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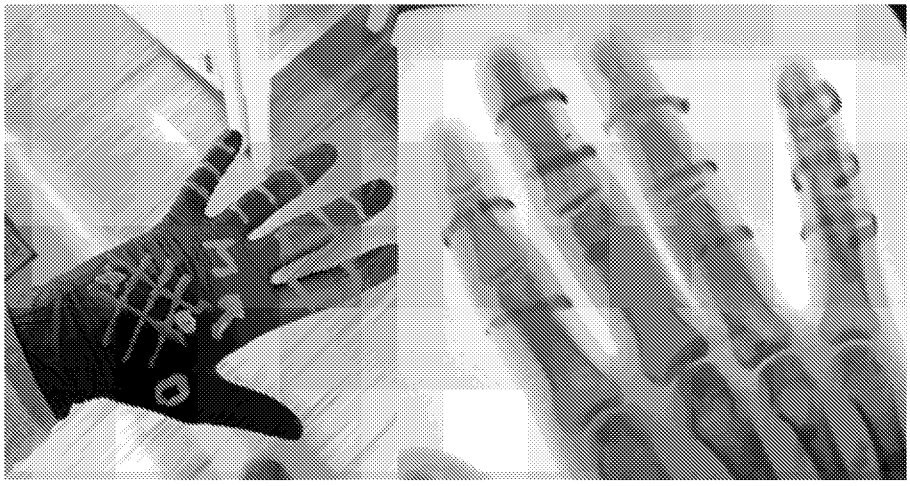

FIG. 1

(57) Abstract: A radio-opaque composition is formulated to enable a clinician, technician, or alternative user to apply custom markings to a surface, such as a patient's skin or a surgical drape on the patient. More specifically, the radio-opaque composition may be used to write on the surface. The markings may be well-defined and contrast with the surface to which they are applied. Such a composition may include the mixing of two components, each component having a silicone polymer base with radiopaque agents.

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[Continued on next page]

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SPECIFICATION

RADIOPAQUE MARKING COMPOSITIONS AND DELIVERY THEREOF

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial No. 63/123,867 filed December 10, 2020 entitled *Radiopaque Markers and Devices* and U.S. Provisional Application Serial No. 63,126,431 filed December 16, 2020 entitled *Radiopaque Markers and Devices,* each of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] This disclosure relates to radiopaque marking mediums that are also visible in normal light, and particularly to topical radiopaque marking substances and delivery mechanisms therefor.

BACKGROUND

[0003] Topical radiopaque markings are used to delineate anatomical locations in a variety of clinical settings and scenarios. In image-guided surgery, topical markings are used to provide a precise correlation between the patient and their scanned images. Examples include the following: In diagnostic imaging, topical markings are used to define anatomical locations and to orient the interpreting clinician. In cardio-vascular surgery, topical markings are used to define vascular access sites, to size anatomic organs, to define implant location, and to size implants. In select vascular applications like diabetic amputations, topical markings may be used to specifically guide amputation location. In interventional radiology, topical markings are used to guide procedures like CT-guided lung biopsy.

[0004] Other clinical applications include: Bone screws - marking skin entry site; Biliary intervention – triangulating anatomy; Ablation - uses picture of stick area, line up with laser, prep over (chlorohexidine), then puncture through x-marks; Chest tube placement – targeting with CT and making mark with CT and go through with x-ray; G-tube placement – mark colon on scan as a reference point to avoid; Nephrostomy

tube placement – mark relevant structures to avoid; Fistula de-clotting; Stent placement; and, Bone/wire fixation in plastic surgery.

[0005] These applications represent a diverse set of clinical settings and scenarios wherein, for example, radiologists, interventional radiologists, vascular surgeons, interventional cardiologists, and radiologic technicians could use topical markings to guide interventions or diagnostic interpretations.

[0006] In 2006, there were 17 million interventional procedures using radiologic imaging and approximately 360 million diagnostic radiologic imaging scans. Mettler, F. A. *et al.* Radiologic and nuclear medicine studies in the United States and worldwide: Frequency, radiation dose, and comparison with other radiation sources - 1950-2007. *Radiology* **253**, 520–531 (2009). There are numerous producers of topical markings intended for use in conjunction with radiologic imaging. Several of these producers include: Izi Medical, Beekley Medical, Webb Medical, Viscot, LeMaitre, and Speed-E-Mark.

[0007] Current topical radiopaque markers consist of stickers, placards, rulers, "BBs", and lines. These markings are used to identify anatomical sites and targets for intervention in procedures that utilize radiologic imaging. However, no single marking device can be used in all applications because no conformal, flexible marking instrument is known to exist. This leads to scenarios in which other medical equipment must be used to meet the need of the user. For example, hemostats are often used to mark the head of the femoral artery during femoral artery access for interventional cardio-vascular procedures.

[0008] In still other procedures, users place freeform markings on a patient's skin, but these cannot be seen simultaneously under imaging. Burden on the physician could be reduced by a freeform marker that can be used also under imaging.

[0009] The only known freeform radiopaque marking comes in the form of a tattoo However, a tattoo leaves a permanently visible mark on a patient's skin and is consequently undesirable.

[0010] Prior art freeform topical radiopaque markings are known. U.S. Patent No. 9,861,449 entitled Radiopaque Marking Implant (incorporated herein by reference)

discloses a crayon-like marker that applies a topical marking. However, the marking is prone to smearing and is not easily and/or cleanly removed from a patient's skin. U.S. Patent No. 10,709,800 entitled Radiopaque Writing Instruments and Methods of Use (incorporated herein by reference) discloses a liquid marker used to apply a topical marking. However, the marking is prone to smearing, does not apply evenly, dries too slowly and is not easily removed from the patient's skin.

[0011] In view of the foregoing, it is evident that a flexible, freeform marking suitable for any application using radiologic imaging is needed and that such marking has one or more of the following attributes: it applies evenly and efficiently, dries rapidly, it does not smear, that a puncture or incision can be made therethrough, it does not create an unsuitable imaging artifact, and is easily removed (i.e., without pain or the need of solvents). Other desirable attributes will be appreciated and understood by those of skill in the art.

SUMMARY

[0012] This disclosure includes compositions and devices for marking a patient's skin or a covering thereon. A marking composition according to this disclosure, which may also be referred to as an "ink," may provide a mark that is visible to an individual when viewed directly and in images obtained from one or more common imaging modalities (e.g., x-ray, fluoroscopy, CT, etc.). The marking composition may be formulated to enable a clinician to mark a patient's skin clearly and accurately to provide a well-defined and unambiguous marking that contrasts with the surface to which it is applied and that indicates the identity of the patient, the site (e.g., surgical location, etc.) where the patient is to be treated, and/or the procedure, or treatment approach, to be taken, including any patient-specific details of the procedure.

[0013] The marking composition of the present disclosure may be formulated by two components, each of which being composed by at least 50% radiopaque agent in order to provide adequate visibility under radiologic imaging. Lower concentrations of radiopaque agent may be used for more viscous formulations that apply more thickly; however, this increase in viscosity leads to undesirable delivery properties. The radiopaque agent may itself be composed of multiple radiopaque agents.

[0014] In one embodiment the two components are each composed of around 53.6% radiopaque agent. In one embodiment the two components are each composed of around 54% radiopaque agent.

[0015] However, it should be understood by the present disclosure that the composition of the at least two components should be a minimum of 50% radiopaque agent. The applied layer thickness is preferred to be less than 1.5mm. It should be further understood that the components need not each be composed of at least 50% radiopaque agent as long as the composite marking composition, comprised of the two components, of the present disclosure itself is composed of at least 50% radiopaque agent. For example, the two components could each be composed of 25% radiopaque agent and 75% radiopaque agent, respectively, such that, when combined, the composite marking composition is at least 50% radiopaque agent.

[0016] The two components may be comprised of a silicone base.

[0017] The two components are further comprised of a silicone polymer that includes silica, either particulate silica or fumed silica.

[0018] A topical radiopaque marking composition of the present disclosure may include a first radiopaque polymer component comprising a silicone polymer and a radiopaque agent, the radiopaque agent making up at least 50% of the first radiopaque polymer component; and a second radiopaque polymer component comprising a silicone polymer and a radiopaque agent, the radiopaque agent making up at least 50% of the second radiopaque polymer component; wherein the first radiopaque polymer component and said second radiopaque polymer component are mixable to form one topical radiopaque marking substance.

[0019] A method of applying a topical radiopaque marking substance of the present disclosure may include providing a radiopaque polymer A and a radiopaque polymer B, each of which having a radiopaque agent content of at least 50% and then mixing the radiopaque polymer A and radiopaque polymer B to form the topical radiopaque marking substance; and performing the mixing just prior to applying the topical radiopaque marking substance to a target site.

[0020] A method of making a topical radiopaque marking substance of the present disclosure may include providing a silicone base; formulating a silicone polymer A and a silicone polymer B from the silicone base wherein the composition of silicone polymer A is different than the composition of silicone polymer A; adding at least one radiopaque substance to each of silicone polymer A and silicone polymer B to form a radiopaque polymer A and a radiopaque polymer B, respectively; and, mixing radiopaque polymer A and radiopaque polymer B to form the topical radiopaque marking substance.

[0021] A method of making a topical radiopaque marking substance of the present disclosure may include providing a silicone base; formulating a silicone polymer from said silicone base; adding at least one radiopaque substance to the silicone polymer to form a radiopaque base; formulating a radiopaque polymer A and a radiopaque polymer B from the radiopaque base, wherein the composition of radiopaque polymer A is different from the composition of radiopaque polymer B; and mixing radiopaque polymer A and radiopaque polymer B to form the topical radiopaque marking substance.

