLUDING PROCESSED HUMAN BLOOD PLASMA

(57) Abstract: Provided herein are settable and non-settable compositions for use in surgical procedures comprising a variety of disclosed particles and optionally including previously unclotted, lyophilized, optionally crosslinked mammalian blood plasma. Also provided are related compositions, including surgical kits and packages, as well as methods of making and using the compositions.



THERAPEUTIC PUTTIES CONTAINING ADDITIVES INCLUDING PROCESSED HUMAN BLOOD PLASMA

RELATED APPLICATIONS

[01] The application claims priority to United States Patent Application No. 62/512,482 filed May 30, 2017, the contents of which are herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

[02] The present disclosure relates to the field of medical implants, optionally settable, implantable compositions for medical use in tissue hemostasis, repair and reconstruction.

BACKGROUND

[03] Biodegradable polymers have become increasingly important for a variety of biomedical applications including biomedical implants, such as stents, and coatings applied to those implants, tissue engineering scaffolds, and soft-tissue adhesives. Segmented polyurethane elastomers in particular have come into wide use as biomaterials due to their superior mechanical properties and chemical versatility. PCT International Application Publication No. WO 2004/009227 describes certain degradable polyurethane compositions for use as tissue engineering scaffolds. U.S. Patent No. 6,306,177 (Felt *et al.*) describes curable polyurethane compositions comprising a plurality of parts capable of being sterilized, stably stored, and mixed at the time of use in order to provide a flowable composition upon mixing that is sufficiently flowable to permit it to be delivered to the body by minimally invasive means. U.S. Patent Application Publication No. 2005/0013793 (Beckman *et al.*) also describes degradable polyurethanes for *e.g.*, tissue engineering and particularly for bone repair and replacement. U.S. Patent No. 4,829,099 (Fuller *et al.*) describes certain absorbable polyisocyanates for use as surgical adhesives. U.S. Patent Nos. 8,002,843 and 7,985,414 (Knaack *et al.*) describe a biodegradable polyisocyanate (such as lysine diisocyanate) with an optionally hydroxylated biomolecule used to form a degradable polyurethane. U.S. Patent No. 7,964,207 (Deslaurier *et al.*) describes osteoconductive polyurethane compositions having mechanical properties consistent for use in bone repair.

[04] For certain applications, in addition to being biodegradable, it is advantageous for a

surgical implant to be moldable or formable, for example to optimize its placement at the implant site and/or to fill voids in hard or soft tissue at the site of implantation. US 8,431,147 and US 8,282,953 (Warsaw Orthopedic, Inc) describe malleable implants containing demineralized bone matrix (“DBM”). The “malleable implant compositions” described in these patents contain a particulate solid collagen material and a particulate solid DBM material along with a liquid carrier that comprises an aqueous gel of alginate. Alginate/DBM based compositions are also described in US 8,506,983 (Warsaw Orthopedic, Inc). US 20130236513 (Guelcher *et al.*) describes polyurethane composites that, in some aspects, may be “processed” as a reactive liquid that subsequently cures *in situ* to form a solid composite.

[05] These and similar materials may contain polymers, ceramics, solid fatty acid and inorganic salts, dispersants, free radical scavengers and solvents, as well as other optional additives such as catalysts, colorants, radiopaque agents, analgesics, anesthetics, antimicrobials, natural and recombinant growth factors and other bioactive peptides and proteins, antineoplastic and anti-inflammatory drugs, mineralized, partially demineralized and completely demineralized bone particles, adhesives, sealants, and porogens. *See e.g.*, U.S. 7,989,000 (Orthocon, Inc.), U.S. 8,603,528 (Abyrx, Inc.), and U.S. 9,314,547 (Abyrx, Inc.).

[06] There is a continuing need for improved surgical materials for use in hard and soft tissue repair.

SUMMARY OF THE INVENTION

[07] The present disclosure provides compositions and methods relating to moldable surgical implants suitable for use in hard and soft tissue repair. It has now been discovered and disclosed in this application, that previously unclotted human pooled or autologous plasma, prescreened for pathogens, and optionally containing trehalose as a lyophilization stabilizer, could be dried by lyophilization or simple evaporation and then cold-ground or -milled and sieved into a uniform particulate form that can be optionally added to moldable surgical implants, as described herein, to provide exceptional bone, cartilage and soft tissue hemostasis and healing characteristics. As described in more detail *infra*, anhydrous implants are preferred, so that the dry plasma particulate component remains active during ambient storage, preferably in moisture resistant packaging.

[08] Provided herein are mechanically hemostatic putty compositions including a particulate component and a liquid component. For example, the particulate component can include particles

of previously unclotted lyophilized mammalian blood plasma. In some embodiments, the particles of blood plasma are crosslinked (*e.g.*, using genipin, heat, a carbodiimide, formaldehyde, glutaraldehyde, calcium, aluminum, chromium, iron, tin, magnesium and zinc salts of phosphate, sulfate, carbonate, bicarbonate, and/or any combinations thereof prior to lyophilization). In other embodiments, the particles are not crosslinked.

[09] By way of non-limiting example, in any of the compositions described herein, the particulate component may further contain a carboxylic acid salt or a fatty acid ester of polyethylene glycol (*e.g.*, a carboxylic acid salt can be selected from a calcium, magnesium, zinc, aluminum, or barium salt of stearic acid; or a calcium, magnesium, zinc, aluminum, or barium salt of palmitic acid and/or a fatty acid ester can be polyethylene oxide stearate).

[10] In any of the compositions described herein, the liquid component may contain a block or random copolymer of ethylene oxide and propylene oxide (*e.g.*, the block copolymer may include one or more Pluronics), polyethylene oxide, triethylcitrate, acetyltriethylcitrate or an N-alkylpyrrolidone and combinations thereof. The liquid component can also include a tocopherol or an ester thereof (*e.g.*, tocopherol acetate). In some embodiments, the liquid component may additionally or alternatively contain triacetin and/or glycerol.

[11] In preferred embodiments, the putty compositions described herein are anhydrous or substantially anhydrous.

[12] By way of non-limiting example, the particulate component of the compositions described herein can include a mono- or di- fatty acid ester of a poly(alkyleneoxy)diol (*e.g.*, polyethylene glycol (PEG) laurate, PEG stearate, PEG palmitate, and/or PEG behenate).

[13] In any of the compositions described herein, the particulate component may further include a carboxylic acid salt (*e.g.*, a calcium, magnesium, zinc, aluminum and/or barium salt of an even-numbered-carbon-atom homologous series comprising lauric, myristic, palmitic, stearic, arachidic, and/or behenic acids (*i.e.*, a calcium, magnesium, zinc, aluminum and/or barium salt of lauric acid; a calcium, magnesium, zinc, aluminum and/or barium salt of myristic acid; a calcium, magnesium, zinc, aluminum and/or barium salt of palmitic acid; a calcium, magnesium, zinc, aluminum and/or barium salt of stearic acid; a calcium, magnesium, zinc, aluminum and/or barium salt of arachidic acid; and/or a calcium, magnesium, zinc, aluminum and/or barium salt of behenic acid).

[14] Any of the compositions described herein can additionally include an effective amount of one or more additional therapeutic additives. By way of non-limiting example, the one or more

additional therapeutic additives are selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats (*e.g.*, thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch (*e.g.*, Arista), and/or combinations thereof), and/or combinations thereof.

[15] In embodiments, any of the compositions described herein are sterile or sterilizable (*i.e.*, the product, after mixing and packaging the components, can be terminally sterilized).

[16] Additionally (or alternatively), any of the compositions described herein can be body absorbable.

[17] Also provided are two putty settable bone hemostatic and adhesive compositions, wherein the first putty (Putty A) includes a polyfunctional isocyanate, tocopheryl acetate, calcium phosphate particles and a polyol and the second putty (Putty B) includes a polyfunctional isocyanate, calcium phosphate particles, at least one polyol, a fatty acid salt and tocopheryl acetate. The first putty and the second putty may be mixable together to form a mixed putty (Putty C). Immediately after the two putties are thoroughly mixed to form a mixed putty (Putty C), particles of previously unclotted, lyophilized mammalian blood plasma may be added to the mixed putty and uniformly distributed throughout the mixed putty. Also provided, therefore, is a composition obtainable by mixing the first putty and the second putty to form a mixed putty, adding particles of previously unclotted, lyophilized mammalian blood plasma to the mixed putty and uniformly distributing said particles throughout the mixed putty.

[18] In any of these two-putty compositions, the first putty, the second putty, or both the first putty and the second putty may include one or more particulate materials selected from calcium sulfate, calcium phosphosilicate, sodium phosphate, calcium aluminate, and/or calcium phosphate and/or the second putty may include one or more of hydroxyapatite, biomimetic carbonate apatite, demineralized bone, and/or mineralized bone.

[19] In some embodiments, the first putty, the second putty, or both the first putty and the second putty includes one or more particulate materials selected from a polyaryletherketone-based material, a polymethylmethacrylate-based material, and/or a tantalum- or titanium-based filler.

[20] In other embodiments, in any of these two putty compositions the first putty, the second putty, or both the first putty and the second putty comprises one or more particulate materials selected from calcium sulfate, sodium phosphate, calcium aluminate, strontium phosphate,

calcium strontium phosphate, tricalcium phosphate, calcium pyrophosphate, and/or magnesium phosphate. By way of non-limiting example, in these compositions, the second putty may include one or more particulate materials selected from hydroxyapatite, biomimetic carbonate apatite, biphasic calcium phosphate/hydroxyapatite, mineralized bone matrix, demineralized bone matrix, and/or glass ionomer. In some embodiments, the first putty, the second putty, or both the first putty and the second putty can include one or more particulate materials selected from absorbable phosphate glass, nonresorbable particulate metallic materials (*e.g.*, stainless steel powder, titanium powder, stainless steel nanoparticles, and/or titanium nanoparticles), and/or nonresorbable polymeric materials (*e.g.*, polyurethane particles, polyurethane particles, polymethacrylic acid particles, and polyarylether ketone particles (*e.g.*, (polyether ketone (PEK), polyether ether ketone (PEEK), polyether ketone ketone (PEKK), polyether ether ketone ketone (PEEKK) and/or polyether ketone ether ketone ketone (PEKEKK) particles)).

[21] Any of the compositions described herein can additionally include an effective amount of one or more additional therapeutic additives. By way of non-limiting example, the one or more additional therapeutic additives are selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats (*e.g.*, thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch (*e.g.*, Arista), and/or combinations thereof), and/or combinations thereof.

[22] Also provided herein is a composition comprising two putty components, the first putty (Putty A) including a dialkyl methylenemalonate ester and a poly(methylenemalonate) ester and the second putty (Putty B) including a poly(methylenemalonate) ester and particles of previously unclothed mammalian blood plasma. In some embodiments of these compositions, when thoroughly admixed, the first putty and the second putty result in the formation of a third putty (Putty C) that is a moldable, settable surgical implant suitable for hard and soft tissue repair.

[23] In some embodiments, the second putty can include an effective amount of one or more additional therapeutic additives (*e.g.*, antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats (*e.g.*, thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch, and/or combinations thereof), and/or combinations thereof).

[24] Also provided is a composition comprising two putty components, the first putty (Putty A) including a cyanoacrylate ester at least one free radical scavenger (*e.g.*, hydroquinone, vitamin E acetate, beta carotene and/or selenium acetate) and at least one acidifying agent (*e.g.*, sulfur dioxide, sulfur trioxide and/or nitrogen dioxide) as anti-polymerization stabilizers and the second putty (Putty B) including a poly(cyanoacrylate) ester and particles of previously unclothed mammalian blood plasma. In these compositions, when thoroughly admixed, the first putty and the second putty can result in the formation of a third putty that is a moldable, settable surgical implant suitable for hard and soft tissue repair.

[25] In some embodiments, the second putty can additionally include an effective amount of one or more additional therapeutic additives. By way of non-limiting example, the one or more additional therapeutic additives may be selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats (*e.g.*, thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch (*e.g.*, Arista), and/or combinations thereof), and/or combinations thereof.

[26] Also provided are compositions containing two putty components, the first putty (Putty A) including a mixture of potassium dihydrogen phosphate, magnesium oxide and at least one calcium-containing compound (*e.g.*, tricalcium phosphate, hydroxyapatite, and/or combinations thereof) all suspended in one or a mixture of anhydrous, non-toxic, partially water-miscible, inert suspension vehicles and the second putty (Putty B) including water, particles of previously unclothed mammalian blood plasma, and one or more viscosity-building agents (*e.g.*, sodium carboxymethyl cellulose, sodium alginate, carrageenan, gelatin, collagen chitosan, and combinations thereof). In these compositions, when thoroughly admixed, the first putty and the second putty can result in the formation of a third putty (Putty C) that is a moldable, settable surgical implant that is suitable for hard and soft tissue repair.

[27] In some embodiments, the second putty can additionally include an effective amount of one or more additional therapeutic additives. By way of non-limiting example, the one or more additional therapeutic additives may be selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats (*e.g.*, thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified

plant starch (*e.g.*, Arista), and/or combinations thereof), and/or combinations thereof.

[28] In embodiments, the compositions described herein are particularly suitable for use in bone repair, as bone void fillers, bone cements, and/or bone hemostats. In other embodiments, the compositions are suitable for soft tissue repair, for example as soft tissue adhesives.

[29] In embodiments, the compositions are provided in the form of a curable or settable composition, the composition being optionally sterile.

[30] In embodiments, the composition is a putty-like composition comprising 30-50% (*i.e.*, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 30-35, 30-40, 30-45, 35-40, 35-45, 35-50, 40-45, 40-50, or 45-50%) and preferably 40% of calcium stearate, 1-10% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10, or 9-10%) and preferably 5% of tocopheryl acetate, 20-40% (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 20-25, 20-30, 20-35, 25-30, 25-35, 25-40, 30-35, 30-40, or 35-40%) and preferably 30% of Pluronic L-35 (*i.e.*, a nonionic triblock copolymer composed of a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of polyoxyethylene in liquid form, wherein the molecular weight of the hydrophobe is approximately 900 g/mol and an polyethylene content of approximately 50%), 10-30% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30% or 10-15, 10-20, 10-25, 15-20, 15-25, 15-30, 20-25, 20-30, or 25-30%) and preferably 20% of ground and sieved human plasma lyophilizate and 1-8% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, or 8% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 3-4, 3-5, 3-6, 3-7, 3-8, 4-5, 4-6, 4-7, 4-8, 5-6, 5-7, 5-8, 6-7, 6-8 or 7-8%) and preferably 5% of an antimicrobial agent, *e.g.*, tobramycin or gentamycin. In embodiments, this composition provides instant (within 0-5 (*i.e.*, 0, 1, 2, 3, 4, or 5) seconds) hemostasis when applied to bleeding bone, is body absorbable within 30 days of implantation, and maintains zones of inhibition against MRSA (Methicillin-resistant *Staphylococcus aureus*) for at least 4 days. In one embodiment, the calcium stearate is completely replaced by unclotted lyophilized human blood plasma.

[31] In embodiments, the composition is a putty-like composition comprising 45-65% (*i.e.*, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, or 65% or 45-50, 45-55, 45-60, 50-55, 50-60, 50-65, 55-60, 55-65, or 60-65%) and preferably 54% of PEG stearate, 1-10% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7,

2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10%) and preferably 5% tocopheryl acetate, 3-10% (*i.e.*, 3, 4, 5, 6, 7, 8, 9, or 10% or 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10%) and preferably 6% of sodium carboxymethylcellulose, 5-15% (*i.e.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 5-10 or 10-15%) and preferably 10% of propylene oxide, 5-15% (*i.e.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 5-10 or 10-15%) and preferably 10% of Pluronic L-121 (*i.e.*, a nonionic triblock copolymer composed of a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of polyoxyethylene in liquid form, wherein the molecular weight of the hydrophobe is approximately 3,600 g/mol and an polyethylene content of approximately 10%) and 10-20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20%) and preferably 15% of milled and sieved human plasma lyophilizate. In embodiments, this composition provides instant (within 0-5 (*i.e.*, 0, 1, 2, 3, 4, or 5) seconds) hemostasis when applied to bleeding bone, is body absorbable within 8 days of implantation.

