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(71) Applicants: BAXTER INTERNATIONAL INC.

[US/US]; One Baxter Parkway, Deerfield, Illinois 60015 (US). BAXTER HEALTHCARE SA [CH/CH]; Thurgauerstrasse 130, 8152 Glattpark (Opfikon) (CH).

(72) Inventors: SANDERS, Paul Jefferey; 5240 Oakton Lane,

Greendale, Wisconsin 53129 (US). BARRY, John Joseph Anthony; 723 Greenwood Road, Northbrook, Illinois 60062 (US).

(74) Agent: PLUMMER, Kelly A.; c/o Foreign Patents, K&L

Gates LLP, P.O. Box 1135, Chicago, Illinois 60690-1135 (US).

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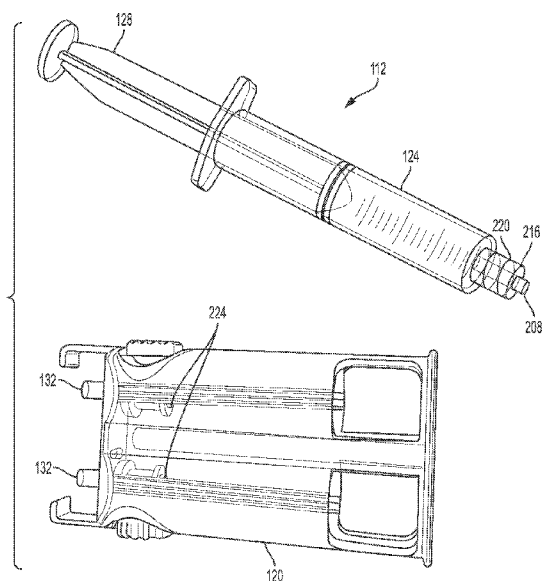


FIG. 5

(57) Abstract: Devices and methods for quickly and easily forming and delivering a tissue sealant are described. The disclosed devices and methods utilize a dual syringe device that contains a first solid protein (such as a lyophilized procoagulant) in one syringe and a sealer polymer (such as a lyophilized sealer protein) in another syringe. When a tissue sealant is needed, for example, for application to a wound, the dual syringe device can be easily and quickly connected to another dual syringe device that contains respective diluents for the solid components, such that the solid components can be mixed and reconstituted and/or hydrated with the respective diluents. Using a mixing and dispensing device, the mixtures can be combined to form the tissue sealant, and the tissue sealant can be applied to the wound.

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DEVICES AND METHODS FOR FORMING AND DELIVERING A TISSUE SEALANT

Field of the Disclosure

[0001] The present disclosure is generally directed to tissue sealants and, more particularly, to devices and methods for quickly and easily forming and delivering a tissue sealant to a wound site.

Brief Description of Related Technology

[0002] Tissue sealants are often applied to wounds (e.g., open wounds of a human) to close the wound, stop bleeding, and/or prevent infectious agents and other substances from entering the wound. A number of biocompatible and biodegradable tissue sealants capable of forming closures in soft tissues are known. Synthetic biocompatible and biodegradable tissue sealants are typically based on polyurethane, polyethylene glycol, and/or polyester. *See* Annabi et. al., Eur. J. Pharm. Biopharm, vol. 97, pp. 25-39 (2015). Naturally occurring biocompatible and biodegradable tissue sealants are typically based on proteins or polysaccharides. *Id.*

[0003] Tissue sealants can be formed, for example, by mixing sealer protein and thrombin solutions. For example, one FDA-approved tissue sealant, TISSEEL® fibrin sealant (Baxter International Inc.), is formed by mixing sealer protein and thrombin solutions. TISSEEL® fibrin sealant is currently available in “ready to use” and “kit” configurations.

[0004] The ready to use configuration is provided as a dual syringe device having first and second syringes incorporated therein, the first syringe containing a frozen thrombin solution and the second syringe containing a frozen sealer protein solution. Care must be taken when warming the ready to use configuration to thaw the frozen thrombin and sealer protein solutions because (i) the activities of the proteins can be significantly diminished by heating the dual syringe above 37°C as this can cause the proteins to denature and (ii) contaminants can easily be introduced during the warming process. As a result of having to closely control the thawing temperature to preserve protein activity, it takes at least 5 minutes (with the pouch packaging removed in a sterile 33-37°C water bath) and up to 105 minutes (in a pouch packaging in an incubator held at 33-37°C) to thaw the thrombin and sealer protein solutions, which can make use in critical care situations cumbersome. After

warming the dual syringe to thaw the frozen thrombin and sealer protein solutions, the resulting warmed thrombin and sealer protein solutions can be combined to form a tissue sealant via actuation of the dual syringe device at a site where such a sealant is needed (e.g., a wound site to close the wound). The TISSEEL® fibrin sealant package insert teaches that long term storage requires that the dual syringe device be maintained at a temperature less than -20°C. The TISSEEL® fibrin sealant package insert further teaches that the product must be used within four hours after warming to 33-37°C and within 48 hours of removal from the freezer.