[0022] A device for delivering a topical radiopaque marking substance in accordance with the present disclosure may include dual chambers disposed in the housing, one chamber containing a silicone based radiopaque polymer A and one chamber containing a silicone based radiopaque polymer B; a mixer disposed at a distal end of the housing; a dual chamber plunger interoperative with the dual chamber; a spring for urging movement of the dual chamber plunger into said dual chamber; and a push button to actuate movement of the dual chamber plunger.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] These and other aspects, features and advantages of which embodiments of the invention are capable of will be apparent and elucidated from the following description of embodiments of the present invention, reference being made to the accompanying drawings, in which

[0024] Figs. 1 is two photographs, both of the same hand with a topical radiopaque composition in accordance with the present disclosure, one photograph in normal light and one photograph under radiologic imaging;

[0025] Fig. 2 is a photograph of an animal with a topical radiopaque composition in accordance with the present disclosure when viewed in normal light;

[0026] Fig. 3 is a photograph of the animal of Fig. 2 when viewed under fluoroscopic radiologic imaging;

[0027] Fig. 4 is series of photographs of a topical radiopaque composition in accordance with the present disclosure, one under normal light and two under computed tomography (CT) imaging;

[0028] Fig. 5 is a photograph of a topical radiopaque composition in accordance with the present disclosure being removed from the skin of subject;

[0029] Fig. 6 is a flow chart for a formulation of a topical radiopaque composition in accordance with the present disclosure;

[0030] Fig. 7 is a flow chart for a formulation of a topical radiopaque composition in accordance with the present disclosure

[0031] Fig. 8 is a cross-sectional schematic view of a mixer and applicator mechanism for a dual component substance in accordance with the present disclosure;

[0032] Fig. 9 is a cross-sectional schematic view of a mixer and applicator mechanism for a dual component substance in accordance with the present disclosure;

[0033] Fig. 10 is a perspective view of a housing usable with a dual component mixer and applicator in accordance with the present disclosure;

[0034] Figs 11A-11C are perspective views of a housing usable with a dual component mixer and applicator in accordance with the present disclosure;

[0035] Fig. 12 is a perspective view of a housing usable with a dual component mixer and applicator in accordance with the present disclosure;

[0036] Figs 13A-13B are perspective views of a housing usable with a dual component mixer and applicator in accordance with the present disclosure; and,

[0037] Fig. 14 is a perspective view of a housing usable with a dual component mixer and applicator in accordance with the present disclosure.

DETAILED DESCRIPTION

[0038] Specific embodiments of the invention will now be described with reference to the accompanying drawings. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. The terminology used in the detailed description of the embodiments illustrated in the accompanying drawings is not intended to be limiting of the invention. In the drawings, like numbers refer to like elements.

[0039] This disclosure is directed to a topical freeform radiopaque marking composition and a marking mechanism useful in making clear and unambiguous markings on a patient in preparation for medical procedures such as surgeries and other procedures, and particularly in surgeries and procedures that require radiographic imaging (e.g., X-Ray, CT scanning, fluoroscopy, SPECT, MRI, PET-CT, MRA, nuclear medicine scans). The markings may identify the patient, one or more treatment sites on the patient, the procedure(s) to be conducted at each treatment site (e.g., surgical approaches, etc.), one or more anatomic landmarks, the interventional approach or the like. The markings are versatile and helpful both in surgeries and procedures that don't require the aid of radiographic imaging and those that do.

[0040] In one example, a topical freeform radiopaque marking composition in accordance with this disclosure is shown Figs. 1-3 in connection with a procedure involving hand surgery (Fig. 1) and a procedure involving a vascular operation (Figs. 2-3) where the marking composition is clearly seen both under normal vision and in radiographic imaging.

[0041] In another example, the topical freeform radiopaque marking composition in accordance with this disclosure is useful in CT imaging as shown in Fig. 4. In this example, a grid is drawn on a torso phantom in a simulated CT-guided lung biopsy. The far left photos is the composition in normal light and the remaining two photos show the composition in CT images. The marking composition is visible and shows no imaging artifact.

[0042] The topical freeform radiopaque composition is also easily removable from the skin of a patient as shown in Fig. 5.

[0043] It has been determined that a topical freeform radiopaque marking composition according to this disclosure has superior properties in its viewing properties under radiographic imaging, in its non-smearing properties, in its ease in removal from a patient's skin; in its ease in delivery and in its versatility.

[0044] One reason for the superior properties may be that the topical freeform radiopaque marking composition has a radiopaque agent that makes up at least 50% of the composition. Another reason may be that it is formulated from a silicone base. Another reason may be that its viscosity is in a range of 5000-7500 CPS, preferably 6500 CPS. Another reason may be that its cure time is in a range of 10 seconds to 3 minutes, and preferably 10 seconds to 60 seconds. Another reason may be that it is comprised of two components that polymerize and cross-link when mixed.

[0045] Similarly, the topical radiopaque marking composition of the present disclosure need not be formulated from only two components. As will be appreciated by one of skill in the art, more than two components could be used without departing from the scope of this disclosure and still arrive at a topical radiopaque marking composition that has at least 50% radiopaque composition, has a viscosity in a range of 5000-7500 CPS and a cure time in a range of 10 seconds to 3 minutes. In this regard, the example formulations contained herein are not limiting to the scope of the invention..

[0046] I. <u>Topical Freeform Radiopaque Marking Composition</u>

[0047] A topical freeform radiopaque marking composition according to this disclosure may comprise two components which, when mixed together, provide a

topical freeform radiopaque marking substance. Each component may include one or more radio-opaque components. Each component may include a silicone base. Each component may also include a pigment. Each component may include one or more of the following: a siloxane, a chain extender and a cross-linker. Each component may have a radiopaque agent of over 50%.

[0048] The formulations set forth below are non-limiting examples for a topical radiopaque marking composition of the present disclosure. One of ordinary skill in the art will appreciate that modifications to these formulations can be made and still arrive at a radiopaque marking composition that has at least 50% radiopaque agent, a viscosity in a range of 5000-7500 CPS and a cure time in a range of 10 seconds to 3 minutes.

[0049] For example, radiopaque agents and combinations thereof can differ from those disclosed in the examples and still result in a radiopaque marking composition in accordance with the present disclosure.

[0050] For example, different combinations of siloxanes and combinations thereof can differ from those disclosed in the examples and still result in a radiopaque marking composition in accordance with the present disclosure.

[0051] For example, different catalysts, chain extenders and cross-linkers and combinations thereof can differ from those disclosed in the examples and still result in a radiopaque marking composition in accordance with the present disclosure.

[0052] Example 1

[0053] One embodiment of a topical freeform radiopaque marking substance of the present disclosure may have the formulation set forth below:

Resultant	Component	Material %
Silicone Base	HMDZ Treated Precipitated Silica	31.000%
	10,000 Vinyl Siloxane	69.000%

Resultant	Component	Material %
Silicone Polymer A	Silicone Base	18.868%
	200 Vinyl Siloxane	37.736%
	70 Vinyl Siloxane	37.736%
	3% Platinum Catalyst	0.940%
	White Silicone Pigment	4.730%

Resultant	Component	Material %
Silicone Polymer B	Silicone Base	19.052%
	200 Vinyl Siloxane	38.104%
	70 Vinyl Siloxane	38.104%
	DH-6 Hydride (Chain Extender)	0.300%
	Cross Linker Siltech 3H (3H = 16.1 mmoles/g hydride)	2.000%
	Blue Silicone Pigment	2.440%

Resultant	Component	Material %
Radiopaque Polymer A (54% Radiopaque Agent)	Silicone Polymer A	46.000%
	Barium Sulfate	26.000%
	Sodium Diatrizoate	16.000%
	Bismuth III Oxide	12.000%

Resultant	Component	Material %
Radiopaque Polymer B (54% Radiopaque Agent)	Silicone Polymer B	46.000%
	Barium Sulfate	26.000%
	Sodium Diatrizoate	16.000%
	Bismuth III Oxide	12.000%

[0054] Compared to prior art topical radiopaque marker substances (e.g., those mentioned in the patents identified above), the formulation of Example 1 was found to have improved curing times, negligible smearing, reduced preparation time of the application site (e.g., can use standard preparation like betadine and wipes), and is easily removed from the skin as shown in Fig. 5.

[0055] With reference to Fig. 6, the process by which the Radiopaque Polymer A and Radiopaque Polymer B of the chart above may be formed is where a Silicone Base is used to form a Silicone Polymer A and a Silicone Polymer B which, in turn, are used to make Radiopaque Polymer A and Radiopaque Polymer B, respectively. Then, during use, Radiopaque Polymer A and Radiopaque Polymer B are mixed together during ejection from an applicator onto, for example, a patient, in the form of a freeform topical radiopaque marking substance in accordance with this disclosure.

[0056] In one embodiment, the freeform topical radiopaque marker substance of Example 1 may be produced in the following manner:

[0057] The silicone base is produced by mixing HMDZ treated precipitated silica with 10,000 vinyl siloxane.

[0058] The silicone base and the vinyl siloxanes (VIN 70 & VIN 200) to be used in producing Silicone Polymer A and Silicone Polymer B (the "Silicone Polymers") are weighed out in a container.

[0059] The silicone base and the vinyl siloxanes (VIN 70 and VIN 200) are then mixed using a high speed/high shear disperser blade until homogenous.

[0060] While mixing, the radiopaque agents (barium sulfate, sodium diatrizoate, and bismuth III oxide) are slowly added until a thick mixture is achieved.

[0061] The viscosity of the mixture should be where it is pourable but once poured the mixture will not drip or run. In one embodiment the viscosity is in a range of 6,500 to 7,200 cps).

[0062] Once the radiopaque agents are dispersed, the mixture is placed under a rotator-stator homogenizer and thoroughly mixed until the radiopaque agents are thoroughly dispersed. Once the mixture is homogenous, the mixture is split into two equal parts, Part A and Part B.

[0063] White silicone pigment and a 3% platinum catalyst is added to Part A and mixed using a high-speed disperser blade

[0064] Blue pigment, a chain extender (DH6) and a hydride cross linking agent is added to Part B and mixed using a high-speed disperser blade.

[0065] In one embodiment, the mixing process can take between 6-8 hours to achieve a desired viscosity.

[0066] Once thoroughly mixed, the Part A and Part B mixtures are placed in a vacuum chamber until there are no visible bubbles.

[0067] The resulting Part A and Part B mixtures constitute the Radiopaque Polymer A and Radiopaque Polymer B formulations set forth in the chart for Example A.

[0068] During use the radiopaque polymer A and radiopaque polymer B of Example 1 are mixed when exiting an applicator. The two radiopaque polymers contain different agents that, when mixed, enable polymerization and cross-linking of the vinyl monomers via the formation of a siloxane bond. The resulting freeform topical radiopaque marker substance has a cure time of around 3 minutes and a viscosity of 5000 CPS.

[0069] The shelf life of radiopaque polymer A and radiopaque polymer B of Example 1 is formulated to be 1 year.

[0070] In another embodiment, the freeform topical radiopaque marking substance may have a formulation as set forth below.