[32] In embodiments, the composition is a putty-like composition comprising 20-50% (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 20-25, 20-30, 20-35, 20-40, 20-45, 25-30, 25-35, 25-40, 25-45, 25-50, 30-35, 30-40, 30-45, 30-50, 35-40, 35-45, 35-50, 40-45, 40-50, or 45-50%) and preferably 35% of phosphate-based ceramic, 20-40% (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 20-25, 20-30, 20-35, 25-30, 25-35, 25-40, 30-35, 30-40, or 35-40%) and preferably 30% of PEG stearate, 1-8% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, or 8% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 3-4, 3-5, 3-6, 3-7, 3-8, 4-5, 4-6, 4-7, 4-8, 5-6, 5-7, 5-8, 6-7, 6-8 or 7-8%) and preferably 5% of sodium carboxymethyl cellulose, 1-10% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 2-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10%) and preferably 5% of tocopheryl acetate, 1-9% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, or 9% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 5-6, 5-7, 5-8, 5-9, 6-7, 6-8, 6-9, 7-8, 7-9 or 8-9%)) and preferably 5% of Pluronic L-121 (*i.e.*, a nonionic triblock copolymer composed of a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of polyoxyethylene in liquid form, wherein the molecular weight of the hydrophobe is approximately 3,600 g/mol and an

polyethylene content of approximately 10%) and 8-35% (*i.e.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35% or 8-10, 8-15, 8-20, 8-25, 8-30, 10-15, 10-20, 10-25, 10-30, 10-35, 15-20, 15-25, 15-30, 15-35, 20-25, 20-30, 20-35, 25-30, 25-35, or 30-35%) and preferably 20% of milled and sieved human plasma lyophilizate. In embodiments, this composition provides instant (within 0-5 (*i.e.*, 0, 1, 2, 3, 4, or 5) seconds) hemostasis when applied to bleeding bone and reorganizes into new bone as it is resorbed.

[33] In embodiments, the composition is a putty-like composition comprising a resorbable polymer derived from 10-20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20%) and preferably 15% of lactyldiester (*i.e.*, esters of lactic acid) and 10-20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20%) and preferably 15% of a polyesterpolyol, (*i.e.*, esters of any polyol) 40-70% (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% or 40-45, 40-50, 40-55, 40-60, 40-65, 45-50, 45-55, 45-60, 45-65, 45-70, 50-55, 50-60, 50-65, 50-70, 55-60, 55-65, 55-70, 60-65, 60-70, or 65-70%) and preferably 55% of powdered calcium phosphate, 1-10% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 20-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10, or 9-10%) and preferably 5% of tocopheryl acetate, 1-10% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 20-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-6, 4-7, 4-8, 4-9, 4-10, 5-7, 5-8, 5-9, 5-10, 6-8, 6-9, 6-10, 7-9, 7-10, 8-10 or 9-10%) and preferably 5% of glyceryl triester. Immediately after mixing these components into a putty, 10-20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20%) and preferably 15% of milled and sieved human plasma lyophilizate is mixed into the putty. In embodiments, this composition provides instant (within 0-5 (0, 1, 2, 3, 4, or 5) seconds) hemostasis when applied to bleeding bone and is sufficiently adhesive 6 hours after application to prevent postoperative micromotion in a wire-supported reconstructed sheep sternotomy.

[34] In embodiments, the compositions are provided in the form of a curable or settable composition comprising a plurality of component parts packaged separately, each of the component parts being sterile, and adapted to be mixed at time of use, where upon mixing a curing reaction is initiated. Additives such as lyophilized blood plasma may be added at this time. Preferably, the component parts, once mixed, do not require a catalyst for curing.

[35] In embodiments, the composition comprises four separately packaged components that are combined and thoroughly mixed just prior to use. The first component is 25-35% (*i.e.*, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35% or 25-30 or 30-35%), preferably 30% of the composition and comprises a liquid prepolymer containing methylene-bis-diphenyldiisocyanate. The second component is 25-35% (*i.e.*, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35% or 25-35 or 30-35%), preferably 30% of the composition and comprises a liquid Castor oil-based polyol. The third component is 20-30% (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30% or 25-30 or 30-35%), preferably 25% of the composition and comprises powdered calcium carbonate and the fourth component, added after the first three components have been mixed and transformed into a settable taffy-like phase, is 10-20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20%), preferably 15% of the composition and comprises ground and sieved human plasma lyophilizate. In embodiments, this composition provides instant (within 0-5 (*i.e.*, 0, 1, 2, 3, 4, or 5) seconds) hemostasis when applied to bleeding bone and is sufficiently adhesive after 12 hours to securely adhere two non-weight bearing bone surfaces together.

[36] The terms “settable” and “curable” and the like are used interchangeably herein. In one embodiment, the fully cured composition has mechanical properties suitable for drilling and/or accepting a surgical screw without shattering or splintering. In one embodiment, the component parts of the composition are in the form of a putty or paste which is moldable, preferably hand-moldable, and in some embodiments sufficiently flowable for extrusion, for example, from a syringe. The homogenous composition formed from the mixture of the component parts is also in the form of a putty or paste which is moldable, preferably hand-moldable, and in some embodiments sufficiently flowable for extrusion, for a period of time after mixing and during curing. In one embodiment, the period of time for complete cure into a hardened final form is from about 6 to 12 (*i.e.*, 6, 7, 8, 9, 10, 11, or 12) hours or from about 6 to 24 (*i.e.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24) hours. In one embodiment, the fully cured composition is drillable or machineable. In one embodiment, the settable composition cures into a final form that is thermoplastic and can be softened to return it to a hand-moldable state by applying heat sufficient to warm the composition to a temperature at least higher than 40 °C, preferably between 40 °C and 100 °C (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 °C). In accordance

with this embodiment, where the composition sets or cures prematurely during use, it may be heated until it becomes moldable again for a period of time until it cools. The compositions described herein and their component parts are preferably not in a low viscosity liquid form.

[37] In one embodiment, the component parts may each comprise an additive, such as a colorant or dye, that imparts a color to the component. In one embodiment, each component comprises a different colorant or dye such that when the component parts are combined to form the settable composition, the different colors mix to form a new color, which new color is also indicative that the composition has been mixed to homogeneity. In one embodiment, the component parts can be mixed to homogeneity within about 1 minute or less, or within about 2 minutes.

[38] The disclosure also provides related compositions, including surgical kits and packages, as well as methods of making and using any of the settable compositions described herein. In one embodiment, the disclosure provides a package comprising one or a plurality of settable compositions, each composition consisting of a set of two or more individual components, the components of a set comprising amounts of reagents which, upon mixing, react and cure into a final hardened form over a period of time, preferably at room or body temperature. Each component is physically separated from the other components of the set within the package, and optionally, from other sets of components. In one embodiment, the set consists of 2, 3, or 4 individual components. In one embodiment, the components are sterile. In one embodiment, the package is adapted to permit the removal of one set of components at a time while leaving the remaining sets in a sealed, sterile, environment. In one embodiment, the package comprises an upper peelable film configured to allow the exposure of one set of putties at a time. In one embodiment, each component is physically separated from the other components of its set within the package by means of a compartment or plurality of compartments in the package. In a further embodiment, each set of components may optionally be separated from other sets of the package by perforations allowing the set to be conveniently separated either before or after opening and removing the contents.

[39] In one embodiment, the plurality of compartments comprises depressions or wells in a heat-sealable metal foil-based sheet. In one embodiment, the compartments of a set are flexible and separated by at least one breakable seal adapted to allow the component putties of the set to be mixed together when the seal is broken. In one embodiment, the compartments are in the form of one or more syringes, preferably one or more foil-enclosed syringes. In one embodiment, the

compartments are in the form of a single syringe, preferably a foil-enclosed syringe, adapted to maintain individual component putties of a set separated from each other within the single syringe. In one embodiment, the compartments are in the form of a plurality of syringes and each syringe contains a single component of a set. In one embodiment, each compartment comprises one or more surfaces in contact with an individual component, the one or more surfaces comprising or consisting of a low surface energy material selected, for example, from the group consisting of polytetrafluoroethylene (PTFE), silicone, polypropylene, polyethylene, and polystyrene.

[40] In one embodiment, the package further comprises an outer, heat sealable, preferably water impermeable or water resistant envelope completely surrounding the package, and a desiccant. In one embodiment, the outer envelope is a heat sealed, water impermeable or water resistant foil package.

[41] In one embodiment, the settable composition consists of a set of components, each in the form of a putty, that, upon mixing, react and cure into a polyurethane or polyurethane composition. In one embodiment, at least one or at least two of the putty components of the set comprises an isocyanate component, a polyol/polyamine component, and a particulate component (for example, the first putty may comprise a polyfunctional isocyanate, tocopheryl acetate, calcium phosphate particles and a polyol and the second putty may comprise a polyfunctional isocyanate, calcium phosphate particles, at least one polyol, a fatty acid salt and tocopherol acetate). In one embodiment, the particulate component is present in an amount of about 5-85 wt % (*i.e.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85 wt% or 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 5-45, 5-50, 5-55, 5-60, 5-65, 5-70, 5-75, 5-80, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-45, 10-50, 10-55, 10-60, 10-65, 10-70, 10-75, 10-80, 10-85, 15-20, 15-25, 15-30, 15-35, 15-40, 15-45, 15-50, 15-55, 15-60, 15-65, 15-70, 15-75, 15-80, 15-85, 20-25, 20-30, 20-35, 20-40, 20-45, 20-50, 20-55, 20-60, 20-65, 20-70, 20-75, 20-80, 20-85, 25-30, 25-35, 25-40, 25-45, 25-50, 25-55, 25-60, 25-65, 25-70, 25-75, 25-80, 25-85, 30-35, 30-40, 30-45, 30-50, 30-55, 30-60, 30-65, 30-70, 30-75, 30-80, 30-85, 35-40, 35-45, 35-50, 35-55, 35-60, 35-65, 35-70, 35-75, 35-80, 35-85, 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 40-80, 40-85, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 45-80, 45-85, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 50-85, 55-60, 55-65, 55-70, 55-75, 55-80, 55-85, 60-65, 60-70, 60-75, 60-75, 60-80, 60-85, 65-70,

65-75, 65-80, 65-85, 70-75, 70-80, 70-85, 75-80, 75-85, or 80-85 wt%) based on the weight of the putty component. In one embodiment, the particulate component is selected from one or more of calcium sulfate, calcium phosphosilicate, sodium phosphate, calcium aluminate, calcium phosphate, magnesium phosphate, hydroxyapatite, phosphate glass, biomimetic carbonate apatite, biphasic calcium phosphate/hydroxyapatite, demineralized bone matrix, mineralized bone, lyophilized human blood plasma, or non-resorbable metallic or polymeric materials, such as polytetrafluoroethylene, polymethylmethacrylate, micronized titanium and powdered stainless steel. The particulate component may comprise two or more different particulates.

[42] In one embodiment, the set consists of two putties, A and B, and the isocyanate component consists of a diisocyanate which is aromatic or aliphatic. Putty A comprises 15-40 % (*i.e.*, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 15-20, 15-25, 15-30, 15-35, 20-25, 20-30, 20-35, 20-40, 25-30, 25-35, 25-40, 30-35, 30-40, or 35-40%) of the isocyanate component, 0.5-5 % (*i.e.*, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3.0, 0.5-3.5, 0.5-4.0, 0.5-4.5, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 3-3.5, 3-4, 3-4.5, 3-5, 3.5-4, 3.5-4.5, 3.5-5, 4-4.5, 4-5, or 4.5-5%) of the polyol component, and 50-75 % (*i.e.*, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, or 75% or 50-55, 50-60, 50-65, 50-70, 55-60, 55-65, 55-70, 55-75, 60-65, 60-70, 60-75, 65-70, 65-75, or 70-75%) particulate material, based upon total weight of Putty A; Putty B comprises 1-10 % (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10) of the isocyanate component, 3-15 % (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 3-5, 3-10, 5-10, 5-15, or 10-15%) of the polyol component, and 65-95% (*i.e.*, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, or 95% or 65-70, 65-75, 65-80, 65-90, 70-75, 70-80, 70-85, 70-90, 70-95, 75-80, 75-85, 75-90, 75-95, 80-85, 80-90, 80-95, 85-90, 85-95, or 90-95%) or 75-85 % (*i.e.*, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 75-80 or 80-85) particulate material, based upon total weight of Putty B. In one embodiment, the polyol in Putty A is present in a prepolymer with the isocyanate component such that there is substantially no unreacted polyol

in Putty A and the isocyanate component in Putty B is present in a prepolymer such that there is substantially no unreacted isocyanate in Putty B.

[43] In one embodiment, the set consists of two putties, A and B. Putty A comprises 15-40 % (*i.e.*, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 15-20, 15-25, 15-30, 15-35, 20-25, 20-30, 20-35, 20-40, 25-30, 25-35, 25-40, 30-35, 30-40, or 35-40%) of the isocyanate component, 0.5-5 % (*i.e.*, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3.0, 0.5-3.5, 0.5-4.0, 0.5-4.5, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 3-3.5, 3-4, 3-4.5, 3-5, 3.5-4, 3.5-4.5, 3.5-5, 4-4.5, 4-5, or 4.5-5%) of the polyol component, and 40-85 % (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 40-80, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 45-80, 45-85, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 50-85, 55-60, 55-65, 55-70, 55-75, 55-80, 55-85, 60-65, 60-70, 60-75, 60-80, 60-85, 65-70, 65-75, 65-80, 65-85, 70-75, 70-80, 70-85, 75-80, 75-85, or 80-85%) particulate material, based upon total weight of Putty A; Putty B comprises 1-10 % (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10) of the isocyanate component, 3-15 % (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 3-5, 3-10, 5-10, 5-15, or 10-15%) of the polyol component, and 65-95% (*i.e.*, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, or 95%) or 75-85 % (*i.e.*, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 65-70, 65-75, 65-80, 65-90, 70-75, 70-80, 70-85, 70-90, 70-95, 75-80, 75-85, 75-90, 75-95, 80-85, 80-90, 80-95, 85-90, 85-95, or 90-95%) particulate material, based upon total weight of Putty B.

[44] In one embodiment, the set consists of two pastes, A and B. Paste A comprises 15-40 % (*i.e.*, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 15-20, 15-25, 15-30, 15-35, 20-25, 20-30, 20-35, 20-40, 25-30, 25-35, 25-40, 30-35, 30-40, or 35-40%) of the isocyanate component, 0.5-5 % (*i.e.*, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5,

3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4., 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3.0, 0.5-3.5, 0.5-4.0, 0.5-4.5, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 3-3.5, 3-4, 3-4.5, 3-5, 3.5-4, 3.5-4.5, 3.5-5, 4-4.5, 4-5, or 4.5-5%) of the polyol component, and 50-75 % (*i.e.*, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, or 75%, 50-55, 50-60, 50-65, 50-70, 55-60, 55-65, 55-70, 55-75, 60-65, 60-70, 60-75, 65-70, 65-75, or 70-75%) particulate material, based upon total weight of Paste A; Paste B comprises 1-10 % (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10%) of the isocyanate component, 3-15 % (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 3-5, 3-10, 5-10, 5-15, or 10-15%) of the polyol component, and 25-50% (*i.e.*, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 25-30, 25-35, 25-40, 25-45, 30-35, 30-40, 30-45, 30-50, 35-40, 35-45, 35-50, 40-45, or 45-50%) or 5-25 % (*i.e.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25% or 5-10, 5-15, 5-20, 10-15, 10-20, 10-25, 15-20, 15-25, or 20-25%) particulate material, based upon total weight of Paste B.