[0005] The kit configuration is provided as a set of four vials: one vial contains lyophilized sealer protein and a magnetic stir bar, one vial contains lyophilized thrombin and a magnetic stir bar, one vial contains fibrinolysis inhibitor-containing diluent, and the last vial contains calcium chloride diluent. The four vials are first pre-warmed by placing them into a heating unit such as a FIBRINOTHERM® heating and stirring device (Baxter International Inc.). After warming, the fibrinolysis inhibitor-containing diluent is transferred from its vial, using a sterile needle, into the vial containing the lyophilized sealer protein. This vial is then further warmed in the heating and stirring device with the stirrer on, until the solid lyophilized sealer protein dissolves. Next, the calcium chloride diluent is transferred from its vial, using a sterile needle, into the vial containing lyophilized thrombin. This vial is then further warmed in the heating and stirring device with the stirrer on, until the solid thrombin dissolves. Once the sealer protein and the thrombin are fully reconstituted, the sealer protein and the thrombin are transferred from their respective vials to separate, first and second syringes chambers of a dual syringe device. The reconstituted thrombin and sealer protein solutions can then be combined to form a tissue sealant via actuation of the dual syringe at a site where such a sealant is needed (e.g., a wound site to close a wound). The TISSEEL® fibrin sealant package insert teaches that the product must be used within four hours after reconstitution.

SUMMARY

[0006] In accordance with one exemplary aspect of the present invention, a dual syringe device is provided. The dual syringe device is adapted to be connected to another dual syringe device and form a tissue sealant. The dual syringe device includes a first syringe and a second syringe connected to the first syringe. The first syringe includes a first

chamber and a first solid protein in the first chamber. The first chamber containing the first solid protein is configured to mix with a first liquid diluent contained in the other dual syringe device. The second syringe includes a second chamber and a solid sealer polymer, typically a second solid protein, in the second chamber. The second chamber containing the solid sealer polymer is configured to mix with a second liquid diluent contained in the other dual syringe device.

[0007] In accordance with another exemplary aspect of the present invention, a syringe assembly is provided for forming a tissue sealant. The syringe assembly includes a first dual syringe device and a second dual syringe device removably connectable to the first dual syringe device. The first dual syringe device includes a first syringe and a second syringe connected to the first syringe, the first syringe including a first chamber and either a first solid protein or a first diluent in the first chamber, and the second syringe including a second chamber and either a solid sealer polymer, typically a second solid protein, or a second diluent in the second chamber. The second dual syringe device includes a third syringe and a fourth syringe connected to the third syringe, the third syringe including a third chamber and the other of the first solid protein and the first diluent in the third chamber, and the fourth syringe including a fourth chamber and the other of the solid sealer polymer and the second diluent in the fourth chamber. When the second dual syringe device is connected to the first dual syringe device, the third chamber is in fluid communication with the first chamber, such that the first diluent can mix with the first protein to form a first mixture, and the fourth chamber is in fluid communication with the second chamber, such that the second diluent can mix with the solid sealer polymer to form a second mixture, the first and second mixtures being combinable to form the tissue sealant.

[0008] In accordance with yet another exemplary aspect of the present invention, a method of forming a tissue sealant is provided. The method includes providing a first dual syringe device including a first syringe and a second syringe connected to the first syringe, the first syringe including either a first solid protein or a first diluent and the second syringe including either a solid sealer polymer, typically a second solid protein, or a second diluent. The method includes providing a second dual syringe device including a third syringe and a fourth syringe connected to the third syringe, the third syringe

including the other of the first solid protein and the first diluent and the fourth syringe including the other of the solid sealer polymer and the second diluent. The method also includes connecting the second dual syringe device to the first dual syringe device such that the third syringe is in fluid communication with the first syringe and the fourth syringe is in fluid communication with the second syringe, thereby forming a syringe assembly. The method includes moving the syringe assembly such that the first solid protein mixes with the first diluent to form a first mixture and the solid sealer polymer mixes with the second diluent to form a second mixture, the first and second mixtures being arranged in one of the first and second dual syringe devices. The method also includes disconnecting the second dual syringe device from the first dual syringe device. The method further includes combining the first mixture and the second mixture to form the tissue sealant.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The disclosure may be best understood by reference to the following description taken in conjunction with the accompanying drawings, in which like reference numerals identify like elements in the several FIGS., in which

[0010] FIG. 1 is a perspective view illustrating representative components for assembling an exemplary syringe assembly in accordance with the principles of the present disclosure;

[0011] FIG. 2 is a perspective view showing an exemplary syringe assembly in which the first and second dual syringe devices of the syringe assembly are connected together to mix the solid components and diluents contained therein;

[0012] FIG. 3 illustrates one of the first and second dual syringe devices, after the syringe assembly has been moved to mix the solid components (i.e., the solid sealer polymers described herein, which are typically proteins, and the solid proteins, which are typically procoagulants), and diluents and arrange the mixtures in one of the first and second dual syringe devices, and the first and second dual syringe devices have been disconnected from one another, with a mixing and dispensing device connected to the dual syringe device containing the mixed solutions, such that a tissue sealant can be formed and delivered;

[0013] FIG. 4 is a flowchart of an example method of forming a tissue sealant using a syringe assembly comprising first and second dual syringe devices according to the disclosure;

[0014] FIG. 5 shows additional exemplary components for assembling a dual syringe device in accordance with the principles of the present disclosure; and

[0015] FIG. 6 shows additional exemplary components for assembling a dual syringe device in accordance with the principles of the present disclosure.

DETAILED DESCRIPTION

[0016] The present invention is directed to ready to use devices and methods for quickly and easily forming and delivering a tissue sealant to a wound site (for example, to close a wound). The disclosed devices and methods utilize a dual syringe device that contains a solid protein (typically, a procoagulant such as lyophilized thrombin) in one syringe and a solid sealer polymer, typically another solid protein (for example, a lyophilized sealer protein such as fibrinogen or gelatin) in another syringe. When a tissue sealant is needed (e.g., for application to a wound), the dual syringe device can be easily and quickly connected to another dual syringe device that contains respective diluents for the solid components, such that the solid components can be mixed with the respective diluents and thereby hydrated and/or reconstituted. The solutions of hydrated and/or reconstituted components (most typically, proteins) can then be combined to form the tissue sealant, and the tissue sealant can be applied to the wound. Of course, when a syringe assembly comprising first and second dual syringe devices according to the disclosure is provided, the solid components and the diluents can be arranged differently in the dual syringe devices, e.g., the solid components need not initially be contained in the same dual syringe device and, similarly, the diluents need not initially be contained in the same dual syringe device, as long as mixing and reconstitution of the solid components and the respective diluents can be accomplished by moving the contents of the various individual syringes as described herein.