[0071] Example 2

Resultant	Component	Weight (g)	Material %
Silicone Base	HMDZ Treated Fumed Silica	31.0	31.000%
	10,000 Vinyl Siloxane	69.0	69.000%

Resultant	Component	Weight (g)	Material %
Silicone Polymer	Silicone Base	100.0	20.833%
	200 Vinyl Siloxane	380.0	79.167%

Resultant	Component	Weight (g)	Material %
Radiopaque Base (53.6% Radiopaque Agent)	Silicone Polymer	368.0	45.658%
	Barium Sulfate	144.0	17.866%
	Sodium Diatrizoate	64.0	7.940%
	Bismuth III Oxide	224.0	27.792%
	Fumed Silica	6.0	0.744%

Resultant	Component	Weight (g)	Material %
Radiopaque Polymer A (White)	Radiopaque Base (53.6% Radiopaque Agent)	383.4	94.182%
	White Silicone Pigment	20.1	4.926%
	3% Platinum Catalyst	3.6	0.892%

Resultant	Component	Weight (g)	Material %
Radiopaque Polymer B (Blue)	Radiopaque Base (53.6% Radiopaque Agent)	374.1	96.699%
	Blue Silicone Pigment	7.6	1.965%
	DH-6 Hydride Chain Extender	2.3	0.602%
	Cross Linker Siltech 3H (3H = 16.1 mmoles/g hydride)	2.8	0.734%

[0072] With reference to Fig. 7, the process by which the Radiopaque Polymer A and Radiopaque Polymer B of the chart above may be formed is where a Silicone Base is used to form a Silicone Polymer which is then used to form a Radiopaque Base. The Radiopaque Base is then used to form a Radiopaque Polymer A and Radiopaque Polymer B, respectively. Then, during use, Radiopaque Polymer A and Radiopaque Polymer B are mixed together during ejection from an applicator onto, for example, a patient, in the form of a freeform topical radiopaque marking substance in accordance with this disclosure.

[0073] In one embodiment, the freeform topical radiopaque marker substance of Example 2 may be produced in the following manner:

[0074] HMDZ treated fumed silica and 10,000 vinyl siloxane are mixed together to form a silicone base. A quality check may be performed to check viscosity and thixotropic index with expected values being those set forth in Fig. 7

[0075] The silicone base is then mixed together with 200 vinyl siloxane in a plastic container using a Ross mixer to produce a silicone polymer. In one embodiment, the mixing is performed for 30 min.

[0076] In one embodiment, the viscosity of the silicone polymer after mixing at 2 RPM was 912 cps.

[0077] In one embodiment, the viscosity of the silicone polymer after mixing at 20 RPM was 896 cps.

[0078] In one embodiment, the Thixotropic Index of the silicone polymer was 1.018.

[0079] A desired amount of silicone polymer is then move to stainless-steel container and fumed silica is added. Further mixing at high-speed using the ROSS mixer is performed.

[0080] While mixing, sodium diatrizoate is added. In one embodiment the sodium diatrizoate is added over a period of 10-15 minutes.

[0081] Once the sodium diatrizoate is thoroughly dispersed, bismuth III oxide and barium sulfate are added. In one embodiment the mixing is performed for 30-40 minutes.

[0082] The resulting radiopaque base is then placed under a rotor/stator mixer and mixed for 15 min. In one embodiment, the viscosity may be checked for the expected values as set forth in Fig. 7.

[0083] In one embodiment the viscosity of the radiopaque base is 6480 cps.

[0084] The radiopaque base is then placed under vacuum until air is removed.

[0085] To check quality, a sample of the radiopaque base is placed in an 80°F incubator for several days. The viscosity of this sample is again checked for the expected values as set forth in Fig. 7.

[0086] The remainder of the radiopaque base is then divided into 2 equal parts, a Part A and Part B.

[0087] White pigment and 3% platinum catalyst are added to Part A while mixing under a ROSS mixer to form radiopaque polymer A.

[0088] The Part B is placed under a ROSS mixer and while mixing at a medium speed, blue silicone pigment is added. Once the blue pigment is thoroughly mixed in (e.g., 10-15 minutes) DH-6 (hydride chain extender) is added.

[0089] Then the hydride cross linker (Siltech 3H where 3H = 16.1 mmoles/g hydride) is mixed into Part B.

[0090] The resulting compound constitutes radiopaque polymer B.

[0091] In one embodiment, the cure time when the radiopaque polymer A and radiopaque polymer B are combined is then measured. In one embodiment, the cure time is less than 15 seconds.

[0092] The sodium diatrizoate molecule has 3 iodine groups attached which aids in radiopacity. Sodium diatrizoate in an aqueous solution is subject to degradation. Heat and pH effects the stability. In one example 20 grams of Part A and 20 grams of Part B were placed in an oven at 60 C (140 °F) for 8 days. This equals 3 months at ambient temperature (22-25C). There was no material degradation.

[0093] During use the radiopaque polymer A and radiopaque polymer B of Example 2 are mixed when exiting an applicator. The two radiopaque polymers contain different agents that, when mixed together, enable polymerization and cross-linking of the vinyl monomers via the formation of a siloxane bond. The resulting topical radiopaque marker substance has a cure time of around 15 seconds and a viscosity of 6500 CPS.

[0094] The shelf life of radiopaque polymer A and radiopaque polymer B of Example 2 is formulated to be 2 years.

[0095] Compared to prior art topical radiopaque marker substance (e.g., those mentioned in the patents identified above), the formulation of Example 2 was found to have improved curing times, negligible smearing, improved preparation of the application site (e.g., can use standard preparation like betadine and wipes to clean the interventional site; the prior art substances, e.g., those disclosed in the patents identified above, do not allow for preparation because they dissolve and smear when

they interact with preparation agents like betadine or alcohol), and is easily removed from the skin without pain and without leaving a residue. In addition, as compared to Examiner 1, Example 2 shows a faster cure time, increased viscosity, improved visual appearance of the topical marking, and increased shelf stability.

[0096] In one embodiment, a radiopaque polymer A may have a white pigment and a radiopaque polymer B may have a blue pigment wherein the resulting color of the topical radiopaque marker substance has a blue color. It will be appreciated by one of skill in the art that different color pigments are also usable, so long as the color of the resulting topical radiopaque marker substance is visible to a user in normal light.

[0097] II. Device for Mixing and Applying Freeform Topical Radiopaque Composition.

[0098] In one embodiment, the freeform topical radiopaque marking substance in accordance with this disclosure is applied in a two-part mixing apparatus wherein Part A and Part B of the freeform topical radiopaque marking substance as discussed above is mixed during dispensing of the substance from the applicator to a location on a patient.

[0099] Prior two-part mixing applicators are known in the art. Examples of such mixers include U.S. Patent No. 10,464,719 entitled Multi-chambered dispenser and process; U.S. Patent No. 7,882,983 entitled Capsule for Two-Component Materials; U.S. Patent No. 10,130,768 entitled Combination Plunger Device for a Dual Chamber Mixing Syringe, each of which is hereby incorporated by reference. Such devices are characterized, at least in part, by the mixing together of two components of a substance. Often, a spring and a plunger are used to urge each component out of its respective chamber and into a mixing area at the dispensing end of the device.

[00100] Referring to Figs. 8 and 9, schematic of a mechanism 100 for mixing and applying a two-component topical freeform radiopaque substance in accordance with the present disclosure is shown. Fig. 8 depicts the mechanism in a filled but static state and Fig. 9 depicts the mechanism in a dispensing state.

[00101] The mechanism includes dual chambers, 122 and 124 for holding two components to be mixed, e.g., Radiopaque Polymer A and Radiopaque Polymer B,

respectively. A dual chamber plunger 118 seals the dual chambers 122, 124 and also serves as the means by which the components to be mixed are forced out of the mechanism through the mixer 120.

[00102] A plunger spring 116 is disposed between a rear of the housing 102 and the dual chamber plunger 118. In Fig. 8, the plunger spring 116 is in a compressed or "pre-loaded" state. The plunger spring 116 is held in the compressed or "pre-loaded" by the push piece 114 of an actuating rod 112. The actuating rod extends from one end where it couples with the dual chamber plunger 118 (via the push piece 114) to its opposite end which sits between a push button 104 and a push button spring 106.

[00103] The actuator rod 112 also has a series of actuator stop notches 110 which interface with at least one corresponding housing stop notch 108 positioned in the housing 102.

[00104] As depicted in Fig. 8, the two components have been loaded into the dual chambers 122, 124, respectively. The actuator rod 112 has been situated so as to compress the plunger spring 116 via the push piece 114. The actuator rod 112 is secured in this position via the interface and matching shapes of the actuator stop notches 110 and the corresponding housing stop notch 108.

[00105] Furthermore, the push button spring 106 is applying force on the front end of the actuator rod 112 so that it pushes the push button 104 away from the surface of the housing 100.

[00106] Referring to Fig. 9, when the push button 104 is pressed to overcome the resistance of the push button spring 106, this will cause the actuator stop notches 110 to become disengage or decoupled from the housing stop notches 108. As a result, the plunger spring 116 to exert its force against the push piece 114 of the actuator rod 112 which, in turn, will cause the dual chamber plunger 118 to exert force against each component residing in the dual chambers 122, 124, respectively.

[00107] Each component will be urged through the mixer 120 at the distal end of the mechanism 100. The mixer 120 will mix the two components together and the combined, mixed substance will then exit the mechanism.

[00108] In one embodiment, the components are a Radiopaque Polymer A and a Radiopaque Polymer B which, when mixed by mixer 120, will exit the device as a topical freeform radiopaque marking substance in accordance with this disclosure. The destination of the mixed substance can be a patient's skin or a surgical drape, for example.

[00109] A number of possible housings for receiving a dispensing and mixing mechanism such as the mechanism 100 described in one embodiment above are now described. As will be appreciated by one of skill in the art, the interior structure mixing mechanism of these housings are not restricted to the design set forth in Figs. 8 and 9, but, rather, can be any two-component mixing device known to those of skill in the art that can fit or by modified to fit into the housing device, or variations thereof, as depicted herein

[00110] Referring to Fig. 10, a housing 200 includes a clip 206 for use in easily securing the device in the pocket of a user. A mixer 220 extends from a distal end of the housing 200. A push button 204 is located towards a distal end of the housing 200 for mixing and dispensing the two component substances.

[00111] Referring to Figs. 11A-11B, a housing 300 comprises a push button 304 for causing the mixing and dispensing of the two component substances through a mixer 320. The housing further includes a movable distal head enabling access to the two-component mixing and application mechanism. This could allow for re-filling of the pen. It could also allow a user to mitigate a clogged dispensing tip.

[00112] In addition, the housing 300 includes a slot 330 that receives a plunger location indicator 340. The plunger location indicator 340 slides in the slot 330 according to the position of the plunger connected to the dual chambers the housing 300. For example, with reference to the mechanism 100 of Figs. 8 and 9, the plunger location indicator 340 is connected to the dual chamber plunger 118. When the dual plunger spring 116 has caused movement of the dual chamber plunger 118, the plunger location indicator 340 will slide within the housing slot 330 and thereby provide a visual and tactile indicator to the user of the amount of component substances that have been discharged from the dual chambers 122, 124. Of course, such an indication

will also convey to the user the amount of component substances remaining in the dual chambers 122, 124.