[45] In one embodiment, the set consists of two pastes, A and B. Paste A comprises 15-40 % (*i.e.*, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 15-20, 15-25, 15-30, 15-35, 20-25, 20-30, 20-35, 20-40, 25-30, 25-35, 25-40, 30-35, 30-40, or 35-40%) of the isocyanate component, 0.5-5 % (*i.e.*, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4., 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3.0, 0.5-3.5, 0.5-4.0, 0.5-4.5, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 3-3.5, 3-4, 3-4.5, 3-5, 3.5-4, 3.5-4.5, 3.5-5, 4-4.5, 4-5, or 4.5-5%) of the polyol component, and 40-85 % (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 40-80, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 45-80, 45-85, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 50-85, 55-60, 55-65, 55-70, 55-75, 55-80, 55-85, 60-65, 60-70, 60-75, 60-80, 60-85, 65-70, 65-75, 65-80, 65-85, 70-75, 70-80, 70-85, 75-80, 75-85, or 80-85%) particulate material, based upon total weight of Paste A; Paste B

comprises 1-10 % (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10) of the isocyanate component, 3-15 % (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 3-5, 3-10, 5-10, 5-15, or 10-15%) of the polyol component, and 25-50% (*i.e.*, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 25-30, 25-35, 25-40, 25-45, 30-35, 30-40, 30-45, 30-50, 35-40, 35-45, 35-50, 40-45, or 45-50%) or 5-25 % (*i.e.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25% or 5-10, 5-15, 5-20, 10-15, 10-20, 10-25, 15-20, 15-25, or 20-25%) particulate material, based upon total weight of Paste B.

[46] Also provided are methods for closing a wound by applying a composition described herein to a wound in an amount sufficient to achieve wound closure.

[47] In embodiments, methods are provided for achieving hemostasis at a wound site by applying a composition described herein to the bleeding wound in an amount sufficient to stop the flow of blood within a period of time, as described herein.

[48] In one embodiment, provided herein are biocompatible settable compositions consisting of a plurality of component parts which, upon mixing, react to form a cured final composition at room or body temperature over a period time, the final composition optionally being biodegradable under physiological conditions. In one embodiment, the plurality of component parts consists of two parts, A and B, part A comprising a mixture of potassium dihydrogen phosphate, magnesium oxide and at least one calcium-containing compound all suspended in one or a mixture of anhydrous, non-toxic, partially water-miscible, inert suspension vehicles and part B comprising water, particles of previously unclotted mammalian blood plasma, and one or more viscosity-building agents. In one embodiment, the plurality of component parts consists of two parts, A and B, part A comprising potassium dihydrogen phosphate or dibasic sodium phosphate, or optionally magnesium oxide and a calcium containing compound suspended in one or a mixture of anhydrous partially or completely water miscible suspension vehicles and B comprises a viscosity building agent selected from one or more of a sodium, calcium or aluminum phyllosilicate or montmorillonite, a water absorbing clay, a water-absorbing polyacrylic acid, gelatin, sodium carboxymethyl cellulose and hydrocellulose, and, optionally, a particulate material selected from tricalcium phosphate, lyophilized human blood plasma, hydroxyapatite, or a mixture thereof. In one embodiment, the calcium containing compound is selected from tricalcium phosphate and

hydroxyapatite, or a mixture thereof. In one embodiment, component B further comprises one or more additives selected from a colorant, an antioxidant, a lyophilized human blood plasma and one or more therapeutic agents. In one embodiment, the therapeutic agent is selected from one or more of an anticancer agent, an antimicrobial agent, an anesthetic agent, an analgesic agent and/or an osteogenic agent. In one embodiment, each component of a set of two contains a different colorant selected from primary or secondary hues such that when the colored components are mixed, the colors combine to form a third color which may be used to visually indicate homogeneity of the mixture. In one embodiment, the components can be hand mixed to homogeneity in one minute, three minutes, nine minutes, or twelve minutes. In one embodiment, one or more individual components contains an alkylpyrrolidone. In one embodiment, the first component is derived from a putty-like, concentrated aqueous solution of an optionally crosslinkable polyanionic polymer and the second component derived from a putty-like concentrated solution of an optionally crosslinkable polycationic polymer. In one embodiment, about 0.1- 5% (*i.e.*, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.1-1, 0.1-1.5, 0.1-2, 0.1-2.5, 0.1-3, 0.1-3.5, 0.1-4, 0.1-4.5, 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3, 0.5-3.5, 0.5-4, 0.5-4.5, 0.5-5, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 3-3.5, 3-4, 3-4.5, 3-5, 3.5-4, 3.5-4.5, 3.5-5, 4-4.5, 4-5, or 4.5-5%) graphene is added as a particulate component.

[49] Any of the aspects and embodiments described herein can be combined with any other aspect or embodiment as disclosed here in the Summary of the Invention, in the Drawings, and/or in the Detailed Description of the Invention, including the below specific, non-limiting, examples/embodiments of the present invention.

[50] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this application belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise.

[51] Although methods and materials similar to or equivalent to those described herein can be used in the practice and testing of the application, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are

incorporated by reference.

[52] The references cited herein are not admitted to be prior art to the claimed application. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[53] Other features and advantages of the application will become apparent from the following detailed description in conjunction with the examples.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[54] In this disclosure, “comprises,” “comprising,” “containing,” “having,” and the like can have the meaning ascribed to them in U.S. Patent law and can mean “includes,” “including,” and the like; the terms “consisting essentially of” or “consists essentially” likewise have the meaning ascribed in U.S. Patent law and these terms are open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited are not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[55] Unless specifically stated or obvious from context, as used herein, the terms “a,” “an,” and “the” are understood to be singular or plural.

[56] Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive.

[57] As used herein, the term “about,” unless indicated otherwise, refers to the recited value, *e.g.*, amount, dose, temperature, time, percentage, *etc.*, $\pm 10\%$, $\pm 9\%$, $\pm 8\%$, $\pm 7\%$, $\pm 6\%$, $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, or $\pm 1\%$.

[58] As used herein, the terms “patient” or “subject” are used interchangeably herein to refer to any mammal, including humans, domestic and farm animals, and zoo, sports, and pet animals, such as dogs, horses, cats, and agricultural use animals including cattle, sheep, pigs, and goats. One preferred mammal is a human, including adults, children, and the elderly. A subject may also be a pet animal, including dogs, cats and horses. Preferred agricultural animals would be pigs, cattle and goats.

[59] The phrases “therapeutically effective amount” and “effective amount” and the like, as used herein, indicate an amount necessary to administer to a patient, or to a cell, tissue, or organ of a patient, to achieve a therapeutic effect, such as an ameliorating or alternatively a curative

effect. The effective amount is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or clinician. Determination of the appropriate effective amount or therapeutically effective amount is within the routine level of skill in the art.

[60] The terms “administering”, “administer”, “administration” and the like, as used herein, refer to any mode of transferring, delivering, introducing, or transporting a therapeutic agent to a subject in need of treatment with such an agent. Such modes include, but are not limited to, intraocular, oral, topical, intravenous, intraperitoneal, intramuscular, intradermal, intranasal, and subcutaneous administration.

[61] As used herein, the term “substantially” means greater than 85% (*i.e.*, greater than 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100%).

[62] As used herein, the terms “Plurionics” and “polaxmers” are used interchangeably herein to refer to nonionic triblock copolymers containing a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of polyoxyethylene. The name of a given Pluronic starts with a letter to define its physical form at room temperature (L = liquid, P = paste, F = flake (solid)) followed by a two or three digit number. The first digit (or two digits in a three-digit number) multiplied by 300 indicates the approximate molecular weight of the hydrophobe, and the last digit multiplied by 10 gives the percentage polyoxyethylene content.

[63] In 1918, blood plasma was first used for military transfusion purposes. During the second World War, blood was fractionated by separating red and white cells from the plasma that was found to contain many active proteins such as growth factors, platelets, fibrinogen, immunoregulators, *etc.* For safety and convenience during the war, the liquid plasma was provided dry and was reconstituted by adding sterile distilled water just before use on the battlefield, thus preserving the plasma’s beneficial regenerative protein components.

[64] Plasma-derived implant materials are described, for example, in U.S. patents 8,293,530; 8,529,956; 8,529,958; 8,529,959; 8,529,960; 8,529,961; and 8,911,789 (Carmell Therapeutics, Pittsburgh, PA), which are herein incorporated by reference. The present disclosure relates to curable or settable compositions for use in surgery. Also provided are related devices, including surgical kits and packages, as well as methods of making and using the compositions. The terms settable and curable are used interchangeably herein. The settable compositions described herein consist of at least two component parts that are provided as individual units, each containing

reagents in amounts such that when the components are combined they form a single homogenous composition that is settable and that reacts or cures into a final hardened form over a period of time. In one embodiment, the mixture cures into a final hardened composition at either room temperature or body temperature, over a period of time, and without the need to apply additional external heat in excess of the ambient heat of the room (about 24-26 °C (*i.e.*, 24, 25, or 26 °C)) or the heat of the human body (about 37 °C). In one embodiment, the period of time for complete cure into a hardened final form is from about 6 to 12 (*i.e.*, 6, 7, 8, 9, 10, 11, or 12) hours or from about 6 to 24 hours (*i.e.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24). In one embodiment, the fully cured composition is drillable or machinable. In one embodiment, the homogenous composition is thermoplastic and can be softened to return it to a hand-moldable state by applying heat sufficient to warm the composition to a temperature at least higher than 40 °C, preferably between 40 °C and 100 °C (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 °C). In accordance with this embodiment, where the composition sets or cures prematurely during use, it may be heated until it becomes moldable again for a period of time until it cools.

[65] In one embodiment, the individual components are sterile.

[66] In one embodiment, an optional chain extender, such as a diol or diamine, or a crosslinker, such as a triol or triamine, is added to one of the component parts before combining, or to the homogenous settable compositions formed from the combining of the component parts, in an amount sufficient to increase the rate of the curing reaction.

[67] In one embodiment, the component parts of a composition described here are in the form of a putty or paste and may be combined, for example, by hand-kneading, or by extrusion, for example through a syringe, or by otherwise combining or compounding into a single homogenous composition. In one embodiment, the component parts each comprise an additive, such as a colorant or dye, such that the additives impart a different color to each component. In one embodiment, the separate additives, each of a different color, form a third new color when the components have been mixed to homogeneity, such that the new color indicates that a single homogenous composition has been formed. In one embodiment, the component parts consist of part A and part B, part A comprises a colorant or dye which gives part A a red color, part B comprises a colorant or dye which gives part B a blue color, and a composition of a substantially

purple color is formed from the combination of parts A and B to homogeneity. In one embodiment, the component parts can be mixed to homogeneity within about 1 minute or less, or within about 2 minutes.

[68] In one embodiment, each component of a settable compositions described herein is in the form of a putty and the homogenous settable composition that results from their combination is also in the form of a putty for a period of time after initiation of the curing reaction. The term “putty” refers to a composition that is soft, moldable, preferably non-elastic, and cohesive.

[69] In one embodiment, a putty is formed as a suspension or dispersion of particulates within a liquid. As an illustrative example of this general form, one can consider the non-medical putty composition referred to as glaziers putty, which is diatomaceous earth or clay suspended in a drying oil such as linseed oil. In one embodiment, the liquid components are selected from liquids such as the polyol, chain extender and the polyisocyanate. Non-reactive, nontoxic organic liquids such as esters, ethers and hydrocarbons may be employed in this context. In one embodiment, the solid components are particulate materials selected from one or more of calcium phosphate, siliconized calcium phosphate, a substituted calcium phosphate where the substitution is with magnesium, strontium, or silicate, for example, calcium phosphosilicate, calcium pyrophosphate, lyophilized human blood plasma derivatives, hydroxyapatite, polyaryletherketone-based materials (*e.g.*, PEK, PEEK, PEKK, PEEKK and PEKEKK), polyurethanes, polyureaurethanes, polymethylmethacrylate (PMMA), silicone polymers, glass-ionomer, absorbable phosphate glass, calcium sulfate, tricalcium phosphate (*e.g.*, beta tricalcium phosphate), demineralized bone matrix (DBM), or mineralized bone, or any combination of the foregoing.

[70] In one embodiment, the particulate component for inclusion in a component part of the compositions described here is selected from one or more of calcium sulfate, sodium phosphate, calcium aluminate, strontium phosphate, calcium strontium phosphate, tricalcium phosphate, calcium pyrophosphate, magnesium phosphate, hydroxyapatite, biomimetic carbonate apatite, biphasic calcium phosphate/hydroxyapatite, mineralized bone matrix, demineralized bone matrix, glass ionomer, absorbable phosphate glass and nonresorbable particulate metallic or polymeric materials such as stainless steel or titanium powder or nanoparticles, polyurethane, polyureaurethane, polymethacrylic acid and polyarylether ketones such as PEK, PEEK, PEKK, PEEKK and PEKEKK particles. Further examples of particulate materials are provided *infra*.

[71] The particles of a particulate material used in the component parts of the compositions

described here may be porous or non-porous particles. In one embodiment, the particles are porous and the degree of porosity is sufficient to permit the ingress of cells or fluids into the composition after its placement *in situ*. Particle size may also be varied from about 0.05 to less than or equal to 1 millimeter or 2 millimeters in diameter to control the consistency, with smaller particle sizes yielding smoother more cohesive putties.

[72] In one embodiment, the putty consistency is formed by the inclusion of viscous prepolymers in at least one of the component parts of the composition. In this context, a prepolymer comprises reactive components that are liquids and/or powders which are partially reacted by limiting one or more of the reactants to produce more viscous versions of a more liquid component. Softeners such as nonreactive surfactants, hydrophilic compounds or polymers such as polyethylene glycol dialkyl ethers, *etc.*, may also be added.

[73] The settable compositions described herein are biocompatible and suitable for use *in vivo*, particularly during surgery. The term “biocompatible” refers to materials that do not induce undesirable effects when administered or implanted *in vivo*, for example, an immune reaction and/or an inflammatory reaction, or other adverse reaction that is detrimental to wound healing and/or to the implant recipient. A biocompatible material may also be referred to as “nontoxic”. In one aspect, the biocompatible compositions described here form from a low-exotherm reaction and their formation does not produce toxic fumes or tissue-damaging amounts of heat. In another aspect, where the compositions are biodegradable, their degradation under physiological conditions does not produce toxic by-products and/or is not toxic to the implant recipient. In one embodiment, the maximum exotherm (amount of heat *i.e.*, temperature increase, generated by the reaction) of the polymerization reaction is 20 °C or less, most preferably 10 °C or less.

[74] In one embodiment, the compositions are fully or partially biodegradable. The terms “degradable”, “biodegradable”, “resorbable”, and “absorbable” and the like are used interchangeably herein to refer to the ability of the claimed compositions to degrade (partially or completely) under physiological conditions into non-toxic products that can be metabolized or excreted from the body within a period of time, generally several days and up to a year or about 18 to 24 months (*i.e.*, 18, 19, 20, 21, 22, 23, or 24 months) or longer. In one embodiment, the composition is fully biodegradable within about 12 months. Compositions may be considered non-biodegradable if they remain stable *in vivo* for periods exceeding about ten years.

[75] In one embodiment, the compositions are osteopromotive or comprise an osteopromotive

component. The term “osteopromotive” encompasses the ability to support, enhance or accelerate the growth of new bone tissue by one or more of osteoconduction, and osteoinduction. In one embodiment, the compositions further comprise one or more osteopromotive recombinant proteins selected from the group consisting of bone morphogenic proteins (*e.g.*, BMP-2, BMP-7), platelet derived growth factor, transforming growth factor beta, epidermal growth factor, NELL and UCB-1. In one embodiment, the osteopromotive component comprises an osteoconductive component. In one embodiment, the osteoconductive component comprises or consists of particles of an osteoconductive material, such as particles of tricalcium phosphate or bioglass. The term “bioglass” refers to a group of glass-ceramic materials comprising SiO₂, Na₂O, CaOP₂O₅, and combinations of these. Preferably, the particles are in a size range of 1 micron to 2,000 microns (*e.g.*, 100-1900, 200-1800, 300-1700, 400-1600, 500-1500, 600-1400, 700-1300, 800-1200, or 900-1100 microns) average mean diameter.