[0017] Unlike known ready to use devices and methods for forming tissue sealants, the disclosed devices and methods advantageously allow proteins such as thrombin and sealer protein to be shipped and stored at room temperature, such that freezers/refrigerators are

not needed to transport and store the proteins. As a result, the use of heating devices (e.g., an incubator, a water bath, or the like) to thaw frozen solutions of the thrombin and sealer protein and thereby facilitate mixing of thrombin and sealer protein solutions to form the tissue sealant can also be advantageously avoided. In addition, because the disclosed ready to use devices can be stored at room temperature, the use of refrigeration devices for long term storage can be avoided. The disclosed ready to use devices and methods also obviate the need for diluents to be manually withdrawn, e.g., using a needle, from their respective storage vials and transferred to corresponding vials containing solid proteins such as thrombin and sealer protein, as is known in the art, and thereby advantageously eliminate sources of potential contamination and deliberate and time-consuming processing steps that are often required to generate a tissue sealant. Because thawing and/or other aseptic preparation steps to dissolve/reconstitute the proteins are not needed, the disclosed ready to use devices and methods for preparing a tissue sealant are capable of producing a tissue sealant in significantly less time and require significantly less processing steps (at least relative to the existing ready to use and kit configurations discussed above) and are particularly useful in critical care clinical settings, especially when a tissue sealant is needed unexpectedly.

[0018] FIG. 1 illustrates representative components for assembling an exemplary syringe assembly 100 in accordance with the teachings of the present disclosure. The syringe assembly 100 generally includes a first dual syringe device 104 and a second dual syringe device 108 removably connectable to the first dual syringe device 104.

[0019] As shown in FIG. 1, the first dual syringe device 104 includes a first syringe 112, a second syringe 116, and a housing 120 that at least partially houses, and generally serves to connect and align, the first and second syringes 112, 116. The first and second syringes 112, 116 are, in this example, removably disposed in the housing 120, such that they can be removed and replaced and such that the first syringe 112 is oriented along a first longitudinal axis 122 and the second syringe 116 is oriented along a second longitudinal axis 123 that is parallel to but offset from the first longitudinal axis 122.

[0020] The first syringe 112 includes a first chamber 124 and a first plunger 128. The first chamber 124 has a first outlet port 132. The first syringe 112 contains a first solid protein A which is a procoagulant, e.g., thrombin. Additional exemplary procoagulants

include, but are not limited to, clotting factors, such as fibrin, Factor VIII (FVIII), Factor VII (FVII), Factor IX (FIX), von Willebrand Factor (vWF), Factor II (FII), Factor V (FV), Factor X (FX), Factor XI (FXI), Factor XII (FXII), and Factor XIII (FXIII), tissue factor, collagen; styptics including anti-hemorrhagic agents and astringents; and other hemostatic agents. The procoagulant is typically provided in the first chamber 124 as a lyophilized powder, for example, as lyophilized thrombin. The syringe assembly 100, and more specifically the first syringe 112 of the first dual syringe device 104, is configured to mix the first solid protein A with a first diluent C contained in the second dual syringe device 108, as will be described below. The first plunger 128 is movably disposed within the first chamber 124 to facilitate the mixing between the first solid protein A and the first liquid diluent C, via the first outlet port 132, as will also be described in greater detail below. Pre-warming or heating, for example to 33-37°C, is not required to mix the first solid protein A in the first dual syringe device 104 and the first liquid diluent C in the second dual syringe device 108, but may optionally be practiced to facilitate faster dissolution/reconstitution.

[0021] The second syringe 116 includes a second chamber 136 and a second plunger 140. The second chamber 136 has a second outlet port 144 that, at least in the illustrated example, has a diameter substantially equal to a diameter of the first outlet port 132. Different outlet port 132, 144 diameters are also possible. The second chamber 136 contains a solid sealer polymer, typically a second solid protein B, which is a sealer protein, e.g. fibrinogen. Other suitable solid sealer polymers include but are not limited to sealer proteins such as albumin, gelatin, collagen (e.g., soluble collagen), hemoglobin, fibrinogen, fibronectin, elastin, keratin, laminin, and derivatives and combinations thereof. Alternatively, the solid sealer polymer may comprise a polysaccharide, such as a glycosaminoglycan, a starch derivative, a cellulose derivative, a hemicellulose derivative, xylan, agarose, alginate, chitosan, a dextrin such as icodextrin or maltodextrin, amylopectin, amylose, modified forms thereof, and combinations thereof. As a further alternative, the solid sealer polymer may comprise a non-biologic hydrogel-forming polymer, such as polyacrylates, polymethacrylates, polyacrylamides, polyvinyl polymers, polylactide-glycolides, polycaprolactones, polyoxyethylenes, and derivatives and combinations thereof. Suitable solid sealer polymers may comprise solid sealer polymers capable of being hydrated to form a hydrogel. “Derivatives thereof” include any