[00113] Referring to Fig. 12, a housing 400 may have a push button 404 located at the distal end of the housing 400 and also includes a mixer 420. Also located at a distal end of the housing 400 is a window 461 formed by a frame 460 extending around the mixer 420. The window 461 allows a user to observe the mixing of the components as they exit the dual chamber of the mechanism. The frame 460 also provides structural support to the mixer 420 for those uses where a greater force may be exerted on the tip of the mixer 420 during dispensing.

[00114] Referring to Fig. 13A, a housing 500 may have push button 504 located at a proximal end of the housing 500 opposite the distal end where the mixer 520 is located. The housing 500 may also have a window 562 enabling a user to observe the levels of the component substances contained in the dual chambers. The proximal end of the device 563 is contoured. In one embodiment the contour is a beveled or scalloped shape. Such a contoured shape allows a user to spread and arrange the mixed component substance, e.g., a topical freeform radiopaque marker substance, on the patient as needed.

[00115] Referring to Fig. 13B, the housing may also incorporate a self-dispensing tip 564. The self-dispensing tip is driven via a different internal mechanism than described in Figs. 8-9. In this embodiment, the push button 504 is instead a release latch that allows an internal spring to drive a dual chamber plunger. The dual chamber plunger, in turn, urges the two components to flow through the mixer. The user can stop the self-dispensing by pressing the release latch once more. The spring is then engaged and the force on the dual chamber plunger is halted.

[00116] Referring to Fig. 14, a housing 600 may include a push button 604 for mixing and dispensing the two-component substance through an exit hole 665. The mixer is not shown as it is recessed inside the exit hole 665. This embodiment has no internal springs to drive a dual plunger. Instead, the housing for the dual components is made of a compliant polymer bag. This bag is over-sized relative to the dimensions of the housing 600. Due to this physical interference, pressure is exerted on the compliant polymer bag when the two halves of the housing are assembled during manufacturing.

The push button 604 is attached to a compliant valve that opens upon pressing the push button 604. The housing also may have a fin 666 disposed on the nose of the housing 600. The fin 666 enables a user to spread the mixed two component substance after it has been dispensed through the exit hole 665.

[00117] Although the invention has been described in terms of particular embodiments and applications, one of ordinary skill in the art, in light of this teaching, can generate additional embodiments and modifications without departing from the spirit of or exceeding the scope of the claimed invention. Accordingly, it is to be understood that the drawings and descriptions herein are proffered by way of example to facilitate comprehension of the invention and should not be construed to limit the scope thereof.

What is claimed is:

1. A topical radiopaque marking composition comprising:

a first radiopaque polymer component comprising a silicone polymer and a radiopaque agent, the radiopaque agent making up at least 50% of the first radiopaque polymer component;

a second radiopaque polymer component comprising a silicone polymer and a radiopaque agent, the radiopaque agent making up at least 50% of the second radiopaque polymer component;

the first radiopaque polymer component and said second radiopaque polymer component being mixable to form one topical radiopaque marking substance.

2. A topical radiopaque marking composition according to claim 1, wherein the silicone polymer further comprises a silicone base having either precipitated silica or fumed silica.

3. A topical radiopaque marking composition according to claim 1, wherein the radiopaque agent comprises a combination of at least two radiopaque substances.

4. A topical radiopaque marking composition according to claim 3, wherein the radiopaque agent comprises three radiopaque substances.

5. A topical radiopaque marking composition according to claim 1, wherein the radiopaque agent comprises at least one of Barium Sulfate, Sodium Diatrizoate and Bismuth III Oxide.

6. A topical radiopaque marking composition according to claim 1, wherein the first radiopaque polymer substance further comprises a catalyst.

7. A topical radiopaque marking composition according to claim 1, wherein the second radiopaque polymer substance further comprises a chain extender and a cross linker.

8. A topical radiopaque marking composition according to claim 1, wherein the first radiopaque polymer component further comprises a color pigment.

9. A topical radiopaque marking composition according to claim 1 wherein the second radiopaque polymer component further comprises a color pigment.

10. A topical radiopaque marking composition according to claim 1, wherein the topical radiopaque marking substance has a viscosity of at least 6400 cps.

11. A topical radiopaque marking composition according to claim 1, wherein the topical radiopaque marking substance has a curing time of less than 15 seconds.

12. A method of applying a topical radiopaque marking substance comprising:

providing a radiopaque polymer A and a radiopaque polymer B, each of which having a radiopaque agent content of at least 50%;

mixing the radiopaque polymer A and radiopaque polymer B to form the topical radiopaque marking substance;

performing the mixing just prior to applying the topical radiopaque marking substance to a target site.

13. A method according to claim 12, further comprising curing the topical radiopaque marking substance in less than 15 seconds.

14. A method according to claim 12, wherein the mixing comprises a polymerization reaction.

15. A method according to claim 12, wherein the radiopaque polymer A and the radiopaque polymer B are each comprised of silicone based radiopaque polymer.

16. A method of making a topical radiopaque marking substance comprising:

providing a silicone base;

formulating a silicone polymer from said silicone base;

adding at least one radiopaque substance to the silicone polymer to form a radiopaque base;

formulating a radiopaque polymer A and a radiopaque polymer B from the radiopaque base, wherein the composition of radiopaque polymer A is different from the composition of radiopaque polymer B;

mixing radiopaque polymer A and radiopaque polymer B to form the topical radiopaque marking substance.

17. A method according to claim 16, wherein the difference in composition comprises radiopaque polymer A having a catalyst and the radiopaque polymer B having a chain extender and a cross linker.

18. A method of making a topical radiopaque marking substance comprising:

providing a silicone base;

formulating a silicone polymer A and a silicone polymer B from the silicone base wherein the composition of silicone polymer A is different than the composition of silicone polymer A;

adding at least one radiopaque substance to each of silicone polymer A and silicone polymer B to form a radiopaque polymer A and a radiopaque polymer B, respectively;

mixing radiopaque polymer A and radiopaque polymer B to form the topical radiopaque marking substance.

19. A method according to claim 18, wherein the difference in composition comprises silicone polymer A having a catalyst and silicone polymer B having a chain extender and a cross linker.

20. A device for delivering a topical radiopaque marking substance comprising:

a housing;

dual chambers disposed in the housing, one chamber containing a silicone based radiopaque polymer A and one chamber containing a silicone based radiopaque polymer B;

a mixer disposed at a distal end of the housing;

a dual chamber plunger interoperative with the dual chamber;

a spring for urging movement of the dual chamber plunger into said dual chamber;

a push button to actuate movement of the dual chamber plunger.

21. A device according to claim 1 further comprising a clip suitable for securing the device in a pocket of a user.

22. A device according to claim 1, further comprising a plunger locator indicator disposed on said housing and connected to said dual chamber plunger.

23. A device according to claim 1, further comprising a window located at the distal end of the housing exposing the mixer for viewing by a user.

24. A device according to claim 1, further comprising a frame located at a distal end of the housing providing structural support to the mixer.

25. A device according to claim 1, wherein the housing has a proximal end that is contoured to aid in the movement of the topical radiopaque marking substance at a delivery site.

26. A device according to claim 1, further comprising a window in the housing exposing the dual chamber.

27. A device according to claim 1, further comprising a fin disposed on the housing for spreading the topical radiopaque marking substance at a delivery site.

28. A topical radiopaque marking composition comprising:

at least 50% radiopaque agent,

a viscosity in a range of 5000-7500 CPS; and,

a cure time in a range of 10 seconds to 3 minutes.