[76] In certain embodiments, a homogenous settable composition as described here is also mechanically hemostatic. In one embodiment, the homogenous settable composition has the property of adhering to the surface of actively bleeding bone with sufficient strength to stop the bleeding within at least about 1 minute, at least about 2-5 minutes, or at least 5-10 minutes. In accordance with this embodiment, the homogenous settable composition remains both moldable and sufficiently adhesive to adhere to the surface of actively bleeding bone for a period of time following the combination of component parts that initiated the curing reaction. In one embodiment, the period of time is from about 1 to 30 min, about 1 to 15 min, or about 1 to 10 min. It should be understood that characterizing the adhesive properties of the settable composition during a period of time after initiation of the curing reaction in relation to bleeding bone is meant for descriptive purposes only, and not intended to limit the use of the compositions to hard tissues. In some embodiments, the settable compositions described here may also be useful as soft-tissue hemostats. In addition, although the settable compositions are described here as having physical properties suitable for mechanical (tamponade) hemostasis, in certain embodiments any of the hemostatic compositions described herein may also contain one or more agents that act as active chemical hemostats. Non-limiting examples include blood clot-inducing agents such as prothrombin, thrombin, lyophilized clotted or unclotted human blood plasma optionally processed by crosslinking, oxidized cellulose, microcrystalline collagen, gelatin foam, collagen sponge, fibrinogen, and fibrin. In one embodiment, the composition may also comprise one or more of

epinephrine, tannic acid, ferrous sulfate, and the double-sulfates of a trivalent metal and a univalent metal such as potassium aluminum sulfate and ammonium aluminum sulfate. Thus, a settable composition may be hemostatic, mechanically or chemically, or by a combination of mechanical and chemical hemostasis.

Surgical Kits and Packages

[77] Also provided is a surgical kit or package comprising a settable composition described herein. As discussed above, the settable compositions described herein consist of at least two components that are provided as individual units, each containing reagents in amounts such that when the components are mixed, they react or cure into a hardened composition after a period of time, preferably at room or body temperature.

[78] As a practical matter, during use of a settable composition in surgery, freshly made material may be required at widely spaced points in time. If the material is not mixed just before use, its moldability, uniformity, and adherence to the surfaces to which it is applied will be diminished. In this context, the adhesive nature of the material is a function of its uncured state. In some embodiments, the composition as it cures bonds to the tissue at the site of implantation, for example bone tissue. And if the material is compounded too early, it may set before it can be applied. In such a state, it will be insufficiently moldable, insufficiently adhesive, and unsuitable for use.

[79] The surgical kits and packages described herein provide a solution to this problem by providing the availability of freshly made settable material at different times during a surgical procedure.

[80] In one embodiment, the present disclosure provides a container comprising two or more compartments, each compartment containing an amount of a component. Where the container comprises multiple sets of components, the compartments are adapted such that each set can be removed without disturbing the other sets in the package. If the components are sterile, the container is adapted such that each set of components can be aseptically removed without compromising the sterility of the remaining sets. For example, the separate compartments may form the lower part of a vacuum-formed container with an upper peelable film. The construction of the container allows for the removal of a single set of components from their respective compartments just before use. The components, thus exposed, then are removed from the container by a gloved finger or by using an instrument and are kneaded together until homogenous to form a single composition for surgical implantation. The composition thus formed will initially be in a

moldable form. In one embodiment, the composition is in the form of a putty, and the components of each set are also in the form of putties. As the composition sets, it hardens into a solid form. When needed, the next set of compartments in the unit is exposed by peeling down their covering film and kneading the newly exposed putties together until homogeneous and ready for surgical use. In one embodiment, the container comprises pairs of compartments and the set of components is a pair. In one embodiment, the container comprises 2 to 12 sets (*i.e.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 sets) of components.

[81] The compartments of the package may be, for example, in the form of a depression or well, or the compartments may comprise walls made of a flexible material having any shape, or an amorphous shape. In one embodiment in which the package comprises multiple pairs of putties, the package may contain any desired number of putty pairs. In one embodiment, the package consists of 2, 4, 8, 10, or 12 putty pairs. In one embodiment, perforations may be placed between pairs to facilitate removal of a pair before or after opening.

[82] In one embodiment the package comprises separate compartments or wells of a lower, vacuum-formed container with an upper peelable film, designed to allow a single set of putties to be removed from a single set of compartments as needed, *e.g.*, just before use during surgery. In one embodiment, the set consists of two and a single package contains from 2 to 12 sets (*i.e.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 sets) of putties.

[83] In another embodiment, the package comprises a syringe component. In one embodiment, the syringe component is a single syringe pre-loaded with measured amounts of a set of putties in separate internal compartments of the syringe such that when the syringe plunger is depressed, amounts of each component are dispensed or extruded from the syringe to form a composition that will harden into a final solid (cured) form over a period of time at room temperature or body temperature. In one embodiment, the syringe component comprises two or more syringes, each pre-loaded with one component of a set. In one embodiment, the set consists of two components.

[84] In another embodiment, the package comprises separate flexible compartments within a flexible plastic container, each compartment having a seal that, when disrupted, allows the contents of the compartments to mix together into a common flexible plastic compartment that is configured to allow mixing of the contents within the common flexible plastic compartment. In one embodiment, the package is flexible enough to allow mixing by hand-kneading. In a further embodiment, after mixing is complete, an orifice is cut into the container to allow removal of the

mixed components.

[85] In one embodiment, the package comprises or consists of a heat sealed or heat sealable foil package. In one embodiment, the package further comprises an outer envelope completely surrounding the package, and a desiccant. In one embodiment, the outer envelope is a heat sealed, pinhole free foil package.

[86] In one embodiment, the package comprises a surface which is in contact with the components, said surface having a surface energy substantially equal to or less than the surface energy of the components, or both, such that the component does not adhere or adheres weakly to the surface. In one embodiment, the surfaces of the package that are in contact with the components are coated with a surface having a surface energy substantially equal to or less than the surface energy of the components such that they do not adhere, or adhere weakly to, the surface. In one embodiment, the surface is formed of a material selected from the group consisting of polytetrafluoroethylene (PTFE), silicone, polypropylene, polyethylene, and polystyrene.

[87] In certain embodiments, a package has a shelf life of at least 1-2 years. In certain embodiments, the package has a shelf life of 6 months, 12 months, 18 months, 24 months, or 36 months.

[88] Also provided are methods for making a settable composition, the method comprising the steps of providing a package as described herein, the package containing a single set or multiple sets of components which, when mixed together, cure into a final hardened composition, and mixing a set of components into a homogenous mass. In another embodiment, the method comprises the steps of extruding measured amounts of a set from one or more syringes and kneading them together to form a single homogenous mass which cures into a final hardened composition. In one embodiment, the method comprises the steps of providing a package comprising a set of components in separate flexible compartments within a flexible container, the compartments having a breakable seal that, when broken, allows the contents of the compartment to enter into a further flexible compartment, breaking the seal such that the set of components enters into the further compartment, mixing the components into a homogenous mass within the further compartment.

[89] As an aid to manipulating the components after extrusion from the syringe or syringes, or after removal from the packaging, the surgeon may employ a device having a pliable structure with an application surface having a surface energy substantially equal to or less than the surface

energy of the composition such that the composition does not adhere or adheres very weakly to the device. The device is preferably in the form of a sheet. Suitable materials for forming the application surface include, for example, polytetrafluoroethylene (PTFE), silicone, polypropylene, polyethylene, and polystyrene. Such devices are described in US 2012/0035610, which is herein incorporated by reference.

[90] The compositions, packages and methods provided herein are for use in surgical procedures. Preferably, the surgical procedures are practiced on humans, but they may also be used on other mammals such as a dog, a cat, a horse, a cow, a pig, or a non-human primate. In one embodiment, the surgical procedure is a procedure for the repair of cranial defects and cranioplasty applications or for repair and reconstruction of the sternum. In one embodiment, a composition as described herein is suitable for use as a tissue adhesive, a hemostat, a bone cement, or a bone void filler.

[91] In one embodiment, a composition, as described herein, is suitable for an orthopedic application as a bone hemostat, a bone adhesive, a bone void filler, or a bone cement. The term “bone cement” is meant to distinguish related surgical implants, such as soft tissue adhesives, which may not possess the mechanical properties suitable for use in bone repair. A bone cement composition, when fully cured, has compressive strength, tensile strength, and elasticity suitable for use in bone repair or reconstruction. The solid form also bonds to bone or suitable metal surfaces and reaches a supporting bond strength within about 90 minutes and fully cures within about 24 hours. The solid form further bonds with tensile and shear strength comparable with normal bone within about 72 hours. In one embodiment, the mixture of putties fully cures into its solid form at room temperature or body temperature within about 90 minutes or about 120 minutes.

[92] In one embodiment, the fully cured composition is suitable for use in bone repair or as a bone cement or bone void filler and has a compressive strength of from 30 to 150 MPa (*i.e.*, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 MPa), or greater, a tensile strength of from 20 to 80 MPa (*i.e.*, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, or 80 MPa), or greater, and an elasticity defined by a Modulus of Elasticity of from 1,400 to 1,800 MPa (*i.e.*, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, or 1800 MPa), or greater. In certain embodiments, the compressive strength is at least 30 MPa, at least 40 MPa, at least 50 MPa, at least 60 MPa, at least 70 MPa, at least 80 MPa, or at least 100 MPa. In some embodiments, the compressive strength is greater than 100 MPa or greater than 150 MPa. In one

embodiment, the compressive strength is between 100 and 150 MPa (*i.e.*, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 MPa) or between 150 and 200 MPa (*i.e.*, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 MPa). Preferably, the solid form is sufficiently durable to be drillable or machineable. In certain embodiments the solid form has a tensile strength of at least 20 MPa, at least 30 MPa, at least 40 MPa, at least 50 MPa, at least 60 MPa, or at least 80 MPa. In certain embodiments the solid form has a Modulus of Elasticity of at least 1,400 MPa, at least 1,500 MPa, at least 1,600 MPa, or at least 1800 MPa. In one embodiment, the solid form has a compressive strength of at least 60 or 70 MPa, a tensile strength of at least 40 or 50 MPa, and an elasticity of at least 1,600 or 1,800 MPa.

[93] In one embodiment, the fully cured composition is suitable for use in soft tissue and has a compressive strength of from 0 to 25 MPa (*i.e.*, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 MPa), from 0 to 10 MPa (*i.e.*, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 MPa), or from 0 to 5 MPa (*i.e.*, 0, 1, 2, 3, 4, or 5 MPa), and a tensile strength of from .005 to 80 MPa (*i.e.*, 0.005, 0.01, 0.015, 0.02, 0.025, 0.03, 0.035, 0.040, 0.045, 0.05, 0.055, 0.06, 0.065, 0.07, 0.075, 0.08, 0.085, 0.09, 0.095, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 MPa), or from .005 to 20 MPa (*i.e.*, 0.005, 0.01, 0.015, 0.02, 0.025, 0.03, 0.035, 0.040, 0.045, 0.05, 0.055, 0.06, 0.065, 0.07, 0.075, 0.08, 0.085, 0.09, 0.095, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 MPa), or from .005 to 15 MPa (*i.e.*, 0.005, 0.01, 0.015, 0.02, 0.025, 0.03, 0.035, 0.040, 0.045, 0.05, 0.055, 0.06, 0.065, 0.07, 0.075, 0.08, 0.085, 0.09, 0.095, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15). In certain embodiments, the compressive strength is less than 30 MPa, less than 25 MPa, less than 20 MPa, less than 10 MPa, or less than 5 MPa.

[94] The mechanical properties described here refer to the properties of the composition alone, without the addition of other, optional, materials which may further increase these physical properties, especially compressive strength. In one embodiment, the compositions described herein do not comprise an optional particulate material. In certain embodiments, the particulate material, if present, is present in an amount up to about 80% by weight of the composition.

[95] In one embodiment, the compositions are fully or partially degradable under physiological conditions within a period of time. Where the compositions are fully degradable, they are degraded within about 12 months. The degradation may be enzymatic or non-enzymatic or a combination of both. In one embodiment, the compositions are initially degradable into non-toxic products by a non-enzymatic hydrolysis under physiological conditions. In a preferred embodiment, the compositions are fully degradable within a period of time less than 12-24 months. In certain embodiments, the polymer degradation time does not exceed 3 months or 6 months. In one embodiment, a composition is degradable within about 2 to 4 weeks after placement *in vivo*. In other embodiments, a composition is fully degradable within about 4 to 6 weeks, or within about 2 to 4 months, 4 to 6 months, 6 to 8 months, or 8 to 12 months. In certain embodiments, the compositions comprise components that are fully degradable or absorbable. In other embodiments, the compositions are comprised of components that are partially degradable or absorbable, or non-degradable. In certain embodiments, the compositions are formed from a combination of fully degradable, partially degradable, and/or non-degradable components.

Cyanoacrylate- and Methylidene Malonate Ester-Based Compositions

[96] In one embodiment, the settable composition consists of at least two components that, when mixed together, form a mixture that cures into a fully hardened polymer composition comprising either methylidene malonate or alkyl cyanoacrylate esters such as octyl cyanoacrylate polymers. The first component comprises, for example, either diethylmethylidene malonate or octyl cyanoacrylate monomer, a viscosity builder such as a minor amount of poly(diethylmethylidene malonate) or poly(octylcyanoacrylate), a free radical polymerization inhibitor component, *e.g.*, hydroquinone, an acid component to inhibit based-catalyzed polymerization, *e.g.*, sulfur dioxide and an optional anhydrous particulate component. The one or more additional components comprise the viscosity builder of the first component and, optionally, a particulate material, and one or more additional optional additives. In one embodiment, the one or more additional optional additives are selected from a colorant, a therapeutic agent and a radiopaque agent. In one embodiment, the first putty component comprises a dialkyl methylidene malonate ester and a poly(methylidenemalonate) ester and the second putty component comprises a poly(methylidenemalonate) ester and particles of previously unclotted mammalian blood plasma.

[97] The one or more additional components may further comprise an optional therapeutic agent. In one embodiment, the therapeutic agent is selected from one or more of an anti-cancer

agent, an antimicrobial agent, an antibiotic, a local anesthetic or analgesic, and an anti-inflammatory agent.

[98] In one embodiment, the one or more additional components may further comprise a bone-growth promoting agent. In one embodiment, the bone growth promoting agent is selected from bone morphogenic protein and demineralized bone matrix, and mixtures thereof. In one embodiment, the bone-growth promoting agent is an osteopromotive recombinant protein selected from the group consisting of bone morphogenic proteins, platelet derived growth factor, transforming growth factor beta, epidermal growth factor, NELL and UCB-1, and combinations thereof.

[99] In one embodiment, the composition comprises two putty components, A and B; and putty A comprises 20-50 % (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 20-25, 20-30, 20-35, 20-40, 20-45, 25-30, 25-35, 25-40, 25-45, 25-50, 30-35, 30-40, 30-45, 30-50, 35-40, 35-45, 35-50, 40-45, 40-50, or 45-50%) of the diethylmethylenedimaleonate or octyl cyanoacrylate monomer, 1-15 % (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 1-5, 1-10, 5-10, 5-15, or 10-15%) of the viscosity building component, 0-75 % (*i.e.*, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, or 75% or 0-5, 0-10, 0-15, 0-20, 0-25, 0-30, 0-35, 0-40, 0-45, 0-50, 0-55, 0-60, 0-65, 0-70, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 5-45, 5-50, 5-55, 5-60, 5-65, 5-70, 5-75, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-45, 10-50, 10-55, 10-60, 10-65, 10-70, 10-75, 15-20, 15-25, 15-30, 15-35, 15-40, 15-45, 15-50, 15-55, 15-60, 15-65, 15-70, 15-75, 20-25, 20-30, 20-35, 20-40, 20-45, 20-50, 20-55, 20-60, 20-65, 20-70, 20-75, 25-30, 25-35, 25-40, 25-45, 25-50, 25-55, 25-60, 25-65, 25-70, 25-75, 30-35, 30-40, 30-45, 30-50, 30-55, 30-60, 30-65, 30-70, 30-75, 35-40, 35-45, 35-50, 35-55, 35-60, 35-65, 35-70, 35-75, 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 50-55, 50-60, 50-65, 50-70, 50-75, 55-60, 55-65, 55-70, 55-75, 60-65, 60-70, 60-75, 65-70, 65-75, or 70-75%) particulate material, based upon total weight of putty A, a radical polymerization inhibitor component and an acidic polymerization inhibitor component; putty B comprises 3- 40 % (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 3-5, 3-10, 3-15, 3-20, 3-25, 3-30, 3-35, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 15-

20, 15-25, 15-30, 15-35, 15-40, 20-25, 20-30, 20-35, 20-40, 25-30, 25-35, 25-40, 30-35, 30-40, or 35-40%) of the viscosity building component, and, optionally, 0-85 % % (*i.e.*, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 0-5, 0-10, 0-15, 0-20, 0-25, 0-30, 0-35, 0-40, 0-45, 0-50, 0-55, 0-60, 0-65, 0-70, 0-75, 0-80, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 5-45, 5-50, 5-55, 5-60, 5-65, 5-70, 5-75, 5-80, 5-85, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-45, 10-50, 10-55, 10-60, 10-65, 10-70, 10-75, 10-80, 10-85, 15-20, 15-25, 15-30, 15-35, 15-40, 15-45, 15-50, 15-55, 15-60, 15-65, 15-70, 15-75, 15-80, 15-85, 20-25, 20-30, 20-35, 20-40, 20-45, 20-50, 20-55, 20-60, 20-65, 20-70, 20-75, 20-80, 20-85, 25-30, 25-35, 25-40, 25-45, 25-50, 25-55, 25-60, 25-65, 25-70, 25-75, 25-80, 25-85, 30-35, 30-40, 30-45, 30-50, 30-55, 30-60, 30-65, 30-70, 30-75, 30-80, 30-85, 35-40, 35-45, 35-50, 35-55, 35-60, 35-65, 35-70, 35-75, 35-80, 35-85, 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 40-80, 40-85, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 45-80, 45-85, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 50-85, 55-60, 55-65, 55-70, 55-75, 55-80, 55-85, 60-65, 60-70, 60-75, 60-80, 60-85, 65-70, 65-75, 65-80, 65-85, 70-75, 70-80, 70-85, 75-80, 75-85, or 80-85%) of particulate material, based upon the total weight of putty B, and one or more optional therapeutic agents or growth promoting agents. In one embodiment, the viscosity building component comprises polymerized monomer, the radical induced polymerization inhibitor component comprises or consists of hydroquinone and the acid induced polymerization inhibitor component comprises or consists of sulfur dioxide.