chemically modified polymer, such as e.g. a cross-linked polymer, e.g., cross-linked gelatin. The solid sealer protein is typically provided in the second chamber 136 as a lyophilized powder, for example, as lyophilized fibrinogen. The syringe assembly 100, and more specifically the second syringe 116 of the first dual syringe device 104, is configured to mix the second solid protein B with a second diluent D contained in the second dual syringe device 108, as will be described below. The second plunger 140 is movably disposed within the second chamber 136 to facilitate mixing between the second solid protein B and the second liquid diluent D, via the second outlet port 144, as will also be described in greater detail below. In some cases, the second plunger 140 can be connected to the first plunger 128, e.g., via a yoke, such that the first and second plungers 128, 140 move together when the yoke is depressed, while in other cases, the second plunger 140 may be movable relative to or independently of the first plunger 128 (e.g., when no yoke is present). Pre-warming or heating, for example to 33-37°C, is not required to mix the second solid protein B in the first dual syringe device 104 and the second liquid diluent D in the second dual syringe device 108, but may optionally be practiced to facilitate faster dissolution/reconstitution.

[0022] As also shown in FIG. 1, the second dual syringe device 108 is structurally similar to the first dual syringe device 104, in that the second dual syringe device 108 includes a third syringe 150, a fourth syringe 154, and a housing 158 that at least partially houses, and generally serves to connect and align, the third and fourth syringes 150, 154. The third and fourth syringes 150, 154 are, in this example, removably disposed in the housing 158, such that they can be removed and replaced and such that the third syringe 150 is oriented along a third longitudinal axis 162 and the fourth syringe 154 is oriented along a fourth longitudinal axis 166 that is parallel to but offset from the third longitudinal axis 162. It will be appreciated that the third longitudinal axis 162 is co-axial with the first longitudinal axis 122 and the fourth longitudinal axis 166 is co-axial with the second longitudinal axis 123. Non-coaxial configurations are possible, for example, if a flexible, non-linear adapter 192 is used.

[0023] The third syringe 150 includes a third chamber 170 and a third plunger 174. The third chamber 170 has a third outlet port 178 that, at least in the illustrated example, has a diameter equal to the diameter of the first and second outlet ports 132, 144 (though in

other examples, the diameter of the third outlet port 178 can be greater or less than the first and second outlet ports 132, 144). The third chamber 170 contains the first diluent C, which may, for example, be a liquid diluent. The first diluent may comprise an aqueous solution for reconstituting the first solid protein A contained in the first chamber 124, the first diluent optionally further comprising a salt. Representative, exemplary salts include but are not limited to calcium chloride, sodium chloride, potassium chloride, magnesium chloride, and combinations of the foregoing. As mentioned above, the syringe assembly 100, and more specifically the third syringe 150 of the second dual syringe device 108, is configured to mix the first diluent C with the first solid protein A when the first and second syringe devices 104, 108 are connected to one another, as will be described below. The third plunger 174 is movably disposed within the third chamber 170 to facilitate this mixing, via the third outlet port 178, when desired.

[0024] The fourth syringe 154 includes a fourth chamber 182 and a fourth plunger 186. The fourth chamber 182 has a fourth outlet port 190 that, at least in the illustrated example, has a diameter substantially equal to the diameter of each of the first, second, and third outlet ports 132, 144, 178 (though in other examples, the diameter of the fourth outlet port 190 can vary). The fourth chamber 182 contains the second diluent D, which may, for example, be a liquid diluent. The second diluent may comprise an aqueous solution for reconstituting the second solid protein B contained in the second chamber 136, the second diluent optionally further comprising components selected from a buffering agent, a fibrinolysis inhibitor, a surfactant, and combinations of the foregoing. A representative, exemplary buffering agent is tri-sodium citrate. A representative, exemplary fibrinolysis inhibitor is aprotinin. A representative, exemplary surfactant is polysorbate 80. As mentioned above, the syringe assembly 100, and more specifically the fourth syringe 154 of the second dual syringe device 108, is configured to mix the second diluent D with the second solid protein B when the first and second syringe devices 104, 108 are connected to one another. The fourth plunger 186 is movably disposed within the fourth chamber 182 to facilitate this mixing, via the fourth outlet port 190, when desired. In some cases, the fourth plunger 186 can be connected to the third plunger 174, e.g., via a yoke, such that the third and fourth plungers 174, 186 move together when the yoke is depressed, while in other cases, the fourth plunger 186 may be movable relative to or independently of the third plunger 174 (e.g., when no yoke is present).

[0025] The syringe assembly 100 can, in some cases, further include one or more adapters configured to facilitate the removable connection between the first and second dual syringe devices 104, 108, particularly when, as is the case here, the outlet ports 132, 144, 178, and 190 have identical diameters. In this example the syringe assembly 100 includes two adapters 192 to facilitate this removable connection. The illustrated adapters 192 have a substantially cylindrical shape that defines an opening having a diameter that is larger than a diameter of the diameter of each of the outlet ports 132, 144, 178, and 190. As such, the first adapter 192 can be coupled to one of the first and third outlet ports 132, 178, and the second adapter 192 can be coupled to one of the second and fourth outlet ports 144, 190. In turn, by pushing the first and second dual syringe devices 104, 108 toward one another, the first adapter 192 can be coupled to the other of the first and third outlet ports 132, 178, and the second adapter 192 can be coupled to the other of the second and fourth outlet ports 144, 190, thereby removably securing the first and second dual syringe devices 104, 108 together such that the third syringe 150 is in fluid communication with the first syringe 112 and the fourth syringe 154 is in fluid communication with the second syringe 116, as illustrated in FIG. 2. Of course, in other examples, the outlet ports 132, 144, 178, 190 can be configured such that there is no need for one or both adapters 192, e.g., when the outlet ports 132, 144, 178, and 190 have external diameters that facilitate direct coupling therebetween. Additionally, instead of separate first and second adapters 192 as is shown in FIGS. 1 and 2, an integral component configured to facilitate the removable connection between the first and second dual syringe devices 104, 108 can be provided.