29. A topical radiopaque marking composition according to claim 28, further comprising polymerized components.

30. A topical radiopaque marking composition according to claim 29, further comprising two polymerized components.

31. A topical radiopaque marking composition according to claim 28, further comprising a silicone base.

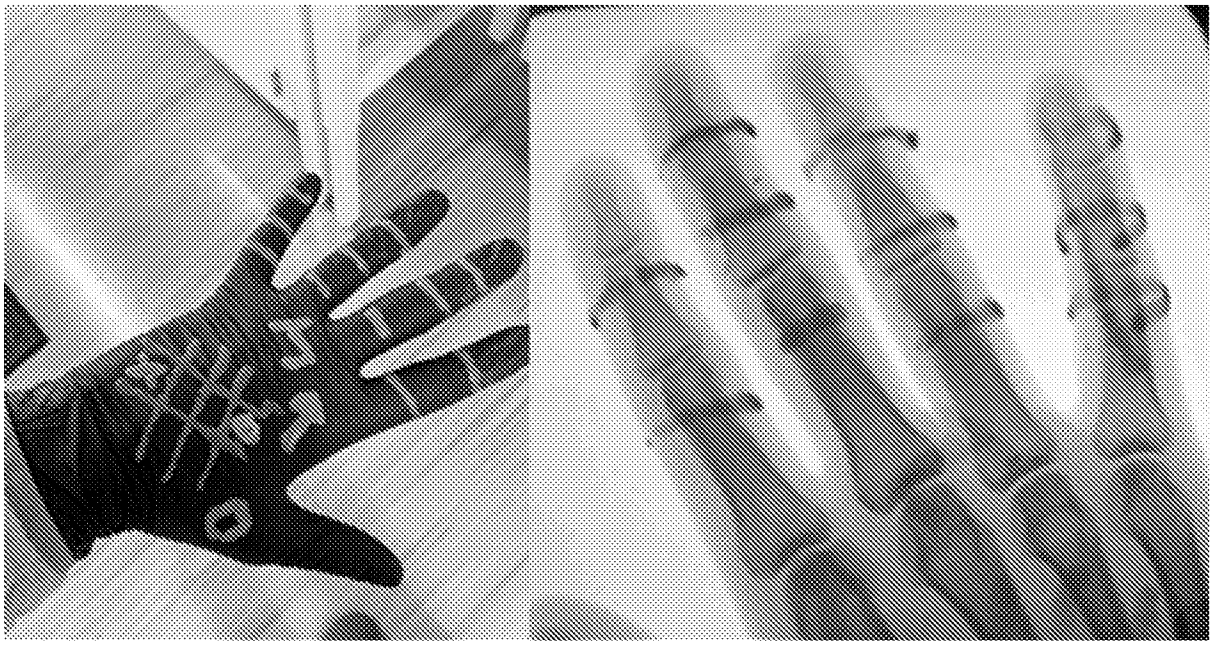


FIG. 1

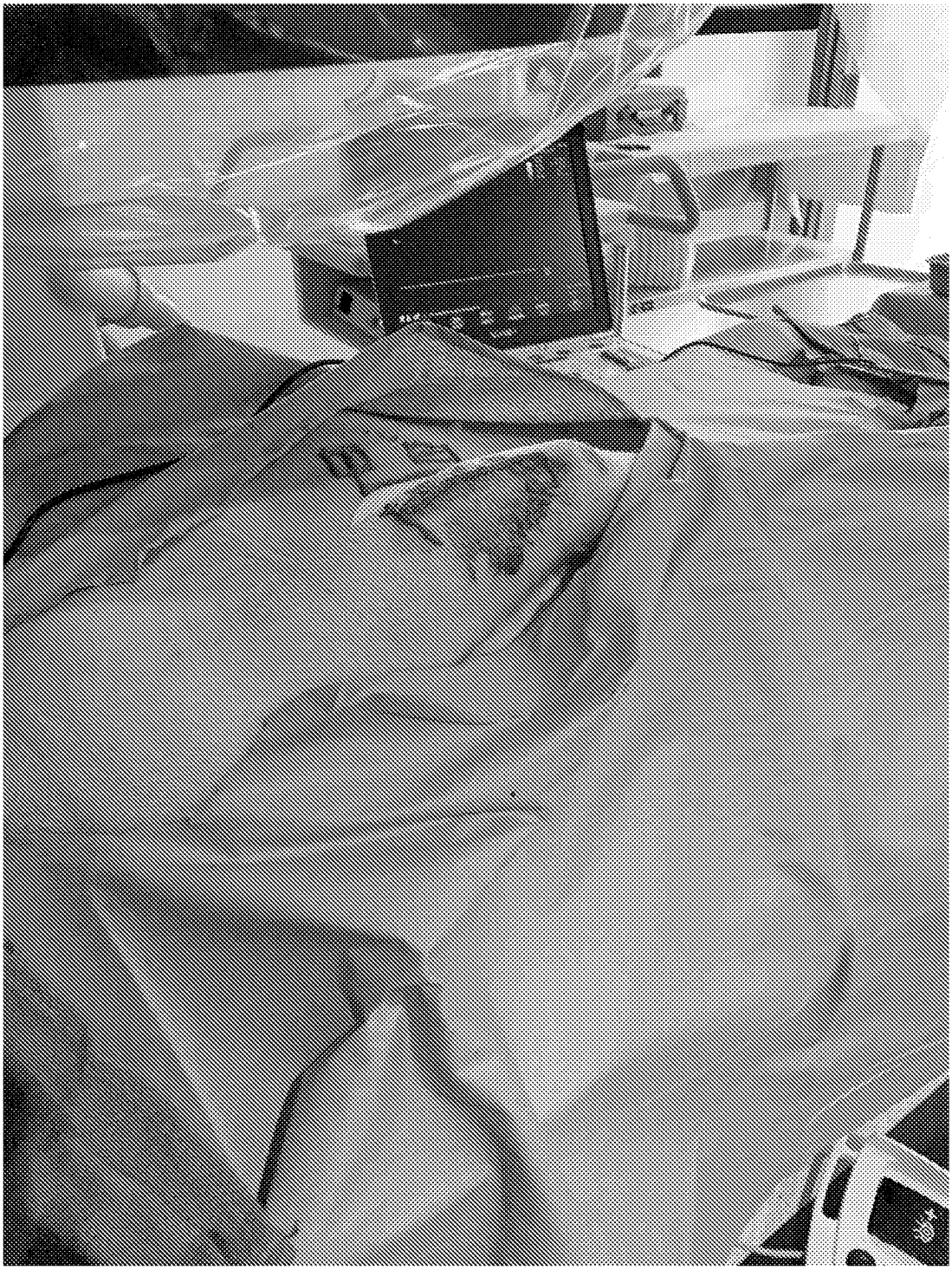


FIG. 2

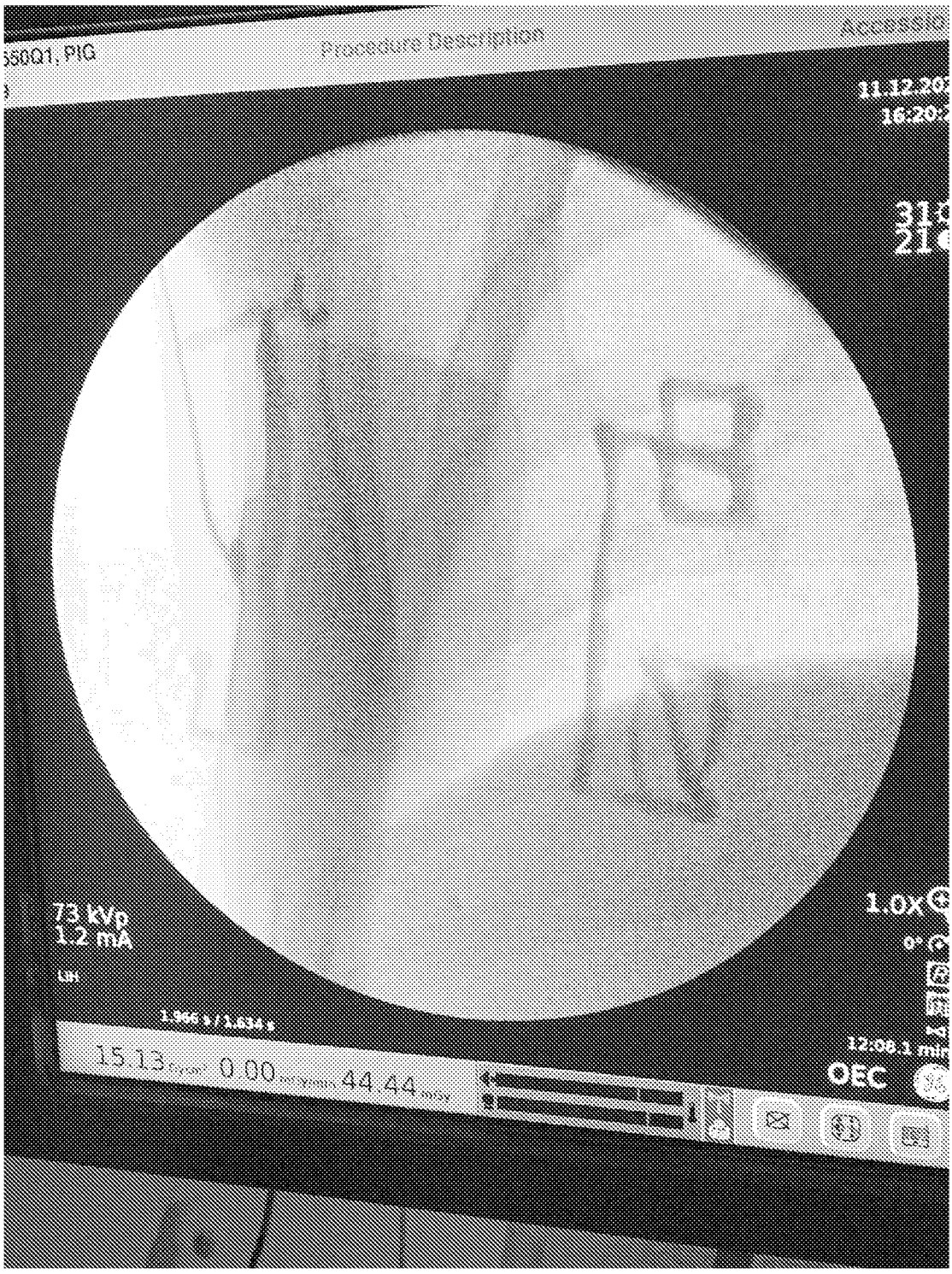


FIG. 3

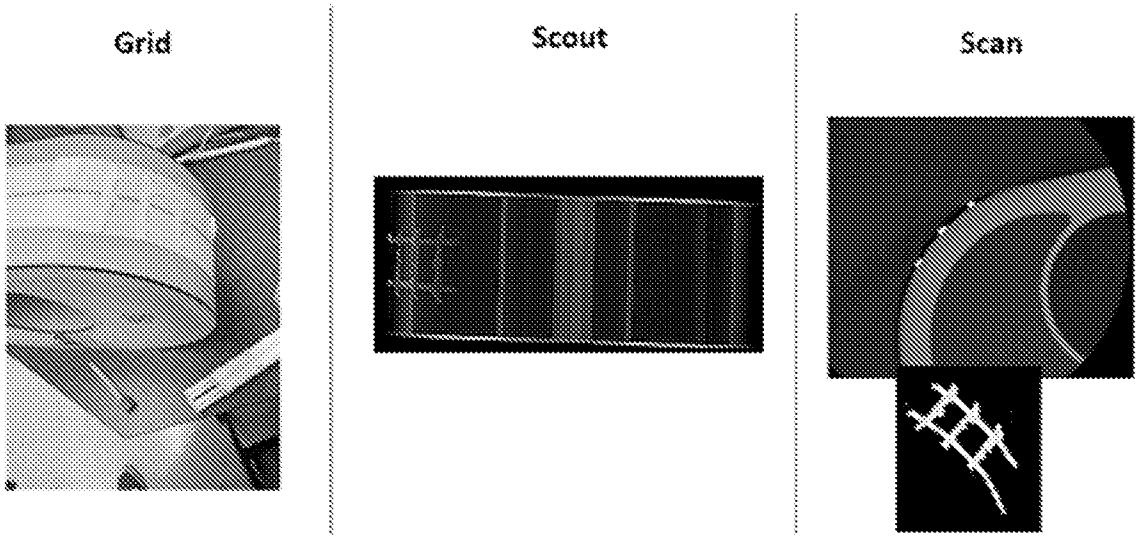


FIG. 4

FIG. 5

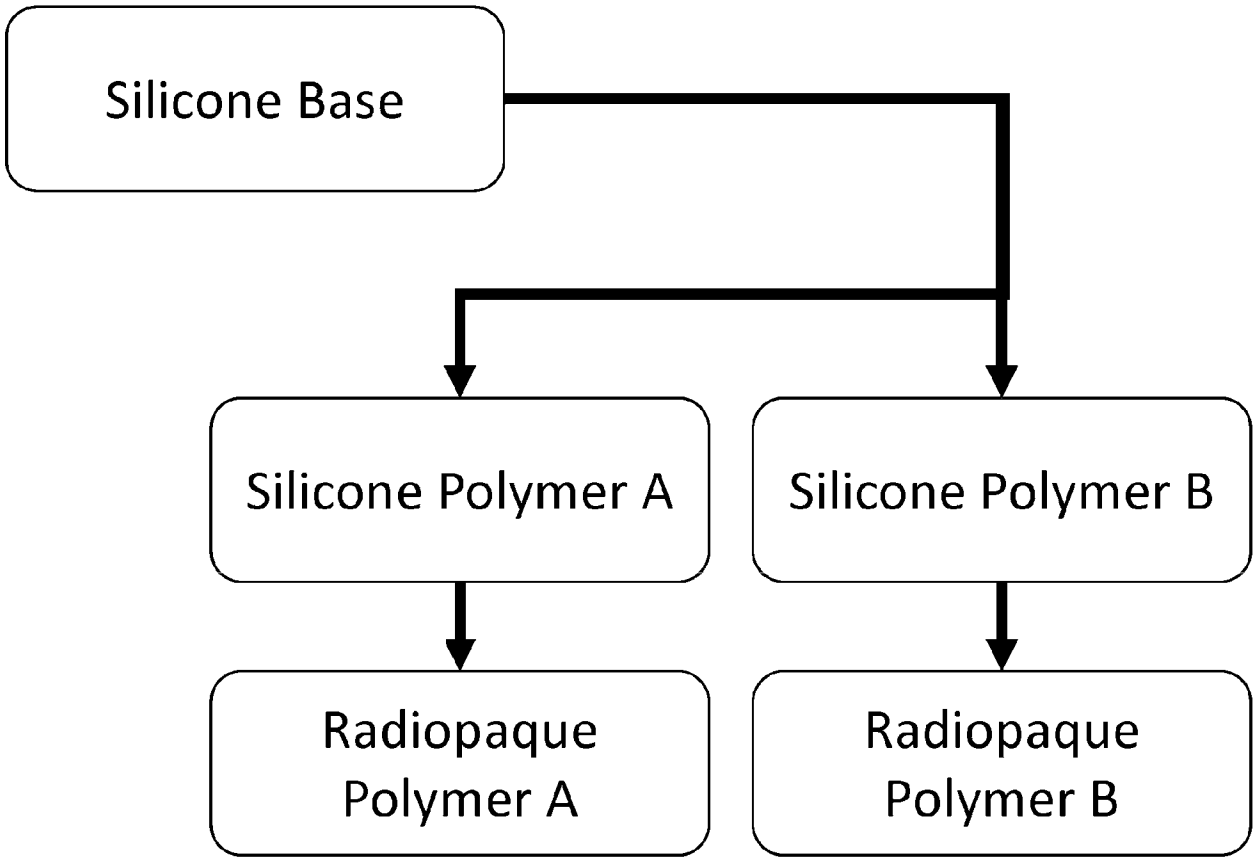

Silicone Base
Silicone Polymer A
Silicone Polymer B
Radiopaque Polymer A
Radiopaque Polymer B