[100] In one embodiment, the composition comprises two putty components, A and B, putty A comprising a methyldene malonate ester and a poly(methyldene malonate ester) in amounts ranging from 30 to 70 % (*i.e.*, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% or 30-35, 30-40, 30-45, 30-50, 30-55, 30-60, 30-65, 35-40, 35-50, 35-55, 35-60, 35-65, 35-70, 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 45-50, 45-55, 45-60, 45-65, 45-70, 50-55, 50-60, 50-65, 50-70, 55-60, 55-65, 55-70, 60-65, 60-70, or 65-70%) and putty B comprising poly(methyldene malonate ester), in amounts ranging from 30 to 100% (*i.e.*, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% or 30-35, 30-40, 30-45, 30-50, 30-55, 30-60, 30-65, 30-70, 30-75, 30-

80, 30-85, 30-90, 30-95, 35-40, 35-50, 35-55, 35-60, 35-65, 35-70, 35-75, 35-80, 35-85, 35-90, 35-95, 35-100, 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 40-80, 40-85, 40-90, 40-95, 40-100, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 45-80, 45-85, 45-90, 45-95, 45-100, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 50-85, 50-90, 50-95, 50-100, 55-60, 55-65, 55-70, 55-75, 55-80, 55-85, 55-90, 55-95, 55-100, 60-65, 60-70, 60-75, 60-80, 60-85, 60-90, 60-95, 60-100, 65-70, 65-75, 65-85, 65-90, 65-95, 65-100, 70-75, 70-80, 70-85, 70-90, 70-95, 70-100, 75-80, 75-85, 75-90, 75-95, 75-100, 80-85, 80-90, 80-95, 80-100, 85-90, 85-95, 85-100, 90-95, 90-100, or 95-100%), wherein the amounts are based upon total weight of the composition. These compositions may additionally contain between 10-20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20%) of a lyophilized blood plasma component (*e.g.*, unclotted human pooled or autologous plasma, prescreened for pathogens, and optionally containing trehalose as a lyophilization stabilizer, that has been dried by lyophilization or simple evaporation and then cold-ground or -milled and sieved into a uniform particulate form).

[101] In one embodiment, the composition comprises two putty component, the first putty comprising a cyanoacrylate ester containing at least one free radical scavenger and one acidifying agent as anti-polymerization stabilizers and the second putty comprising a poly(cyanoacrylate) ester and particles of previously unclotted mammalian blood plasma.

[102] In one embodiment, the composition comprises two putty components, A and B, putty A comprising or consisting of a cyanoacrylate ester in amounts ranging from 30 to 70 % (*i.e.*, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% or 30-35, 30-40, 30-45, 30-50, 30-55, 30-60, 30-65, 35-40, 35-50, 35-55, 35-60, 35-65, 35-70, 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 45-50, 45-55, 45-60, 45-65, 45-70, 50-55, 50-60, 50-65, 50-70, 55-60, 55-65, 55-70, 60-65, 60-70, or 65-70%)) and a poly (cyanoacrylate) ester in amounts ranging from 70 to 30 % (*i.e.*, 70, 69, 68, 67, 66, 65, 64, 63, 62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, or 30% or 70-35, 70-40, 70-45, 70-50, 70-55, 70-60, 70-65, 65-30, 65-35, 65-40, 65-45, 65-50, 65-55, 65-60, 60-30, 60-35, 60-40, 60-45, 60-50, 60-55, 55-30, 55-35, 55-40, 55-45, 55-50, 50-30, 50-35, 50-40, 50-45, 45-30, 45-35, 45-40, 40-30, 40-35 or 35-30%)) and putty B comprising poly(cyanoacrylate) ester in amounts ranging from 97 to 100% (*i.e.*, 97, 98, 99, or 100% or 97-99, 97-100, or 98-100%), wherein the amounts are based upon total weight of the composition. Again, these compositions may additionally contain between 10-20%

(*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20) of a lyophilized blood plasma component.

Magnesium Phosphate-Based Compositions

[103] In one embodiment, the settable composition consists of at least two components that, when mixed together, form a mixture that cures into a fully hardened non-polymeric composition. The first comprises potassium dihydrogen phosphate, magnesium oxide, and a calcium containing compound such as, *e.g.*, tricalcium phosphate and/or hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$). The first component suspended in one or a mixture of anhydrous, nontoxic, partially water-miscible, inert suspension vehicles, for example one or a mixture of two or more of triacetin, a Pluronic (poloxamer) such as Pluronic L-35, and acetyl triethyl citrate, or similar liquids. A nontoxic viscosity building agent may be added, if necessary. The one or more second component comprises water, and one or a mixture of two or more viscosity building agents. In one embodiment, the viscosity building agent or agents are selected from sodium carboxymethyl cellulose, sodium alginate, Carbomer, carrageenan, aluminum silicate (Bentonite), gelatin, collagen, and chitosan. In one embodiment, the viscosity building agent is present at about 75-85 wt % (*i.e.*, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 75-80 or 80-85%). The second putty component may also optionally comprise a particulate material. In one embodiment the particulate material is selected from tricalcium phosphate and hydroxyapatite, or mixtures thereof. In one embodiment, the one or more additional second components may also optionally comprise one or more additional additives selected from a colorant, an antioxidant, and a therapeutic agent, for example, a statin.

[104] In one embodiment, the therapeutic agent is selected from one or more of an anti-cancer agent, an antimicrobial agent, an antibiotic, a local anesthetic or analgesic, a statin and an anti-inflammatory agent. In one embodiment, the one or more additional component putties may further comprise a bone-growth promoting agent.

[105] In one embodiment, the first putty comprises a mixture of potassium dihydrogen phosphate, magnesium oxide and at least one calcium-containing compound all suspended in one or a mixture of anhydrous, non-toxic, partially water-miscible, inert suspension vehicles and the second putty comprises water, particles of previously unclotted mammalian blood plasma, and one or more viscosity-building agents.

Isocyanate-Based Compositions

[106] In one embodiment, the settable composition consists of at least two component parts, A and B, that when combined form a composition that cures into a fully hardened polymeric composition, the polymer selected from a polyurethane, a polyureaurethane, a polyetherurethane, or a polyesterurethane, over a period of time at body temperature (*i.e.*, about 37 C). At least one of the component parts comprises an isocyanate component and one or both component parts comprise a polyol/polyamine component (for example, the first putty component may comprise a polyfunctional isocyanate, tocopherol acetate, calcium phosphate particles and a polyol and the second putty component may comprise a polyfunctional isocyanate, calcium phosphate particles, at least one polyol, a fatty acid salt and tocopherol acetate). The isocyanate component consists of an isocyanate monomer, polymer, prepolymer, or combination thereof. The isocyanate component may thus comprise one or more different isocyanates, as well as an isocyanate in both its monomeric form and its polymer or prepolymer form. The term “isocyanate” is used generically to refer to isocyanates, diisocyanates, and polyisocyanates. The term “polyol” in the context of the “polyol/polyamine component” refers to both diols and polyols. Thus, the polyol or polyamine component may comprise or consist of one or more different diols, polyols, polyamines, or mixtures of two or more diols, polyols and/or polyamines.

[107] In one embodiment, the composition further comprises an additive selected from one or more of tocopherol esters (*e.g.*, tocopheryl acetate), triglycerides, acetyl triethyl citrate, and fatty acid esters, to aid in handling properties and packaging. In one embodiment, the composition further comprises one or more additives selected from an antioxidant, an anhydrous particulate material, a colorant, a therapeutic agent, and a radiopaque agent. In one embodiment, the therapeutic agent is selected from one or more of an anticancer agent, an antimicrobial agent, an anesthetic agent, an analgesic agent, an anti-inflammatory agent, and an osteogenic agent.

[108] In one embodiment, the composition further comprises an osteoconductive component. In one embodiment, the osteoconductive component also confers porosity to the composition and the porosity is sufficient to allow the ingress of fluids and/or cells (*e.g.*, osteoclasts, blood cells) into the composition *in situ*. In one embodiment, the osteoconductive component comprises or consists of particles of an osteoconductive material, such as particles of tricalcium phosphate or bioglass. The term bioglass refers to a group of glass-ceramic materials comprising SiO₂, Na₂O, CaOP₂O₅, and combinations of these.

[109] In one embodiment, porosity is not introduced into the composition as it cures by the addition of water or a carboxylic acid, *e.g.*, benzoic acid, into any of the component parts of the composition. In one embodiment, the component parts do not contain either a carboxylic acid or added water such that the only water present during the curing reaction is water that may optionally be present at the site of implantation in the body.

[110] In one embodiment, the fully hardened polyurethane or polyurethane composition possesses sufficient mechanical properties to be weight bearing, for example for use as a weight-bearing implant in bone, such as a bone void filler, or a bone cement.

[111] In one embodiment, one or more of the components of the composition comprises a prepolymer. A prepolymer is a polymer having reactive end groups, *e.g.*, isocyanate or hydroxyl groups. In one embodiment, the prepolymer comprises an excess of the isocyanate component relative to the polyol/polyamine component. In one embodiment of a two-component composition, one component comprises a prepolymer and no, or substantially no, unreacted polyol; and the second comprises or consists of a hydroxyl terminated prepolymer lacking free isocyanate groups and unreacted polyol or polyamine.

[112] A low molecular weight polymer refers to a polymer having a number average molecular weight in the range of about 500 to 20,000 (*i.e.*, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, or 20,000 or 500-1,000, 500-5,000, 500-10,000, 500-15,000, 1,000-5,000, 1,000-10,000, 1,000-15,000, 1,000-2,0000, 5,000-10,000, 5,000-15,000, 10,000-15,000, 10,000-20,000, or 15,000-20,000) or 500 to 10,000 (*i.e.*, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, or 10,000 or 500-1,000, 500-5,000, 1,000-5,000, 1,000-10,000, or 5,000-10000). A prepolymer containing reactive isocyanate end groups is formed, for example, from the initial reaction of an excess of isocyanate with a limiting amount of polyol or polyamine.

[113] Each of the components may also independently comprise an optional particulate material and an optional chain extender, crosslinker, or curative. For example, the first putty, the second putty, or both the first putty and the second putty may comprise one or more particulate materials selected from calcium sulfate, calcium phosphosilicate, sodium phosphate, calcium aluminate, or calcium phosphate. The first putty, the second putty, or both the first putty and the second putty

may comprise one or more particulate materials selected from a polyaryletherketone-based material, a polymethylmethacrylate-based material, or a tantalum- or titanium-based filler. The first putty, the second putty, or both the first putty and the second putty may comprise one or more particulate materials selected from calcium sulfate, sodium phosphate, calcium aluminate, strontium phosphate, calcium strontium phosphate, tricalcium phosphate, calcium pyrophosphate, or magnesium phosphate. The first putty, the second putty, or both the first putty and the second putty may comprise one or more particulate materials selected from absorbable phosphate glass, nonresorbable particulate metallic materials (*e.g.* stainless steel powder, titanium powder, stainless steel nanoparticles, or titanium nanoparticles), or nonresorbable polymeric materials (*e.g.* polyurethane particles, polyurethane particles, polymethacrylic acid particles, and polyarylether ketone particles). The second putty may comprise one or more particulate materials selected from hydroxyapatite, biomimetic carbonate apatite, biphasic calcium phosphate/hydroxyapatite, mineralized bone matrix, demineralized bone matrix, or glass ionomer.

[114] As discussed above, the components of the settable composition are provided as individual units, each containing reagents in amounts such that when the components are mixed together, they form a mixture that fully reacts or cures into a hardened composition after a period of time at room or body temperature. For example, where the settable composition comprises two putties, A and B, putty A comprises an excess of the isocyanate component relative to the polyol component and putty B comprises less of the isocyanate component and more of the polyol/polyamine component than putty A. Putty B also optionally comprises a chain extender and/or crosslinker. Each putty optionally contains an amount of particulate material suspended in the liquid components to form a composition having a putty-like consistency.

[115] In one embodiment, the particulate material is selected from one or more of a polyurethane, calcium sulfate, calcium phosphosilicate, sodium phosphate, calcium aluminate, calcium phosphate, hydroxyapatite, demineralized bone, or mineralized bone. Other particulate materials may also be used, as described *infra*.

[116] In one embodiment, putty A comprises 15-50 % (*i.e.*, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 15-20, 15-25, 15-30, 15-35, 15-40, 15-45, 20-25, 20-30, 20-35, 20-40, 20-45, 20-50, 25-30, 25-35, 25-40, 25-45, 25-50, 30-35, 30-40, 30-45, 30-50, 35-40, 35-45, 35-50, 40-45, 40-50, or 45-50%) of the isocyanate component, 0.5-5 % (*i.e.*, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5,

1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3.0, 0.5-3.5, 0.5-4.0, 0.5-4.5, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 3-3.5, 3-4, 3-4.5, 3-5, 3.5-4, 3.5-4.5, 3.5-5, 4-4.5, 4-5, or 4.5-5%) of the polyol component, and 40-85 % (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 40-80, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 45-80, 45-85, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 50-85, 55-60, 55-65, 55-70, 55-75, 55-80, 55-85, 60-65, 60-70, 60-75, 60-80, 60-85, 65-70, 65-75, 65-80, 65-85, 70-75, 70-80, 70-85, 75-80, 75-85, or 80-85%) of the polyol component, and 40-75 % (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% or 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 50-55, 50-60, 50-65, 50-70, 50-75, 55-60, 55-65, 55-70, 55-75, 60-65, 60-70, 60-75, 65-70, 65-75, or 70-75%) particulate material, based upon total weight of putty A; putty B comprises 1-10 % (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10%% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10) of the isocyanate component, 3-15 % (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 3-5, 3-10, 5-10, 5-15, or 10-15)) of the polyol component, and 65-85 % (*i.e.*, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 65-70, 65-75, 65-80, 70-75, 70-80, 70-85, 75-80, 75-85, or 80-85%) particulate material, based upon total weight of putty B.