[0026] When the first and second dual syringe devices 104, 108 are connected together as shown in FIG. 2, the syringe assembly 100 can be moved such that the first solid protein A mixes with the first diluent C to form a first mixture M_1 and the second solid protein B mixes with the second diluent D to form a second mixture M_2 . This generally involves manipulating combinations of the first, second, third, and fourth syringes 112, 116, 150, 154 such that (i) the first solid protein A and the first diluent C are mixed and moved, or “swooshed”, back and forth to reconstitute the first solid protein A, and (ii) the second solid protein B and the second diluent D are mixed and moved, or “swooshed”, back and forth to reconstitute the second solid protein B. Such manipulation may, for example, include rotating the syringe assembly 100 (e.g., in a back and forth direction)

and/or moving one or more of the first, second, third, and fourth plungers 128, 140, 174, and 186 relative to the chambers 124, 136, 170, and 182, respectively. Once sufficiently mixed, the solutions may be left in the first dual syringe device 104 (particularly the syringes 112, 116) or the second dual syringe device 108 (particularly the syringes 150, 154), at which time the first and second dual syringe devices 104, 108 can be disconnected from one another by pulling the first and second dual syringe devices 104, 108 apart from one another.

[0027] It should be noted that, for illustration purposes, the syringe assembly 100 is not shown in a “state-of-use” in FIGS. 1 and 2, i.e., the syringe assembly is not shown in a state in which a tissue sealant can be immediately generated. When the syringe assembly 100 is in the state of use, two of plungers 128, 140, 174, and 186 are generally disposed in a forwardly advanced position within corresponding chambers 124, 136, 170, and 182 proximal to corresponding outlet ports 132, 144, 178, and 190, while the remaining two plungers of 128, 140, 174, and 186 are generally disposed in a rearwardly retracted position within corresponding chambers 124, 136, 170, and 182 distal to corresponding outlet ports 132, 144, 178, and 190. As a final step to place the syringe assembly into a state of use, prior to swooshing back and forth the first solid protein A and the first diluent C, and the second solid protein B and the second diluent D, air should be expelled from all syringes 112, 116, 150, and 154.

[0028] As illustrated in FIG. 3, the syringe assembly 100 further includes a mixing and dispensing device 196 that, when the diluents and solid proteins are mixed such that the proteins are reconstituted, the first mixture M_1 and the second mixture M_2 are left in the first dual syringe device 104 or the second dual syringe device 108, and the first and second dual syringe devices 104, 108 are disconnected from one another, can be coupled to one of the first and second dual syringe devices 104, 108 (depending upon which device includes the mixed solutions) to form and dispense the tissue sealant. The mixing and dispensing device 196 in this example takes the form of an applicator tip having a Y-connector 200 and a dispensing needle 204 that is coupled to and projects outward from the Y-connector 200. The Y-connector 200 is adapted to be coupled to the outlet ports 132 and 144, 178 and 190 of the dual syringe device 104, 108 containing the mixed solutions, such that the Y-connector 200 is fluidly coupled to the chambers of the

respective dual syringe device 104, 108. The Y-connector 200 can thus transfer the mixtures M_1 and M_2 from the chambers of the respective dual syringe device to a common chamber (not shown) within the mixing and dispensing device 196, to combine the mixtures M_1 and M_2 and thereby cause formation of the tissue sealant. The tissue sealant can in turn be dispensed to a wound of a person, via the dispensing needle 204, so as to close the wound, to stop the wound from bleeding, and/or to prevent infectious agents and other substances from entering the wound. In other examples, it will be appreciated that the mixing and dispensing device 196 can take the form of a different type of in-line mixing device and/or can include a cannula, catheter, spray head, or some other means of dispensing device instead of the needle 204. Other suitable mixing devices are illustrated and described in combination with a dual syringe device in U.S. Patent No. 8,753,670, which is hereby incorporated herein by reference.

[0029] FIG. 4 is a flow chart that depicts a method 400 of forming a tissue sealant using the syringe assembly 100, though it will be appreciated that the tissue sealant can be formed using a different syringe assembly (e.g., using differently configured dual syringe devices). The method 400 includes six acts – 404, 408, 412, 416, 420, and 424, but in other examples, the method 400 can include more, less, or different acts.

[0030] In act 404, the first dual syringe device 104 is provided. In the illustrated embodiment, the first dual syringe device 104 includes the first syringe 112, which includes the first solid protein A, and the second syringe 116, which includes the second solid protein B. In act 408, which can be performed before, after, or at the same time as act 404, the second dual syringe device 108 is provided. As also shown in the illustrated embodiment, the second dual syringe device 108 includes the third syringe 150, which includes the first diluent C, and the fourth syringe 154, which includes the second diluent D. It should be noted, however, that when a syringe assembly 100 comprising first and second dual syringe devices 104, 108 is provided, the solid proteins A, B and the diluents C, D can be arranged differently in the dual syringe devices 104, 108, i.e., the solid proteins A, B need not initially be contained in the dual syringe device 104 and, similarly, the diluents C, D need not initially be contained in the dual syringe device 108, because mixing and reconstitution of the solid proteins and the respective diluents can be accomplished by moving the contents of the various individual syringes as described

herein as long as the solid protein A and the diluent C and the solid protein B and diluent D are contained in opposing syringes when the dual syringe devices 104, 108 are connected to one another.