FIG. 6

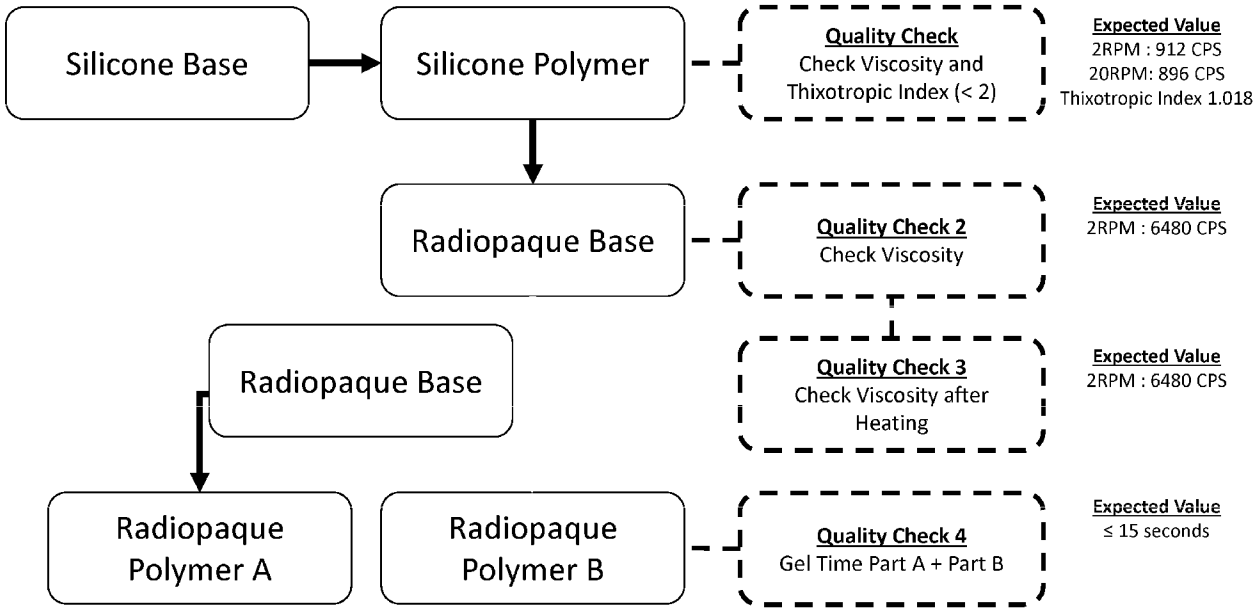

Silicone Base
Silicone Polymer
Quality Check
Check Viscosity and Thixotropic Index (< 2)
Expected Value
2RPM : 912 CPS
20RPM: 896 CPS
Thixotropic Index 1.018
Radiopaque Base
Quality Check 2
Check Viscosity
Expected Value
2RPM : 6480 CPS
Radiopaque Base
Quality Check 3
Check Viscosity after Heating
Expected Value
2RPM : 6480 CPS
Radiopaque Polymer A
Radiopaque Polymer B
Quality Check 4
Gel Time Part A + Part B
Expected Value
≤ 15 seconds

FIG. 7

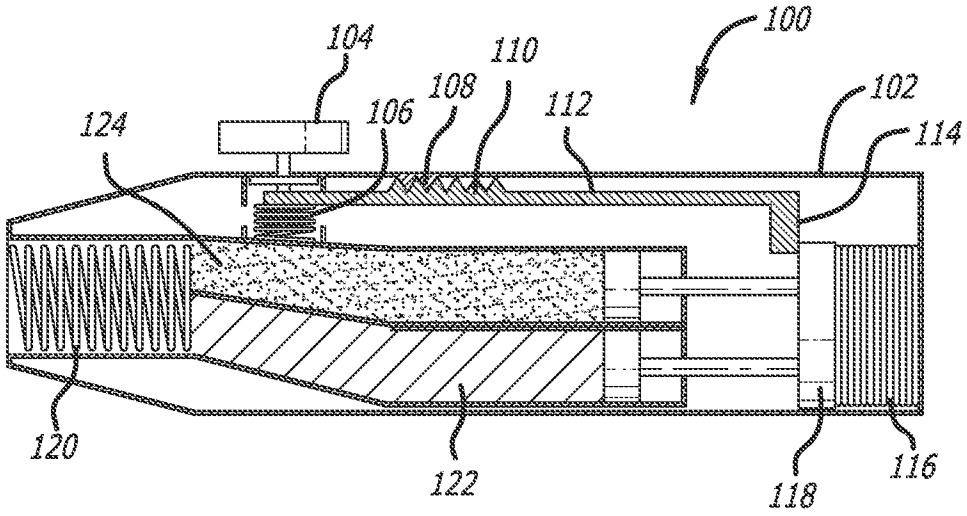

100
104
110
108
106
112
102
114
124
120
122
118
116

FIG. 8

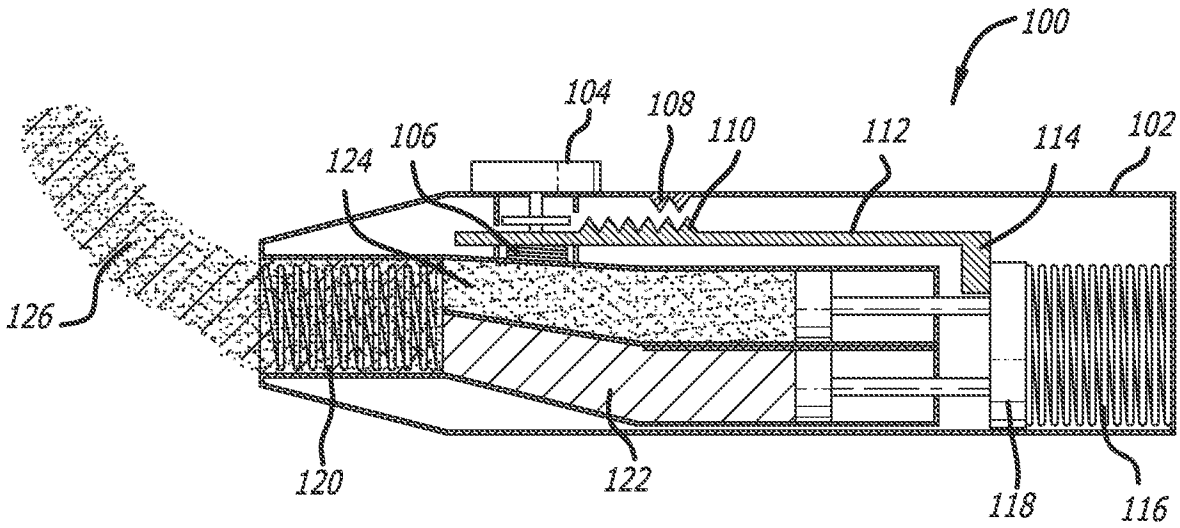
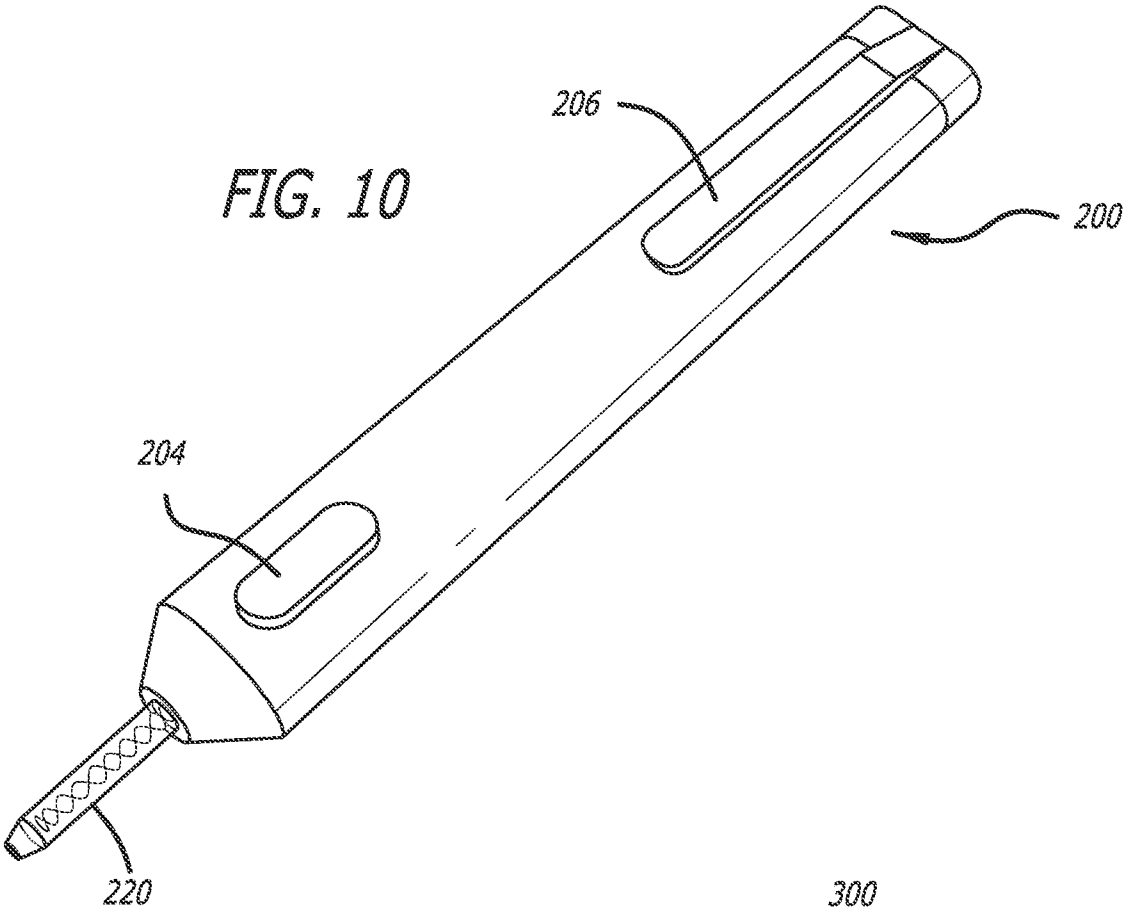