[117] In one embodiment, putty A comprises 20-35 % (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35% or 20-25, 20-30, 25-30, 25-35, or 30-35%) of the isocyanate component, 0.5-5 % (*i.e.*, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.5-1, 0.5-1.5, 0.5-2, 0.5-2.5, 0.5-3.0, 0.5-3.5, 0.5-4.0, 0.5-4.5, 1-1.5, 1-2, 1-2.5, 1-3, 1-3.5, 1-4, 1-4.5, 1-5, 1.5-2, 1.5-2.5, 1.5-3, 1.5-3.5, 1.5-4, 1.5-4.5, 1.5-5, 2-2.5, 2-3, 2-3.5, 2-4, 2-4.5, 2-5, 2.5-3, 2.5-3.5, 2.5-4, 2.5-4.5, 2.5-5, 3-3.5, 3-4, 3-4.5, 3-5, 3.5-4, 3.5-4.5, 3.5-5, 4-4.5, 4-5, or 4.5-5%) of the polyol component, and 40-85 % (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49,

50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 40-80, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 45-80, 45-85, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 50-85, 55-60, 55-65, 55-70, 55-75, 55-80, 55-85, 60-65, 60-70, 60-75, 60-80, 60-85, 65-70, 65-75, 65-80, 65-85, 70-75, 70-80, 70-85, 75-80, 75-85, or 80-85%)) of the polyol component, and 50-75 % particulate material, based upon total weight of putty A; putty B comprises 1-10 % (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% (*i.e.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10) of the isocyanate component, 3-15 % (*i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% *i.e.*, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15% or 3-5, 3-10, 5-10, 5-15, or 10-15%) of the polyol component, and 75-85 % (*i.e.*, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, or 85% or 75-80 or 80-85%) particulate material, based upon total weight of putty B.

The Isocyanate Component

[118] In one embodiment, the isocyanate component comprises or consists of an aromatic isocyanate, an aliphatic isocyanate, a cycloaliphatic isocyanate, or an adduct of an isocyanate, or a mixture of any of the foregoing. A mixture refers to a mixture of two or more of the foregoing. For example, the isocyanate component may comprise or consist of a mixture of two or more isocyanates independently selected from an aromatic isocyanate, an aliphatic isocyanate, a cycloaliphatic isocyanate, and an adduct of an isocyanate.

[119] In one embodiment, the isocyanate is an aliphatic isocyanate selected from the group consisting of ethyl lysine diisocyanate, hexamethylene diisocyanate, cyclohexyl diisocyanate.

[120] In one embodiment, the isocyanate component comprises one or more isocyanates that are relatively non-absorbable. In one embodiment, the isocyanate is an aromatic isocyanate selected from diphenylmethanediisocyanate (MDI), including mixtures thereof such as mixtures of 2,4'-diphenylmethanediisocyanate and 4,4'-diphenylmethanediisocyanate isomers (ISONATE 50 OP, Dow Chemical Co. and RUBINATE 9433, Huntsman Corp.) and its pure 4,4'-diphenylmethanediisocyanate form (MONDUR M, Bayer AG and RUBINATE 44, Huntsman Corp.). In one embodiment, the aromatic isocyanate is one of the commercially available polymeric isocyanates (*e.g.*, polycarbodiimide-modified diphenylmethane diisocyanate

(ISONATE 143L) and polymethylene polyphenylisocyanate that contains MDI (ISONATE PAPI 901 or ISONATE PAPI 27) (Dow Chemical Co.)). These isocyanates, particularly the diphenylmethane derivatives, generally result in non-absorbable or slowly absorbable polyurethanes.

[121] In one embodiment in which the composition is fully or partially absorbable, the isocyanate component comprises or consists of [5-[2-[2-(4-Isocyanatobenzoyl)oxypropanoyloxy]-ethoxy]-1-methyl-2-oxo-pentyl]-4-isocyanatobenzoate, or “ALD”. In one embodiment, the two lactyl moieties of ALD each are racemic. Alternatively, these lactyl moieties may both have D or the L conformations. Alternatively, one lactyl moiety may be D while the other is L, or one may be D, L while the other is D or L. Such changes in stereochemistry may improve the physical and/or biological properties of the resulting polymer.

[122] In one embodiment, the adduct of an isocyanate is selected from a hexamethylene diisocyanate trimer (DESMODUR N-3390) and a hexamethylene diisocyanate biuret (DESMODUR N-100) both commercially available from Bayer AG.

[123] In one embodiment, the settable composition, which may be formed from a polymer selected from a polyurethane, a polyureaurethane, a polyetherurethane, or a polyesterurethane comprises at least one hydrolysable linkage. In one embodiment, the at least one hydrolysable linkage is derived from glycolic acid, lactic acid, caprolactone, or p-dioxanone. In one embodiment, the at least one hydrolysable linkage is selected from the group consisting of ester, amide, anhydride and sulfonamide linkages between the ester-urethane, urethane- or ureaurethane-containing groups. In one embodiment, the composition comprises one or more glycolyl, lactyl, or caprolactyl hydrolysable ester linkages. In one embodiment, the composition comprises one or more ethylene glycol, diethylene glycol, propane diol or butane diol hydrolysable ester linkages. In one embodiment, the composition comprises one or more ethylene diamine, propane diamine, butane diamine, hexamethylene diamine and polyalkylene diamine hydrolysable amide linkages. In one embodiment, the composition comprises one or more lactyl hydrolysable ester linkages and each asymmetric lactyl moiety present in the polymer is selected from one or more of the D, the L or the DL (racemic) stereoisomers.

[124] The hydrolysable isocyanate based compositions are degradable at least due to the presence of functional groups in the polymer chain that are readily hydrolysable under physiological conditions. Thus, the term “partially degradable” as used in the present specification encompasses

the percentage of functional groups in the polymer chain that are hydrolyzed compared to the total number of hydrolysable groups. In this context, a partially degradable isocyanate based composition encompasses compositions in which, after a suitable period of time, about 75% of the hydrolysable groups are hydrolyzed. In certain embodiments, a partially degradable compositions is one in which about 25% to 75% (*i.e.*, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, or 75% or 25-30, 25-35, 25-40, 25-45, 25-50, 25-55, 25-60, 25-65, 25-70, 30-35, 30-40, 30-45, 35-50, 35-55, 35-60, 35-65, 35-70, 35-75, 40-45, 40-50, 40-55, 40-60, 40-65, 40-70, 40-75, 45-50, 45-55, 45-60, 45-65, 45-70, 45-75, 50-55, 50-60, 50-65, 50-70, 50-75, 55-60, 55-65, 55-70, 55-75, 60-65, 60-70, 60-75, 65-70, 65-75, or 70-75%) or 50% to 75% (*i.e.*, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, or 75% or 50-55, 50-60, 50-65, 50-70, 55-60, 55-65, 55-70, 55-75, 60-65, 60-70, 60-75, 65-70, 65-75, or 70-75%) or about 75% to 90% (*i.e.*, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90% or 75-80, 75-85, 75-90, 80-85, 80-90, or 85-90%)) of the hydrolysable groups are hydrolyzed.

[125] The rate of degradation of the compositions can be controlled in order to provide compositions that degrade at a slower or faster rate, compared to a base composition. In general, the rate of degradation is controlled by varying the isocyanate and polyol/polyamine components of the compositions, as well as the optional chain extender component according to the following parameters. In one aspect, the rate of degradation is controlled by choice of the isocyanate and polyol. Generally, the more hydrolysable linkages, the faster it will degrade while less hydrolysable linkages will degrade slower. In another aspect, the rate of degradation is controlled by varying the hydrophobic/hydrophilic balance of the polyol/polyamine component. Generally, the more carbon atoms or methylene groups between the hydrolysable functions, the slower will be the hydrolysis. For example, ethylene glycol will provide a composition that hydrolyses more rapidly than, for example, 1,3 propane diol, which in turn hydrolyses more rapidly than 1,4 butane diol. In addition, the use of hydrolysable diamines as chain extenders may increase the rate of hydrolysis. In another aspect, copolymers of caprolactone and glycolide hydrolyze faster than copolymers of caprolactone and lactide and the addition of D, L-lactide also increases the rate of hydrolysis. Thus, for example, a bis-diphenyldiisocyanate bridged with a polyglycolide, a polyglycolide-co- lactide, a polylactide, a polycaprolactone-co-glycolide, a polycaprolactone-co-

lactide, a polycaprolactone will hydrolyze at increasingly slower rates. For comparison, polyurethanes prepared using methylene bis- diphenyldiisocyanate, with no hydrolyzable linkages, are not significantly degradable under physiological conditions. In other embodiments, enzymatic sensitive sites such as di or polylysines or arginines are incorporated into one or more of the substituents. In another embodiment, the polyol or polyamine component, *e.g.*, hydroxymethylglycolate, may have a hydrolysable linkage to increase the rate of degradation, [126] In one embodiment, the isocyanate component comprises a polyaromatic di- or polyisocyanate having at least one hydrolysable linkage bridging at least two of the aromatic rings. In certain embodiments, the hydrolysable linkage bridging the aromatic rings is derived from glycolic acid, lactic acid, caprolactone, or p-dioxanone. In most cases, the hydrolyzable linkage is an ester which may degrade into an acid and an alcohol as a result of exposure to water or to naturally occurring esterases. Amide linkages are usually more difficult to hydrolyze than esters. Another option is the easily hydrolyzable acid anhydride linkage. Sulfonamides may also be considered in this context. The polyaromatic di- or polyisocyanates described herein are distinct from isocyanates having only a single aromatic ring such as toluene diisocyanate, methylene bis-p-phenyl diisocyanate, and aromatic polyisocyanates generally. Suitable isocyanates are described in U.S. Patent No. 7,772,352 and U.S. Patent Application Publication No. 2009/0292029, each of which is incorporated herein by reference.

[127] In certain embodiments, the fully cured isocyanate based compositions have a defined pore size. Porosity may be controlled through the inclusion of water, surfactants, and/or cell openers during the process of combining the one or more isocyanate components with the polyol/polyamine component to form the isocyanate based compositions. For example, porosity may be controlled by the addition of a small amount of water to a prepolymer containing isocyanate groups. The water reacts with the isocyanate group to form carbon dioxide, resulting in porosity.

[128] In one embodiment, the solid form has an average pore size in the range of from about 5 to 700 microns. In certain embodiments, the average pore size is from about 5 to 100 microns, from about 5 to 300 microns, from about 5 to 500 microns, and from about 5 to 700 microns. In certain embodiments, the average pore size is from about 100 to 300 microns, from about 200 to 500 microns, from about 300 to 600 microns, and from about 500 to 700 microns, or greater.

[129] In another embodiment, the solid form has an average pore size in the submicron range. In certain embodiments, the average pore size is from about 100 to 1000 nanometers, from about 100

to 400 nanometers, from about 400 to 800 nanometers, from about 200 to 600 nanometers, or from about 500 to 900 nanometers.

[130] Porosity may also be introduced into through the use of porous filler materials (*e.g.*, commercially available calcium phosphates with pore sizes of 200 microns or greater).

[131] In one embodiment, the isocyanate based compositions are formed from an isocyanate component that comprises or consists of a glycolide-linked polyaromatic diisocyanate monomer and a polyol component that comprises or consists of a polycaprolactone-co-glycolide polyol. In one embodiment, the isocyanate based compositions are formed from a reaction that also comprises butanediol, *e.g.*, as a chain extender. In one embodiment, the composition is formed from a reaction that further comprises one or more of water, a carboxylic acid, *e.g.*, benzoic acid (as a foaming agent), a divalent or polyvalent metal salt, a metal carbonate or bicarbonate, or a phosphate, *e.g.*, for osteoconductivity. In one embodiment, the glycolide-linked diisocyanate monomer has the following structure:



In one embodiment, the polycaprolactone-co-glycolide polyol has the following structure:



[132] In one embodiment, the isocyanate based compositions are formed from an isocyanate component that comprises or consists of a lactide linked diisocyanate monomer and a polyol component that comprises or consists of a polycaprolactone-co-lactide polyol. In one embodiment, the isocyanate based compositions are formed from a reaction that also comprises butanediol, *e.g.*, as a chain extender. In one embodiment, the composition is formed from a reaction that further comprises one or more of water, a carboxylic acid, *e.g.*, benzoic acid (as a foaming agent), a divalent or polyvalent metal salt, a metal carbonate or bicarbonate, or a phosphate, *e.g.*, for osteoconductivity. In one embodiment, the lactide-linked diisocyanate monomer has the following structure:



In one embodiment, the polycaprolactone-co-lactide polyol has the following structure:



The Polyol/Polyamine Component

[133] The diols, polyols, and polyamines suitable for use in forming absorbable polyurethane-based compositions are either degradable or non-degradable, or a mixture of the two. As used herein, the term “polyol” is meant to refer generically to diols and polyols, unless indicated otherwise. Generally, absorbable isocyanate based compositions are formed by the combination of an excess of the isocyanate component with the polyol/ polyamine component. The relative amounts are calculated as the molar ratio of NCO groups of the isocyanate component (I) to the active hydrogen functional groups (H) (*e.g.*, hydroxyl, amino, and mixtures thereof) of the polyol/ polyamine component. Generally, the ratio of polyisocyanate to polyol/polyamine (I:H) is at least 0.5:1. In certain embodiments, the ratio is about 1:1, about 1.5:1, about 2:1, about 3:1, or about 4:1. In other embodiments, the ratio is about 5:1, about 8:1, about 10:1, about 20:1, or about 50:1.

[134] In certain embodiments, the polyol/ polyamine component is present in an isocyanate prepolymer in an amount of from about 0.5% to about 50% (*i.e.*, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 0.5-1, 0.5-5, 0.5-10, 0.5-15, 0.5-20, 0.5-25, 0.5-30, 0.5-35, 0.5-40, 0.5-45, 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 5-45, 5-50, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-45, 10-50, 15-20, 15-25, 15-30, 15-35, 15-40, 15-45, 15-50, 20-25, 20-30, 20-35, 20-40, 20-45, 20-50, 25-30, 25-35, 25-40, 25-45, 25-50, 30-35, 30-40, 30-45, 30-50, 35-40, 35-45, 35-50, 40-45, 40-50, or 45-50%) by weight of the prepolymer. In certain embodiments, the polyol/ polyamine component is present in an amount of from about 0.5% to 10% (*i.e.* 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10% or 0.5-1, 0.5-2, 0.5-3, 0.5-4, 0.5-5, 0.5-6, 0.5-7, 0.5-8, 0.5-9, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, or 8-10%), from about 10% to 20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15, or 15-20), from about 20% to 35% (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35% or 20-25, 20-30, 25-30, 25-35, or 30-35%), from about 25% to 40% (*i.e.*, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 25-30, 25-35, 30-35, 30-40, or 35-40%), or from about 35% to 50% (*i.e.*, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 35-40, 35-45, 40-45, 40-50, or 45-50%) by weight of the prepolymer.

[135] Polyols suitable for use include biocompatible, naturally occurring polyols, synthetic polyols, and mixtures thereof. In certain embodiments, the polyols comprise at least one ester

group. In certain embodiments, the polyol comprises 2 to 4 (*i.e.*, 2, 3, or 4) ester groups or 5 to 10 (*i.e.*, 5, 6, 7, 8, 9, or 10) ester groups. In one embodiment, the polyol has two or more hydroxyl groups. Suitable polyols include diols and polydiols having repeating units containing up to about 18 carbon atoms. Examples of suitable diols include 1,2-ethanediol (ethylene glycol), 1,2-propanediol (propylene glycol), 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, 1,3-cyclopentanediol, 1,6-hexanediol, 1,8-octanediol and combinations thereof. Examples of preferred polydiols include polyethylene glycol with molecular weights of from about 500 to about 10000 (*i.e.*, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, or 10000 or 500-1000, 500-5000, 1000-5000, 1000-10000, or 5000-10000), polytetramethylene ether glycols, polyols derived from glycolide, lactide, trimethylenecarbonate, p-dioxanone and/or caprolactone with molecular weights of about 500 to about 10000 (*i.e.*, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, or 10000 or 500-1000, 500-5000, 1000-5000, 1000-10000, or 5000-10000).

[136] In one embodiment, one or more alkylpyrrolidones (*see e.g.*, US 7,955,616) may be added to the polyol component to improve healing.

[137] In one embodiment, the polyol is a synthetic polyol selected from a polycaprolactone polyol, polyester polyols, polyadipate polyols (*e.g.*, poly(hexane-adipate) diol, poly(butane-adipate) diol, poly(ethylene/propylene-adipate) diol, poly(hexane/adipate/isophthalate diol)), and polyols that have been derived from a synthetic acid (*e.g.*, isophthalic acid, maleic acid). An example of a suitable biocompatible synthetic polyol is a polycaprolactone diol that is commercially available from Dow Chemical under the trade name TONE 32 B8. Further non-limiting examples of suitable synthetic polyols include poly(oxypropylene) glycols, poly(oxytetramethylene) glycols, and poly(oxyethylene) glycols. In one embodiment, the synthetic polyol is selected from a polycaprolactone co-glycolide or a polycaprolactone co-lactide.