[0031] In act 412, the first and second dual syringe devices 104, 108 are removably connected to one another such that the third syringe 150 is in fluid communication with the first syringe 112 and the fourth syringe 154 is in fluid communication with the second syringe 116 (and thereby forming the syringe assembly 100), as illustrated in FIG. 2. As discussed above, because in the embodiment illustrated in FIG. 1 the outlet ports 132, 144, 178, 190 have identical diameters, the removable connection is facilitated by the adapters 192. In other examples, however, e.g., when the outlet ports 132, 144, 178, and 190 have different diameters, this removable connection may be accomplished in some other way. As an example, this removable connection may be accomplished by arranging the ports of one of the dual syringe devices 104, 108 inside the ports of the other dual syringe device 104, 108.

[0032] In act 416, the syringe assembly 100 is moved such that the first protein A (contained in the first syringe 112) mixes with the first diluent C (contained in the third syringe 150) to form the first mixture M_1 and the second protein B (contained in the second syringe 116) mixes with the second diluent D (contained in the fourth syringe 154) to form the second mixture M_2 . Forming the first and second mixtures M_1 and M_2 generally involves manipulating combinations of the first, second, third, and fourth syringes 112, 116, 150, 154 such that (i) the first solid protein A and the first diluent C are mixed and moved, or “swooshed”, back and forth to reconstitute the first solid protein A, and (ii) the second solid protein B and the second diluent D are mixed and moved, or “swooshed”, back and forth to reconstitute the second solid protein B. Such manipulation may, for example, include rotating the syringe assembly 100 (e.g., in a back and forth direction) and/or moving one or more of the first, second, third, and fourth plungers 128, 140, 174, and 186 relative to the chambers 124, 136, 170, and 182, respectively. In some cases, this movement may further include quickly rotating the syringe assembly 100 (e.g., in a back and forth direction). The first and second mixtures M_1 , M_2 may be left in either the first syringe device 104 (with the first mixture M_1 in the first syringe 112 and the second mixture M_2 in the second syringe 116) or the second syringe device 108 (with the

first mixture M_1 in the third syringe 150 and the second mixture M_2 in the fourth syringe 154).

[0033] In act 420, the second dual syringe device 108 is disconnected from the first dual syringe device 104 (or vice-versa) by, for example, pulling the first and second dual syringe devices 104, 108 apart from one another. In act 424, the first and second mixtures M_1 and M_2 can be combined to form the tissue sealant. The first and second mixtures M_1 and M_2 can, in some cases, be combined using an applicator tip or other mixing and dispensing device coupled to the dual syringe device containing the first and second mixtures. Finally, the tissue sealant, once formed, can be quickly and easily delivered to a wound via the applicator tip or other mixing and dispensing device (or another similar device).

[0034] In another example, as best shown in FIG. 5, a first outlet port 208 may be provided on the first syringe 112. An annular wall 212 terminating in a rim 216 partially surrounds the outlet port 208. The annular wall 212 can include threads 220 on its interior surface. The housing 120 can include an inlet 224 capable of fluid communication with the outlet port 132. In addition, the inlet 224 can include a neck with a collar (or ring) outwardly protruding therefrom (not shown) capable of being received by the threads 220 on the interior surface of the annular wall 212. The collar and threads 220 allow secure and releasable coupling of the first syringe 112 to the housing 120 and thereby facilitate mixing of the contents in the first syringe 112 with the third syringe 150 and ultimate delivery using a mixing and dispensing device 196 as described above. Of course, the second, third, and fourth syringes 116, 150, 154 can include similar outlet ports 208, annular walls 212, rims 216, and threads 220 as described with respect to the first syringe 112, and the housing can include similar inlets 224 for coupling the syringes 116, 150, 154 to the housing 120.

[0035] In other examples, the syringes 112, 116, 150, 154 may be snap fit into the housing 120, so as to releasably couple the syringes 112, 116, 150, 154 to the housing 120 and thereby facilitate mixing of the contents thereof and ultimate delivery using a mixing and dispensing device 196 as described above.

[0036] In an additional example, as best shown in FIG. 6, the dual syringe devices may comprise a unitary housing 320, the unitary housing 320 itself comprising (and providing)

first and second chambers 324, 336 for receiving first and second plungers 328, 340, respectively. The first and second syringes of the unitary housing 320 are formed by inserting the first and second plungers 328, 340 into the first and second chambers 324, 336. The first and second plungers 328, 340 may be provided as separate plungers or may be coupled together via an integral yoke 360 to provide an integral, unitary structure to facilitate simultaneous movement and thereby facilitate mixing of the contents thereof and ultimate delivery using a mixing and dispensing device 196 as described above.

[0037] Although the present invention has been described by reference to certain preferred embodiments, it should be understood that the preferred embodiments are merely illustrative of the principles of the present invention. Therefore, modifications and/or changes may be made by those skilled in the art without departing from the true spirit and scope of the invention as defined by the appended claims.

WHAT IS CLAIMED:

1. A dual syringe device adapted to be connected to another dual syringe device to form a tissue sealant, the dual syringe device comprising:

a first syringe comprising a first chamber and a first solid protein in the first chamber, the first chamber containing the first solid protein being configured to mix with a first liquid diluent contained in the another dual syringe device; and

a second syringe connected to the first syringe and comprising a second chamber and a solid sealer polymer in the second chamber, the second chamber containing the solid sealer polymer being configured to mix with a second liquid diluent contained in the another dual syringe device.

2. The dual syringe device of claim 1, further comprising a housing that connects the first syringe to the second syringe.