100
104
108
110
106
112
114
102
124
126
120
122
118
116

FIG. 9

FIG. 10



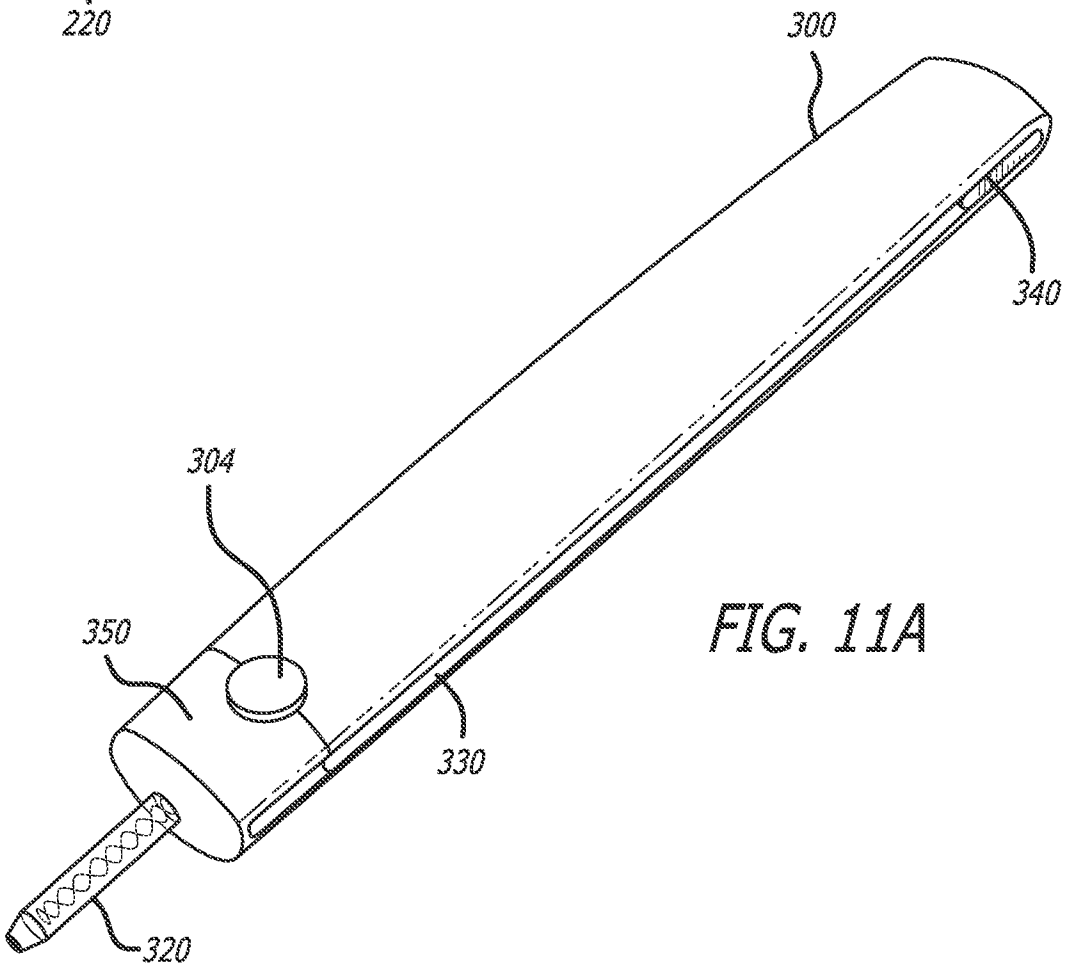


FIG. 11A

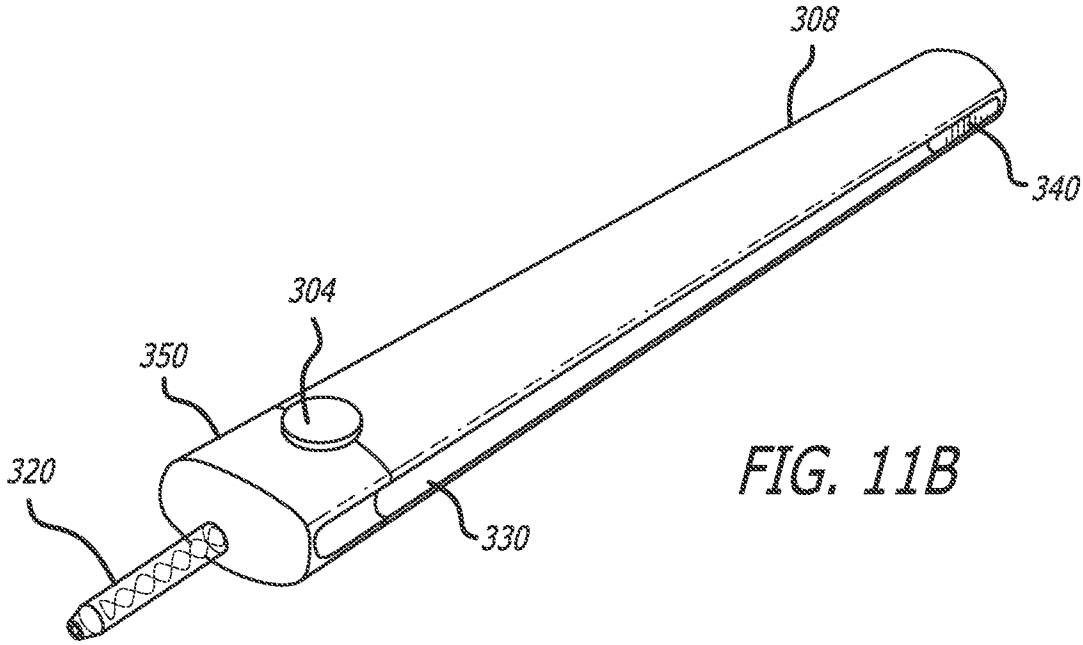


FIG. 11B

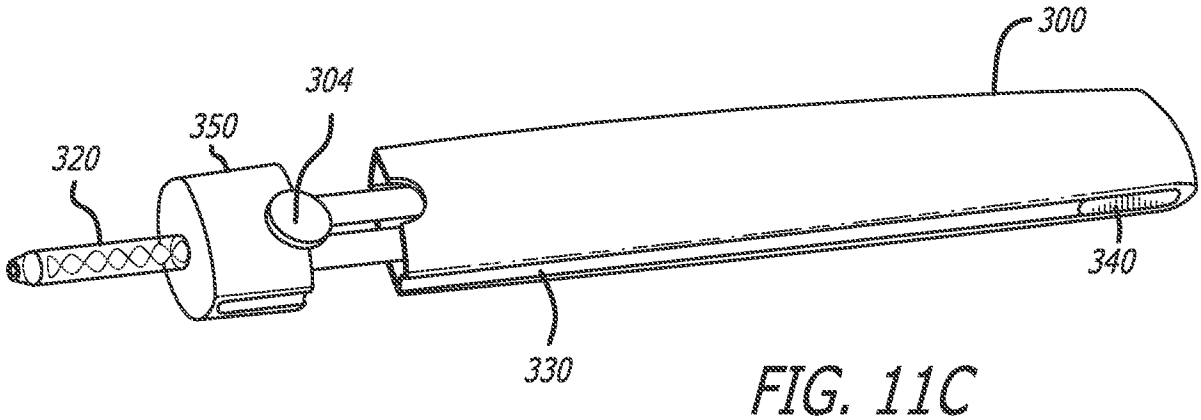
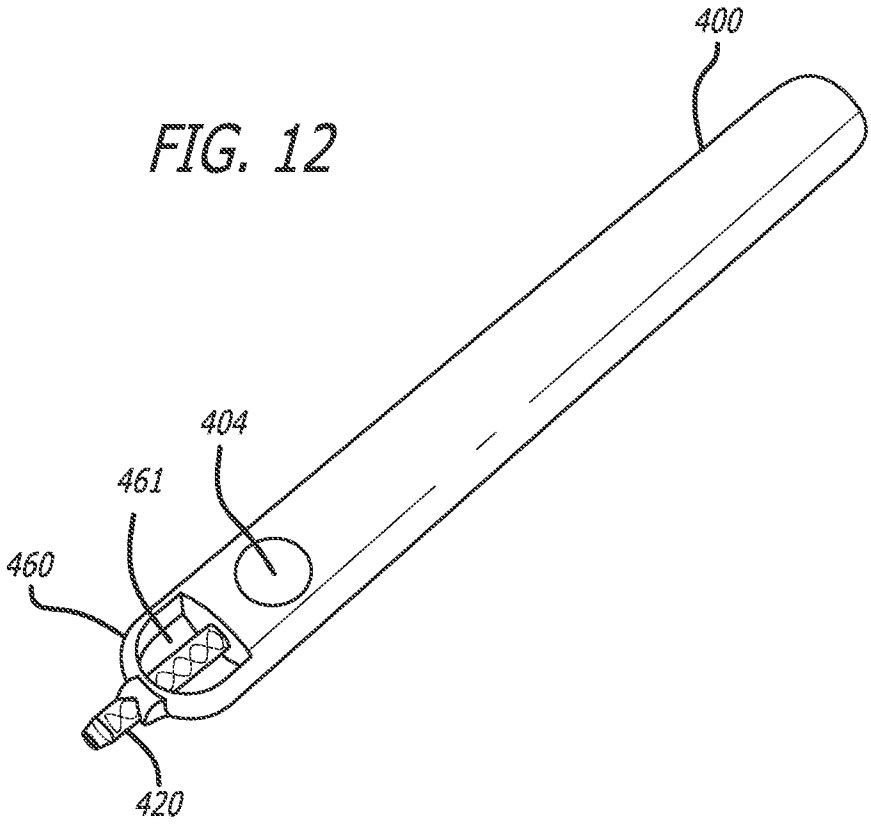