[138] In one embodiment, the polyol is a naturally occurring polyol selected from castor oil and lesquerella oil, the polyols that may be obtained by chemical modification of naturally occurring vegetable oils (*e.g.*, castor oil, olive oil, sesame oil, corn oil), naturally occurring oils that have been trans-esterified (*e.g.*, a modified castor oil polyol that has been prepared by the transesterification reaction of natural castor oil with suitable crosslinkers (*e.g.*, glycerol, trimethylolpropane, and the like) or with acids (such as adipic acid), and naturally occurring oils

that have been hydrogenated. Further non-limiting examples of suitable naturally occurring polyols include the commercially available castor-oil-based polyols CASPOL5001, CASPOL1962, and CASPOL5004 (all available from CasChem, Inc.). In certain embodiments, the polyol is not a naturally occurring polyol such as castor oil and lesquerella oil.

[139] In certain embodiments, an isocyanate prepolymer is combined with a polyamine to form a poly(urethane-urea). The polyamine may be a primary or secondary di-amine, or a hindered amine. Non-limiting examples of suitable polyamines include, hindered diamine (*e.g.*, isophorone diamine, "IPDA"), 1,4-cyclohexyl diamine, 1,3-pentane diamine, and aliphatic secondary diamines, and mixtures thereof. In certain embodiments, aliphatic diamines and cycloaliphatic diamines may be particularly suitable, and may offer improved biocompatibility. Commercially available examples of suitable polyamines include CLEARLINK 1000 (Dorf Ketal).

[140] Amines including diamines that may be suitable for use in the preparation of polyurea and polyureaurethanes include but are not limited to polyethyleneimines, PEG amines with weight average molecular weights from about 500 to about 5,000 (*i.e.*, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, or 5000 or 500-1000, 500-5000, or 1000-5000), polyoxypropylenediamines available under the tradename JEFFAMINES (Huntsman Corporation, Houston, Tex.) and polyetherdiamines in general, spermine, spermidine, hexamethylenediamine, octamethylenediamine, decamethylenediamine, dodecamethylenediamine, hexadecamethylenediamine, octadecamethylenediamine, polyamidoamine dendrimers, dextrans, PEG-dextran conjugates, cysteines, proteins and peptides containing amines, non-biologically active symmetrical and asymmetrical diamino compounds containing saturated and unsaturated, substituted and unsubstituted alkyl, aryl and alkylaryl groups having from about 2 to about 18 carbon atoms. (*i.e.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbon atoms). Further, the diamino compound can be synthesized containing a hydrolyzable link such as one or more ester groups to accelerate the rate of polymer degradation (absorption) in the body. The following structure exemplifies this concept for hexamethylenediamine: $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{COOCH}_2\text{CH}_2\text{NH}_2$.

[141] In certain embodiments, the polyol comprises 2 to 4 (*i.e.*, 2, 3, or 4) ester groups or 5 to 10 (*i.e.*, 5, 6, 7, 8, 9, or 10) ester groups. Suitable polyols have at least two hydroxyl groups. In certain embodiments, the polyol has three or more hydroxyl groups making them crosslinkers.

The Chain-Extender/Crosslinker Component

[142] In certain embodiments, one or more optional chain extenders or crosslinkers is incorporated in the formation of the absorbable isocyanate-based compositions. In certain embodiments, only a chain extender is present. In other embodiments, both a chain extender and a crosslinker are present. In one embodiment, the one or more chain extenders is a low molecular weight polyhydroxyl- and/or polyamine-terminated compound having a molecular weight in the range of 10 to 500 (*i.e.*, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, or 500 or 10-100, 10-200, 10-300, 10-400, 100-200, 100-300, 100-400, 100-500, 200-300, 200-400, 200-500, 300-400, 300-500, or 400-500) Daltons and a functionality of at least two. In certain embodiments, the chain extender is a short-chain diol or diamine. In a particular embodiment, the chain extender or crosslinker is selected from glycerol, 1,4 butanediol, 1,6-hexanediol, diethylene glycol, and combinations thereof. Chain extenders having a functionality of three or more than three are also referred to as crosslinkers. In certain embodiments, the compositions described herein are formed without crosslinkers and the compositions are not crosslinked. In other embodiments, the compositions are formed with one or more crosslinkers. The degree of crosslinking can be controlled, for example, by varying the amount of crosslinker present.

[143] In certain embodiments, the chain-extender or crosslinker is present in an isocyanate prepolymer in an amount in the range of about 5% to about 80% (*i.e.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80% or 5-10, 5-15, 5-20, 5-25, 5-30, 5-35, 5-40, 5-45, 5-50, 5-55, 5-60, 5-65, 5-70, 5-75, 10-15, 10-20, 10-25, 10-30, 10-35, 10-40, 10-45, 10-50, 10-55, 10-60, 10-65, 10-70, 10-75, 10-80, 15-20, 15-25, 15-30, 15-35, 15-40, 15-45, 15-50, 15-55, 15-60, 15-65, 15-70, 15-75, 15-80, 20-25, 20-30, 20-35, 20-40, 20-45, 20-50, 20-55, 20-60, 20-65, 20-70, 20-75, 20-80, 25-30, 25-35, 25-40, 25-45, 25-50, 25-55, 25-60, 25-65, 25-70, 25-75, 30-35, 30-40, 30-45, 30-50, 30-55, 30-60, 30-65, 30-70, 30-75, 30-80, 35-40, 35-45, 35-50, 35-55, 35-60, 35-65, 35-70, 35-75, 35-80, 40-45, 40-50, 45-55, 45-60, 45-65, 45-75, 45-80, 50-55, 50-60, 50-65, 50-70, 50-75, 50-80, 55-60, 55-65, 55-70, 55-75, 55-80, 60-65, 60-70, 60-75, 60-80, 65-70, 65-75, 65-80, 70-75, 70-80, or 75-80%) by weight of the isocyanate prepolymer. In certain

embodiments, the chain-extender or crosslinker is present in an amount of from about 5% to 20% (*i.e.*, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 5-10, 5-15, 10-15, 10-20, or 15-20%), about 20% to 30% (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30% or 20-25 or 25-30%), about 30% to 40% (*i.e.*, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 30-35 or 35-40%), about 40% to 50% (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 40-45 or 45-50%), about 50% to 60% (*i.e.*, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60% or 50-55 or 55-60%), from about 60% to 70% (*i.e.*, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% or 60-65 or 65-70%), or from about 70% to 80% (*i.e.*, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80% or 70-75 or 75-80%) by weight of the isocyanate prepolymer.

[144] The chain extender may be degradable or non-degradable. Preferably, at least one degradable chain extender is used. Suitable degradable chain extenders for use in any of the compositions described herein are described in U.S. Patent Application Serial No. 2009/0082540, which is incorporated herein by reference. In one embodiment, the at least one degradable chain extender is $\text{HOCH}_2\text{CO}_2\text{CH}_2\text{CH}_2\text{OH}$ or $\text{HOCH}_2\text{CO}_2\text{CH}_2\text{CH}_2\text{O}_2\text{CCH}_2\text{OH}$.

[145] Other suitable chain-extendors or crosslinkers include natural or synthetic aliphatic polyols. Suitable polydiols for use in the compositions described herein include diol or diol repeating units with up to 8 carbon atoms. Non-limiting examples include 1,2-ethanediol (ethylene glycol), 1,2-propanediol (propylene glycol), 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, 1,3-cyclopentanediol, 1,6-hexanediol, 1,4-cyclohexanediol, 1,8-octanediol and combinations thereof.

[146] In other embodiments, the chain extender is a polyol selected from polyethylene glycol and polypropylene glycol having molecular weights of 500-10000 (*i.e.*, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, or 10000 or 500-1000, 500-5000, 500-10000, 1000-5000, 1000-10000, or 5000-10000) Daltons. Other examples include CASPOL1962 and CASPOL5004. In certain embodiments the preferred polydiols include polydiols selected from polyethylene glycol and polypropylene glycol with molecular weights of 500-10000 (*i.e.*, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, or 10000 or 500-1000, 500-5000, 500-10000, 1000-5000, 1000-10000, or 5000-10000). In some embodiments, the crosslinker is a non-absorbable crosslinker selected from triethanolamine (TEA), trimethylolpropane, and QUADROL (BASF Corp.). In some embodiments, the chain-extender is a non-degradable chain extender selected from 1,4-butanediol, 1,6-hexanediol, and diethylene glycol. The chain-extender or

crosslinker may be present in an isocyanate prepolymer in an amount in the range of about 10% to about 80% by weight of the isocyanate prepolymer.

[147] In another embodiment, the dual putty system is able to set and adhere in aqueous environments. By nature, the isocyanate component, even containing hydrolysable linkages, is essentially hydrophobic and will resist dissolution in aqueous systems. This is true for diamines in this context. It has been found that making the diol more hydrophobic by adding a hydrophobic hydrocarbon-rich residue to a polyol, *e.g.*, glyceryl-1 or 2-monostearate, a more water resistant system is obtained. A variation of this embodiment involves the substitution of a silicon-based moiety for the hydrocarbon-rich residue although this may affect absorbability. Alternatively hydrophobicity and setting rate in aqueous environments can be improved through the use of hydrophobic fillers such as insoluble or weakly soluble aliphatic molecules and salts thereof, including divalent salts, (*e.g.*, calcium, magnesium, or zinc) of fatty acids. Also useful are cholesterol and its derivatives, as well as silated derivatives of ceramics or bone (Shimp *et al.*, U.S. Patent No. 7,270,813) Another embodiment of a water resistant, settable, dual putty system adds a small amount of hydrophobic isocyanate to the relatively hydrophilic polyol component resulting in a water-resistant mixture of polyol containing a minor amount of hydrophobic polyurethane prepolymer. In one embodiment, the chain extender does not comprise an amino acid group.

Water

[148] In certain embodiments, the compositions contain no added water. In some embodiments, the compositions are anhydrous. In certain embodiments where there is no added water, water may nevertheless be present in small amounts. For example, certain commercially-available polyols comprise a mixture of the polyol and a small amount of water. In addition, certain optional particulate materials as described herein, such as calcium carbonate may comprise bound water. Formulating the compositions in an atmosphere that contains moisture may also result in the incorporation of water into the compositions. In certain embodiments, the compositions are prepared under a nitrogen purge that comprises a desired amount of moisture, thereby controlling the water content of the compositions. In other embodiments, water may be added to the compositions during the process of their formation from the component parts. In other embodiments, the compositions are prepared under essentially water-free conditions with anhydrous components such that the resulting compositions are essentially anhydrous.

[149] In certain embodiments, water is present in the compositions being made in an amount

from at least about 0.01% to about 3% (*i.e.*, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3% or 0.01-1, 0.01-2, 0.1-1, 0.1-2, 0.1-3, 0.5-1, 0.5-2, 0.5-3, or 1-3%) by weight of the composition. In certain embodiments, water is present in an amount of from about 0.05% to 1% (*i.e.*, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1% or 0.05-1, 0.06-1, 0.07-1, 0.08-1, 0.09-1, 0.1-1, 0.2-1, 0.3-1, 0.4-1, 0.5-1, 0.6-1, 0.7-1, 0.8-1, or 0.9-1%), from about 0.05% to 1.5% (*i.e.*, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, or 1.5% or 0.05-1.5, 0.06-1.5, 0.07-1.5, 0.08-1.5, 0.09-1.5, 0.1-1.5, 0.2-1.5, 0.3-1.5, 0.4-1.5, 0.5-1.5, 0.6-1.5, 0.7-1.5, 0.8-1.5, or 0.9-1.5%), from about 0.1% to 1% (*i.e.*, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1% or 0.1-1, 0.2-1, 0.3-1, 0.4-1, 0.5-1, 0.6-1, 0.7-1, 0.8-1, or 0.9-1%), from about 0.1% to 1.5% (*i.e.*, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, or 1.5% or 0.1-1.5, 0.2-1.5, 0.3-1.5, 0.4-1.5, 0.5-1.5, 0.6-1.5, 0.7-1.5, 0.8-1.5, or 0.9-1.5%), from about 0.1% to 2% (*i.e.*, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2% or 0.1-2, 0.2-2, 0.3-2, 0.4-2, 0.5-2, 0.6-2, 0.7-2, 0.8-2, 0.9-2, 1.-2, 1.1-2, 1.2-2, 1.3-2, 1.4-2, 1.5-2, 1.6-2, 1.7-2, 1.8-2, or 1.9-2%), from about 1% to 2% (*i.e.*, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2% or 1.1-2, 1.2-2, 1.3-2, 1.4-2, 1.5-2, 1.6-2, 1.7-2, 1.8-2, or 1.9-2%), or from about 2% to 3% (*i.e.*, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, or 3% or 2.0-3, 2.1-3, 2.2-3, 2.3-3, 2.4-3, 2.5-3, 2.6-3, 2.7-3, 2.8-3, or 2.9-3%).

Particulate Materials

[150] The settable compositions described herein may contain optional particulate materials. In one embodiment, the particulate material is an osteoconductive material. In certain embodiments, the particulate material supports or promotes the growth of bone at the application site. In one embodiment, the particulate material is non-resorbable. In certain embodiments, the mean particle size of the optional particulate material is in the micron or submicron range. In one embodiment, the mean particle size is from about 0.001 to 0.100 microns, from about 0.100 to 5 microns, from about 5 to 100 microns, from about 5 to 500 microns, or from about 500 to 2000 microns.

[151] In one embodiment, the optional particulate material is a carbonate or bicarbonate material. In one embodiment, the carbonate or bicarbonate material comprises or consists of one or more of calcium carbonate, magnesium carbonate, aluminum carbonate, iron carbonate, zinc carbonate, calcium bicarbonate, and sodium bicarbonate. In one embodiment, the optional particulate material comprises or consists of bone (*e.g.*, demineralized bone, bone morphogenetic protein,

allograft bone, and/or autogenous bone), calcium phosphate, siliconized calcium phosphate, substituted calcium phosphates (*e.g.*, with magnesium, strontium, or silicate), calcium pyrophosphate, hydroxyapatite, polymethyl methacrylate, glass-ionomer, absorbable phosphate glass, calcium sulfate, tricalcium phosphate (*e.g.*, beta tricalcium phosphate), or any combination of the foregoing. Other examples include one or more poly ether ether ketones (*e.g.*, PEEK, REPLACE (Cortek, Inc.), EXPANCEL (Akzo Nobel)). In other embodiments, the particulate material is a ceramic such as substituted calcium phosphates (*e.g.*, silicate, strontium or magnesium substitution) or a glass such as bioglass. In one embodiment, the particulate material comprises or consists of one or more of calcium sulfate, calcium phosphosilicate, sodium phosphate, calcium aluminate, calcium phosphate, hydroxyapatite, demineralized bone, or mineralized bone.

[152] The optional particulate material, when present, may comprise any one or more of the materials listed in the embodiments above. In one embodiment, the particulate material, if present in the composition, does not comprise calcium carbonate. In one embodiment, the particulate material may be polymeric such as a polyurethane.

[153] In one embodiment, the particulate material is present in an amount of from about 0.01% to about 10% (*i.e.*, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10% or 0.01-1, 0.01-2, 0.01-3, 0.01-4, 0.01-5, 0.01-6, 0.01-7, 0.01-8, 0.01-9, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10, or 9-10%) by weight of the composition. In certain embodiments, the optional particulate material is present in an amount of 0.10% to 10% (*i.e.*, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10% or 0.1-1, 0.1-2, 0.1-3, 0.1-4, 0.1-5, 0.1-6, 0.1-7, 0.1-8, 0.1-9, 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6,

5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10, or 9-10%), 1% to 10% (*i.e.*, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10% or 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, 5-6, 5-7, 5-8, 5-9, 5-10, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10 or 9-10%) , or 5% to 10% (*i.e.*, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10% or 5-6, 5-7, 5-8, 5-9, 6-7, 6-8, 6-9, 6-10, 7-8, 7-9, 7-10, 8-9, 8-10, or 9-10%) . In other embodiments, the optional particulate material is present in an amount of from about 10% to about 20% (*i.e.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20% or 10-15 or 15-20%) by weight of the composition, or from about 20% to 30% (*i.e.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30% or 20-25 or 25-30%), about 30% to 40% (*i.e.*, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40% or 30-35 or 40-45%), about 40% to 50% (*i.e.*, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50% or 40-45 or 45-50%), about 50% to 60% (*i.e.*, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, or 60% or 50-55 or 55-60%), about 60% to 70% (*i.e.*, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, or 70% or 60-65 or 65-70%) or about 70% to 80% (*i.e.*, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80% or 70-75 or 75-80%) by weight of the composition.