3. The dual syringe device of claim 2, wherein the first and second syringes are removably disposed within the housing.

4. The dual syringe device of any preceding claim, wherein the first syringe is oriented along a first longitudinal axis and the second syringe is oriented along a second longitudinal axis, the second longitudinal axis being parallel to but offset from the first longitudinal axis.

5. The dual syringe device of any preceding claim, wherein the first solid protein comprises a lyophilized procoagulant.

6. The dual syringe device of any preceding claim, wherein the first solid protein comprises a procoagulant selected from the group consisting of thrombin, clotting factors, fibrin, Factor VIII (FVIII), Factor VII (FVII), Factor IX (FIX), von Willebrand Factor (vWF), Factor II (FII), Factor V (FV), Factor X (FX), Factor XI (FXI), Factor XII (FXII), Factor XIII (FXIII), tissue factor, collagen, styptics, anti-hemorrhagic agents, astringents, hemostatic agents, and combinations thereof.

7. The dual syringe device of any preceding claim, wherein the solid sealer polymer comprises lyophilized sealer protein.

8. The dual syringe device of any preceding claim, wherein the solid sealer polymer is selected from the group consisting of albumin, gelatin, collagen, hemoglobin, fibrinogen, fibronectin, elastin, keratin, laminin, polysaccharides, glycosaminoglycan, a starch derivative, a cellulose derivative, a hemicellulose derivative, xylan, agarose, alginate, chitosan, dextrin, icodextrin, maltodextrin, amylopectin, amylose, modified polysaccharides, modified glycosaminoglycan, a modified starch derivative, a modified cellulose derivative, a modified hemicellulose derivative, modified xylan, modified agarose, modified alginate, modified chitosan, modified dextrin, modified icodextrin, modified maltodextrin, modified amylopectin, modified amylose, polyacrylates, polymethacrylates, polyacrylamides, polyvinyl polymers, polylactide-glycolides, polycaprolactones, polyoxyethylenes, and derivatives and combinations thereof.

9. The dual syringe device of any preceding claim, wherein the first and second syringes comprise first and second plungers, the first and second plungers being connected by a yoke.

10. A syringe assembly for forming a tissue sealant, the syringe assembly comprising:

a first dual syringe device comprising:

a first syringe comprising a first chamber and either a first solid protein or a first diluent in the first chamber; and

a second syringe connected to the first syringe and comprising a second chamber and a solid sealer polymer or a second diluent in the second chamber; and

a second dual syringe device removably connectable to the first dual syringe device, the second dual syringe device comprising:

a third syringe comprising a third chamber and the other of the first solid protein and the first diluent in the third chamber; and

a fourth syringe connected to the third syringe and comprising a fourth chamber and the other of the solid sealer polymer and the second diluent in the fourth chamber;

wherein when the second dual syringe device is connected to the first dual syringe device, the third chamber is in fluid communication with the first chamber, such that the first diluent can mix with the first protein to form a first mixture, and the fourth chamber is in fluid communication with the second chamber, such that the second diluent can mix with the solid sealer polymer to form a second mixture, the first and second mixtures being combinable to form the tissue sealant.

11. The syringe assembly of claim 10, wherein the first and second syringes are oriented along first and second longitudinal axes, respectively, the third and fourth syringes are oriented along third and fourth longitudinal axes, respectively, the third longitudinal axis being co-axial with the first longitudinal axis, and the fourth longitudinal axis being co-axial with the second longitudinal axis.

12. The syringe assembly of claim 11, wherein the second longitudinal axis is parallel to but spaced from the first longitudinal axis, and wherein the fourth longitudinal axis is parallel to but spaced from the third longitudinal axis.

13. The syringe assembly of any of claims 10-12, wherein the first and second chambers comprise first and second outlet ports, respectively, and wherein the third and fourth chambers comprise third and fourth outlet ports, respectively, the third and fourth outlet ports sized to be arranged within the first and second outlet ports, respectively, to removably connect the second dual syringe device to the first dual syringe device.

14. The syringe assembly of any of claims 10-12, wherein the first and second chambers comprise first and second outlet ports, respectively, wherein the third and fourth chambers comprise third and fourth outlet ports, respectively, the syringe assembly further comprising a first adapter coupled to the first outlet port and a second adapter coupled to the second outlet port, the first and second adapters each having a diameter that is larger than a diameter of the third and fourth outlet ports, respectively.

15. The syringe assembly of any of claims 10-14, wherein the first dual syringe device comprises a first housing that connects the second syringe to the first syringe, and the second dual syringe device comprises a second housing that connects the fourth syringe to the third syringe, the second housing being removably connectable to the first housing to removably connect the second dual syringe device to the first dual syringe device.

16. The syringe assembly of claim 15, wherein the first and second syringes are removably disposed within the first housing, and wherein the third and fourth syringes are removably disposed within the second housing.

17. The syringe assembly of any of claims 10-16, further comprising an applicator tip removably connectable to one of the first and second syringe devices and configured to combine the first and second mixtures to form the tissue sealant.

18. The syringe assembly of claim 17, wherein the applicator tip comprises a Y-connector.

19. The syringe assembly of any of claims 10-18, further comprising a dispensing needle coupled to the applicator tip and configured to apply the tissue sealant to a patient.

20. The syringe assembly of any of claims 10-19, wherein the first diluent comprises a salt.

21. The syringe assembly of any of claims 10-20, wherein the second diluent comprises a fibrinolysis inhibitor.

22. The dual syringe device of any of claims 10-21, wherein the first protein comprises a lyophilized procoagulant.

23. The dual syringe device of any of claims 10-21, wherein the solid sealer polymer comprises lyophilized sealer protein.