FIG. 11C

FIG. 12



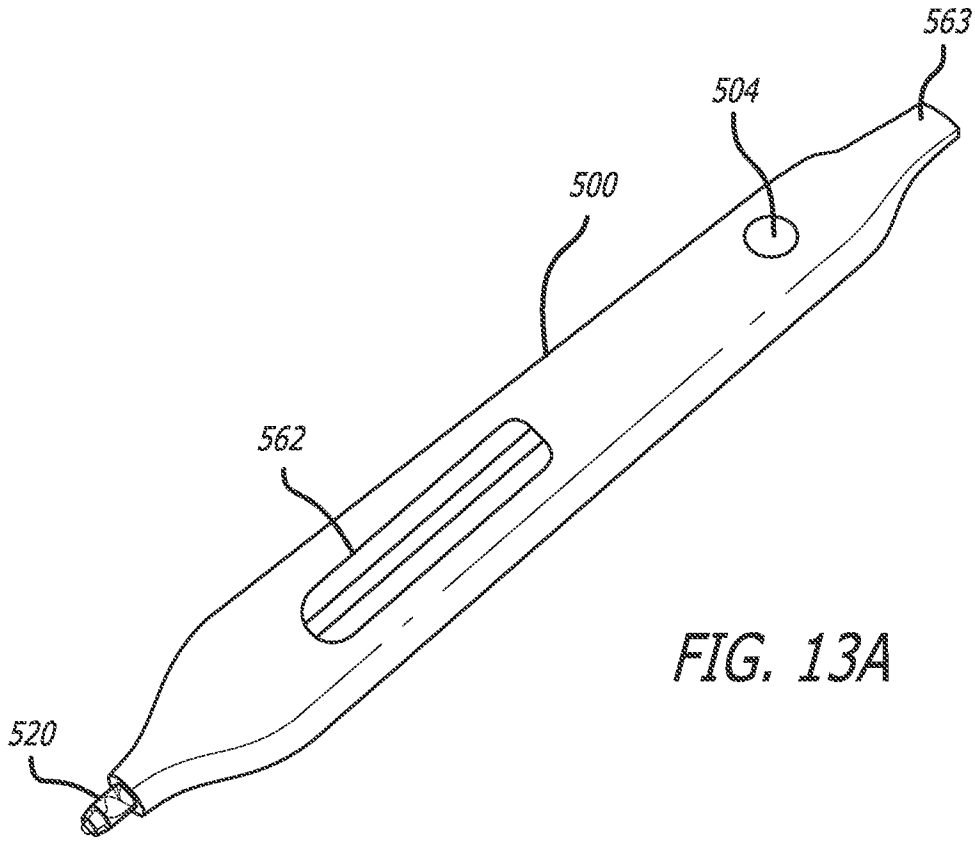
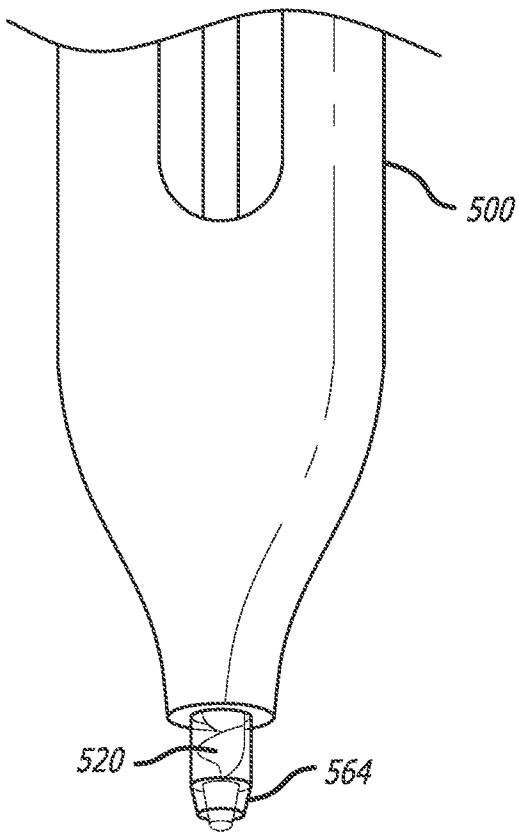


FIG. 13A

FIG. 13B



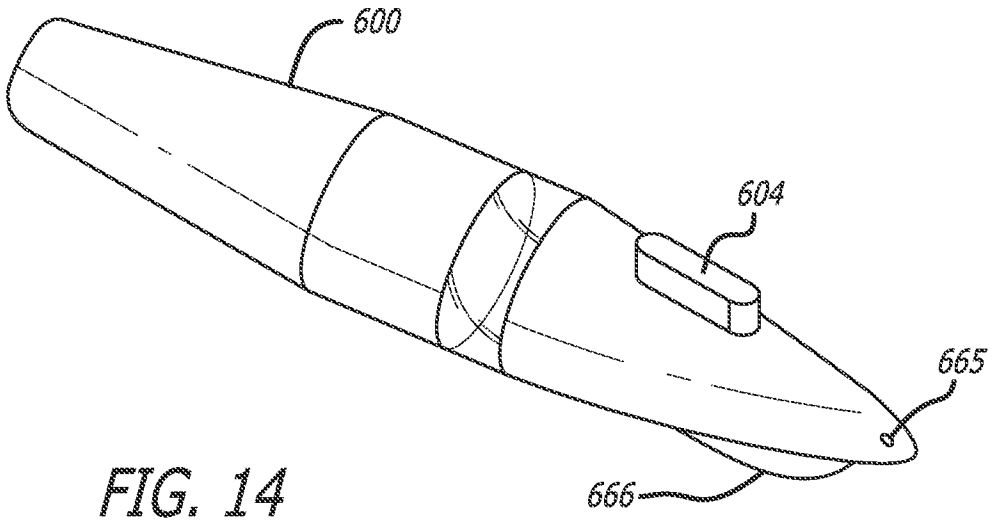


FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/72842

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 8/25; A61K 31/74; A61K 8/891; A61K 8/895 (2021.01)

CPC - A61K 8/25; A61K 31/74; A61K 8/891; A61K 8/895

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2018/052951 A1 (BIO-SILICOTE) 22 March 2018; page 3, paragraph 3-4; page 4, paragraph 2; page 5, paragraph 3; page 11, paragraph 3; page 12, paragraph 3; page 13, paragraph 2; page 15, paragraphs 1-2; page 16, paragraph 1; page 24, paragraph 1; page 34, paragraph 2; table 2	16, 18 --- 1-15, 17, 19, 28-31
Y	US 2005/0064223 A1 (BAVARO ET AL.) 24 March 2005; paragraphs [0006]-[0011]	1-14, 28-31
Y	WO 2015/043792 A1 (DANMARKS TEKNISKE UNIVERSITET) 02 April 2015; page 2, lines 15-26	7, 17, 19
Y	US 9,682,230 B2 (CARDIAC PACEMAKERS, INC.) 20 June 2017; column 6, lines 45-47	3-4
Y	WO 2018/005830 A1 (OTONOMY, INC.) 04 January 2018; paragraphs [0006]-[0011], [00766]	10, 28-31
Y	WO 2020/243047 A1 (BAMBU VAULT LLC) 03 December 2020; paragraph [0355]	11, 13

☐ 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
"D" document cited by the applicant in the international application
"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	Date of mailing of the international search report
03 March 2022 (03.03.2022)	MAY 06 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/72842

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:
-***-Please See Supplemental Page-***-

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 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.:
Group I, Claims 1-19 and 28-31

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.

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, Claims 1-19 and 28-31 are directed towards topical radiopaque marking compositions and methods with radiopaque polymers comprising at least 50% radiopaque agent.

Group II, Claims 20-27 are directed towards devices with dual chambers.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include a radiopaque polymer component with a radiopaque agent making up 50% of the radiopaque polymer component, not present in Group II; the special technical features of Group II include a device with dual chambers disposed in a housing, not present in Group I.

Groups I and II share the technical features including: a topical radiopaque marking substance; a silicone based radiopaque polymer A; a silicone based radiopaque polymer B.

However, these shared technical features are previously disclosed by WO 2018/052951 A1 (BIO-SILICOTE) (hereinafter 'Bio-Silicote').

Bio-Silicote discloses a topical radiopaque marking substance (a polymer substance was applied to an arm, where the polymer substance comprises radio opaque particles; page 13, second paragraph; page 15, second paragraph; table 2); a silicone based radiopaque polymer A (a silicone based polymer part 1 where a radio opaque agent is added; page 13, second paragraph; page 15, second paragraph; table 2); a silicone based radiopaque polymer B (a silicone based polymer part 2 where a radio opaque agent is added; page 13, second paragraph; page 15, second paragraph; table 2).

Since none of the special technical features of the Groups I-II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Bio-Silicote reference, unity of invention is lacking.

It is noted that claims 21-27 refer to "A device according to claim 1". These claims lack clarity since it is unclear if the applicant is trying to introduce a new second device or refer to a previously introduced device. In addition, there is a lack of antecedent basis for a "device" in claim 1. For the purposes of this opinion, as best understood, to restore clarity and provide antecedent basis, claims 21-27 are interpreted to read "The device according to claim 20".