[154] In one embodiment, the particulate additive material is graphene (available from Applied Graphene Materials and Thomas Swan, Ltd.), a single atomic layer of graphite that is electrically conductive, highly elastic, is about 100 times stronger than steel and which may be of value improving the quality of tissue healing and new bone stimulation.

Other Optional Additives

[155] The compositions may also optionally comprise one or more "cell openers." Non-limiting examples include ORTOGEL501 (Goldschmidt) (an anti-foaming additive) and X-AIR (Specialty Polymers & Services). In certain embodiments, the cell openers are present in an amount in of from about 0.1% to 5% (*i.e.*, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.1-1, 0.1-2, 0.1-3, 0.1-4, 1-3, 1-4, 1-5, 2-4, 2-5, or 1-2, 1-3, 1-4, 1-5, 2-3, 2-4, 2-5, 3-4, 3-5, or 4-5%) by weight of the composition. In one

embodiment, the cell openers are present in an amount in of from about 1% to 2% or 1% to 3% by weight of the composition. Optional additives can be added to the magnesium based section but for the malonate/cyanoacrylate section, no active hydrogen atoms can be present including those in water because they will initiate polymerization.

[156] The compositions may also optionally comprise one or more therapeutic agents. In one embodiment, the one or more therapeutic agents are selected from an anti-cancer agent, an antimicrobial agent, an antibiotic, a local anesthetic or analgesic, a statin and an anti-inflammatory agent. In one embodiment, the antibiotic is selected from a broad spectrum antibiotic, such as gentamicin, clindamycin, and erythromycin, or a gram positive and gram negative family antibiotic such as an ampicillin and a cephalosporin. In one embodiment, the local anesthetic or analgesic is selected from lidocaine, bupivacaine, tetracaine, and ropivacaine. In one embodiment, the local anesthetic or analgesic is selected from lidocaine, benzocaine and fentanyl (a potent non-opioid anesthetic). In one embodiment, the one or more anti-inflammatory substances is selected from a non-specific anti-inflammatory such as ibuprofen and aspirin, or a COX-2 specific inhibitor such as rofecoxib and celecoxib.

[157] In one embodiment, component A is a putty comprised of a concentrated aqueous solution of a polyanionic polymer, *e.g.*, carboxymethylcellulose, and component B is a putty comprised of a concentrated aqueous solution of a polycationic polymer. *e.g.*, chitosan, either of which may be optionally crosslinked. The combined materials are hemostatic when applied to a bleeding surface.

[158] In one embodiment, the compositions further comprise one or more of an antioxidant, a colorant, a steroid, calcium stearate, tocopheryl acetate, and triacetin. In one embodiment, the antioxidant is selected from IRGANOX 1010 and IRGANOX 1035 (Ciba Geigy), and CYANOX 1790 and CYANOX 2777 (Cytec Industries). In certain embodiments, the antioxidant is present in an amount of from about 0.01% to 0.5% (*i.e.*, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, or 0.5% or 0.01-0.1, 0.01-0.2, 0.01-0.3, 0.01-0.4, 0.01-0.5, 0.1-0.2, 0.1-0.3, 0.1-0.4, 0.1-0.5, 0.2-0.3, 0.3-0.4, 0.3-0.5, or 0.4-0.5%) by weight of the composition. In one embodiment, the composition comprises one or more of calcium stearate, tocopheryl acetate, and triacetin, each present in a component putty of the composition in an amount ranging from 0.1 to 5% (*i.e.*, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5% or 0.1-1, 0.1-2, 0.1-3, 0.1-4, 1-2, 1-3, 1-4, 1-5, 2-3, 2-4, 2-5, 3-4, 3-5,

or 4-5%) based upon the weight of the component putty. Non-limiting examples of colorants that may be included in the compositions are gentian violet, D&C Violet #2, and D&C Green #6.

[159] In one embodiment, the steroid is a steroid-based compound, such as an intracellular messenger, effective to modulate the rate of tissue growth, including bone growth.

[160] In one embodiment, the compositions further comprise one or more growth factors, for example BMP-2, BMP-7, PDGF, EGF, *etc.*

EQUIVALENTS

[161] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[162] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[163] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[164] Unless indicated otherwise, all percentages by are percentages by weight, parts are parts by weight, temperature is in degrees Celsius, and pressure is at or near atmospheric. There are numerous variations and combinations of reaction conditions, *e.g.*, component concentrations, desired solvents, solvent mixtures, temperatures, pressures and other reaction ranges and conditions that can be used to optimize the product purity and yield obtained from the described process. Only reasonable and routine experimentation will be required to optimize such process conditions.

What is claimed is:

1. A mechanically hemostatic putty composition comprising a particulate component and a liquid component, the particulate component comprising particles of previously unclotted lyophilized mammalian blood plasma.
2. The composition of claim 1, wherein the particles of blood plasma are crosslinked.
3. The composition of claim 2, wherein the particles of blood plasma are crosslinked with genipin, heat, a carbodiimide, formaldehyde, glutaraldehyde, calcium, aluminum, chromium, iron, tin, magnesium and zinc salts of phosphate, sulfate, carbonate, bicarbonate, or any combinations thereof prior to lyophilization.
4. The composition of claim 3, wherein the particles of blood plasma are crosslinked by heat.
5. The composition of claim 1, wherein the particles of blood plasma are not crosslinked.
6. The composition of any one of claims 1-5, wherein the particulate component further comprises a carboxylic acid salt or a fatty acid ester of polyethylene glycol.
7. The composition of claim 6, wherein the carboxylic acid salt is selected from a calcium, magnesium, zinc, aluminum, or barium salt of stearic acid.
8. The composition of claim 6, wherein the carboxylic acid salt is selected from a calcium, magnesium, zinc, aluminum, or barium salt of palmitic acid.
9. The composition of any one of claims 1-8, wherein the liquid component comprises a block or random copolymer of ethylene oxide and propylene oxide, polyethylene oxide, triethylcitrate, acetyltrihydroxyethylcitrate or an N-alkylpyrrolidone and combinations thereof.
10. The composition of claim 9 wherein the liquid component comprises a block copolymer of ethylene oxide and propylene oxide.

11. The composition of any one of claims 1-10, wherein the liquid component further comprises a tocopherol or an ester thereof.
12. The composition of any one of claims 1-11, wherein the liquid component comprises triacetin, glycerol, or a combination thereof.
13. The composition of any one of claims 1-12, wherein the putty composition is substantially anhydrous.
14. The composition of any one of claims 1-13, wherein the particulate component further comprises a mono- or di- fatty acid ester of a poly(alkyleneoxy)diol.
15. The composition of claim 14, wherein the mono- or di- fatty acid ester of a poly(alkyleneoxy)diol is selected from the group consisting of PEG laurate, PEG stearate, PEG palmitate, and PEG behenate.
16. The composition of any one of claims 1-15, wherein the particulate component further comprises a carboxylic acid salt.
17. The composition of claim 16, wherein the carboxylic acid salt is selected from a calcium, magnesium, zinc, aluminum or barium salt of an even-numbered-carbon-atom homologous series comprising lauric, myristic, palmitic, stearic, arachidic, or behenic acids.
18. The composition of any one of claims 1-17, wherein the composition further comprises an effective amount of one or more additional therapeutic additives.
19. The composition of claim 18, wherein the one or more additional therapeutic additives are selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats, and combinations thereof.
20. The composition of claim 19, wherein the chemical-based hemostats are selected from the

group consisting of thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch, and combinations thereof.

21. The composition of any one of claims 1-20, wherein the composition is sterile or sterilizable.

22. The composition of any one of claims 1-21, wherein the composition is body absorbable.

23. A two putty settable bone hemostatic and adhesive composition, wherein the first putty comprises a polyfunctional isocyanate, tocopheryl acetate, calcium phosphate particles and a polyol and the second putty comprises a polyfunctional isocyanate, calcium phosphate particles, at least one polyol, a fatty acid salt and tocopheryl acetate.

24. The two putty settable bone hemostatic and adhesive composition of claim 23, wherein, immediately after the two putties are thoroughly mixed to form a mixed putty, particles of previously unclotted, lyophilized mammalian blood plasma are added to the mixed putty and uniformly distributed throughout the mixed putty.

25. A composition obtainable by mixing the first putty and the second putty of claim 23 to form a mixed putty, adding particles of previously unclotted, lyophilized mammalian blood plasma to the mixed putty and uniformly distributing said particles throughout the mixed putty.

26. The composition of any one of claims 22 to 25, wherein the first putty, the second putty, or both the first putty and the second putty comprise one or more particulate materials selected from calcium sulfate, calcium phosphosilicate, sodium phosphate, calcium aluminate, or calcium phosphate.

27. The composition of any one of claims 23-26, wherein the second putty comprises one or more of hydroxyapatite, biomimetic carbonate apatite, demineralized bone, or mineralized bone.

28. The composition of any one of claims 23 to 25, wherein the first putty, the second putty, or both the first putty and the second putty comprises one or more particulate materials selected

from a polyaryletherketone-based material, a polymethylmethacrylate-based material, or a tantalum- or titanium-based filler.

29. The composition of any one of claims 23 to 25, wherein the first putty, the second putty, or both the first putty and the second putty comprises one or more particulate materials selected from calcium sulfate, sodium phosphate, calcium aluminate, strontium phosphate, calcium strontium phosphate, tricalcium phosphate, calcium pyrophosphate, or magnesium phosphate.

30. The composition of any one of claims 22 to 25, or 29, wherein the second putty comprises one or more particulate materials selected from hydroxyapatite, biomimetic carbonate apatite, biphasic calcium phosphate/hydroxyapatite, mineralized bone matrix, demineralized bone matrix, or glass ionomer.

31. The composition of any one of claims 22 to 25, 29, or 30, wherein the first putty, the second putty, or both the first putty and the second putty comprises one or more particulate materials selected from absorbable phosphate glass, nonresorbable particulate metallic materials, or nonresorbable polymeric materials.

32. The composition of claim 31, wherein the nonresorbable particulate metallic material is selected from the group consisting of stainless steel powder, titanium powder, stainless steel nanoparticles, and titanium nanoparticles.

33. The composition of claim 31, wherein the nonresorbable polymeric materials are selected from the group consisting of polyurethane particles, polyureaurethane particles, polymethacrylic acid particles, and polyarylether ketone particles.

34. The composition of claim 33, wherein the polyarylether ketone particles are selected from the group consisting of PEK, PEEK, PEKK, PEEKK and PEKEKK particles.

35. A composition comprising two putty components, the first putty comprising a dialkyl methyldene malonate ester and a poly(methyldenenemalonate) ester and the second putty comprising a poly(methyldenenemalonate) ester and particles of previously unclotted mammalian

blood plasma.

36. The composition of claim 35, wherein when thoroughly admixed, the first putty and the second putty result in the formation of a third putty that is a moldable, settable surgical implant suitable for hard and soft tissue repair.

37. The composition of claim 35 or claim 36, wherein the second putty comprises an effective amount of one or more additional therapeutic additives.

38. The composition of claim 37, wherein the one or more additional therapeutic additives are selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats, and combinations thereof.

39. The composition of claim 38, wherein the chemical-based hemostats are selected from the group consisting of thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch, and combinations thereof.

40. A composition comprising two putty components, the first putty comprising a cyanoacrylate ester, at least one free radical scavenger and at least one acidifying agent as anti-polymerization stabilizers and the second putty comprising a poly(cyanoacrylate) ester and particles of previously unclothed mammalian blood plasma.

41. The composition of claim 40, wherein the free radical scavenger is selected from the group consisting of hydroquinone, vitamin E acetate, beta carotene and selenium acetate.

42. The composition of claim 40 or 41, wherein the acidifying agent is selected from the group consisting of sulfur dioxide, sulfur trioxide and nitrogen dioxide.

43. The composition of any one of claims 40-42, wherein when thoroughly admixed, the first putty and the second putty result in the formation of a third putty that is a moldable, settable surgical implant suitable for hard and soft tissue repair.

44. The composition of any one of claims 40-43, wherein the second putty comprises an effective amount of one or more additional therapeutic additives.
45. The composition of claim 44, wherein the one or more additional therapeutic additives are selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats, and combinations thereof.
46. The composition of claim 45, wherein the chemical-based hemostats are selected from the group consisting of thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch, and combinations thereof.
47. A composition comprising two putty components, the first putty comprising a mixture of potassium dihydrogen phosphate, magnesium oxide and at least one calcium-containing compound all suspended in one or a mixture of anhydrous, non-toxic, partially water-miscible, inert suspension vehicles and the second putty comprising water, particles of previously unclotted mammalian blood plasma, and one or more viscosity-building agents.
48. The composition of claim 47, wherein the at least one calcium-containing compound is selected from the group consisting of tricalcium phosphate, hydroxyapatite, and combinations thereof.
49. The composition of claim 47, wherein the one or more viscosity-building agents are selected from the group consisting of sodium carboxymethyl cellulose, sodium alginate, carrageenan, gelatin, collagen chitosan, and combinations thereof.
50. The composition of any one of claims 47-49, wherein, when thoroughly admixed, the first putty and the second putty result in the formation of a third putty that is a moldable, settable surgical implant that is suitable for hard and soft tissue repair.
51. The composition of any one of claims 47-50, wherein the second putty comprises an effective amount of one or more additional therapeutic additives.

52. The composition of claim 51, wherein the one or more additional therapeutic additives are selected from the group consisting of antimicrobial agents, analgesics, anesthetics, antineoplastic agents, anti-inflammatories, radiopaque agents, biocompatible colorants, osteopromotive agents, growth factors, chemical-based hemostats, and combinations thereof.

53. The composition of claim 52, wherein the chemical-based hemostats are selected from the group consisting of thrombin, fibrin, oxidized cellulose, styptic agents, protamine, chitosan, cross-linked, purified plant starch, and combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/035172

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L24/00 A61L27/36
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/036525 A2 (ORTHOCON INC [US]; BEZWADA RAO [US]; DARR ANIQ [US]; KRONENTHAL RICHAR) 14 March 2013 (2013-03-14) page 1, paragraph 1 page 3, paragraph 7 -----	1-22, 24-53
A	US 2012/003279 A1 (CAMPBELL PHIL G [US] ET AL) 5 January 2012 (2012-01-05) claims 19, 21, 27, 28 -----	1-22, 24-53



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

31 August 2018

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Heck, Georg

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/035172

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-22, 24, 25, 35-53(completely); 26-34(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/035172

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013036525 A2	14-03-2013	CA 2844680 A1	14-03-2013
		EP 2753371 A2	16-07-2014
		HK 1200023 A1	31-07-2015
		US 2014213688 A1	31-07-2014
		US 2016250374 A1	01-09-2016
		WO 2013036525 A2	14-03-2013

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		US 2012003324 A1	05-01-2012
		US 2012177694 A1	12-07-2012
		US 2013189370 A1	25-07-2013
		US 2015165093 A1	18-06-2015

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-22, 24, 25, 35-53(completely); 26-34(partially)

Hemostatic putty composition comprising particles of previously unclotted lyophilized mammalian blood plasma.

2. claims: 23(completely); 26-34(partially)

Two putty settable bone hemostatic and adhesive composition, wherein the first putty comprises a polyfunctional isocyanate, tocopheryl acetate, calcium phosphate particles and a polyol and the second putty comprises a polyfunctional isocyanate, calcium phosphate particles, at least one polyol, a fatty acid salt and tocopheryl acetate.