24. The dual syringe device of claim 23, wherein the lyophilized sealer protein is selected from the group consisting of albumin, gelatin, collagen, hemoglobin, fibrinogen, fibronectin, elastin, keratin, laminin, and derivatives and combinations thereof.

25. A method of forming a tissue sealant, the method comprising:

providing a first dual syringe device comprising a first syringe and a second syringe connected to the first syringe, the first syringe comprising either a first solid protein or a first diluent and the second syringe comprising either a solid sealer polymer or a second diluent;

providing a second dual syringe device comprising a third syringe and a fourth syringe connected to the third syringe, the third syringe comprising the other of the first solid protein and the first diluent and the fourth syringe comprising the other of the solid sealer polymer and the second diluent;

connecting the second dual syringe device to the first dual syringe device such that the third syringe is in fluid communication with the first syringe and the fourth syringe is in fluid communication with the second syringe, thereby forming a syringe assembly;

moving the syringe assembly such that the first solid protein mixes with the first diluent to form a first mixture and the solid sealer polymer mixes with the second diluent to form a second mixture, the first and second mixtures being arranged in one of the first and second dual syringe devices;

disconnecting the second dual syringe device from the first dual syringe device;
and

combining the first mixture and the second mixture to form the tissue sealant.

26. The method of claim 25, wherein moving the syringe assembly comprises moving the syringe assembly such that the first mixture is arranged in the first syringe and the second mixture is arranged in the second syringe.

27. The method of any of claims 26 and 27, wherein combining the first and second mixtures comprises combining the first and second mixtures via an applicator tip coupled to one of the first and second dual syringe devices.

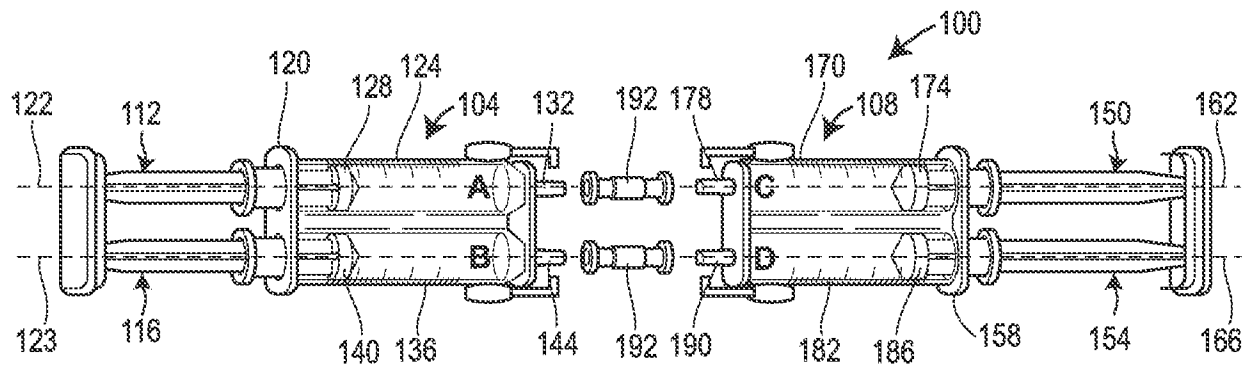


FIG. 1

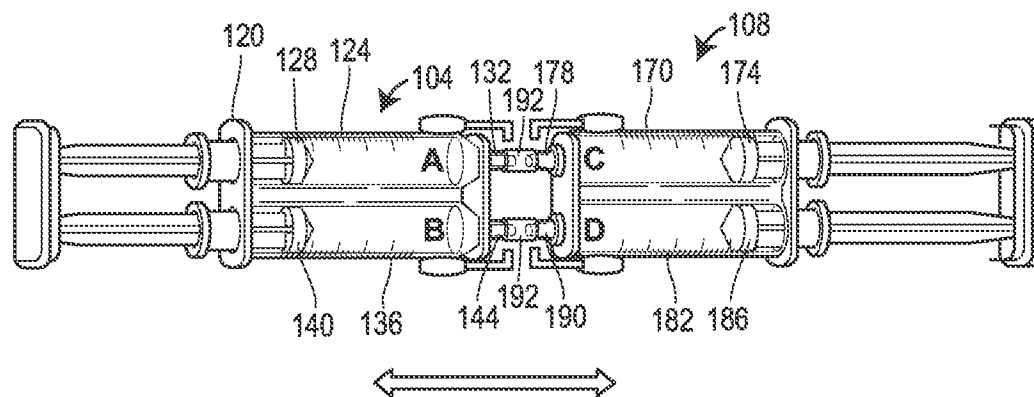


FIG. 2

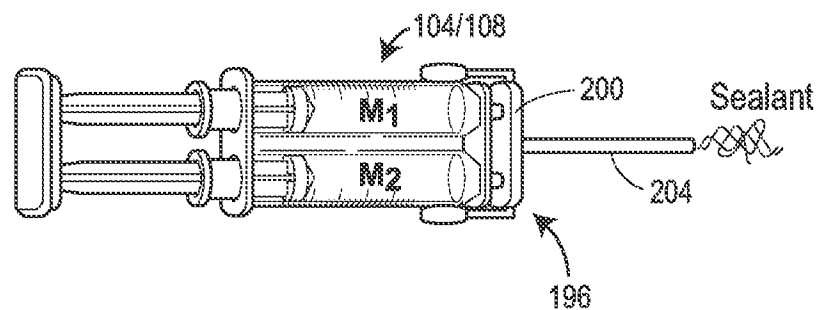
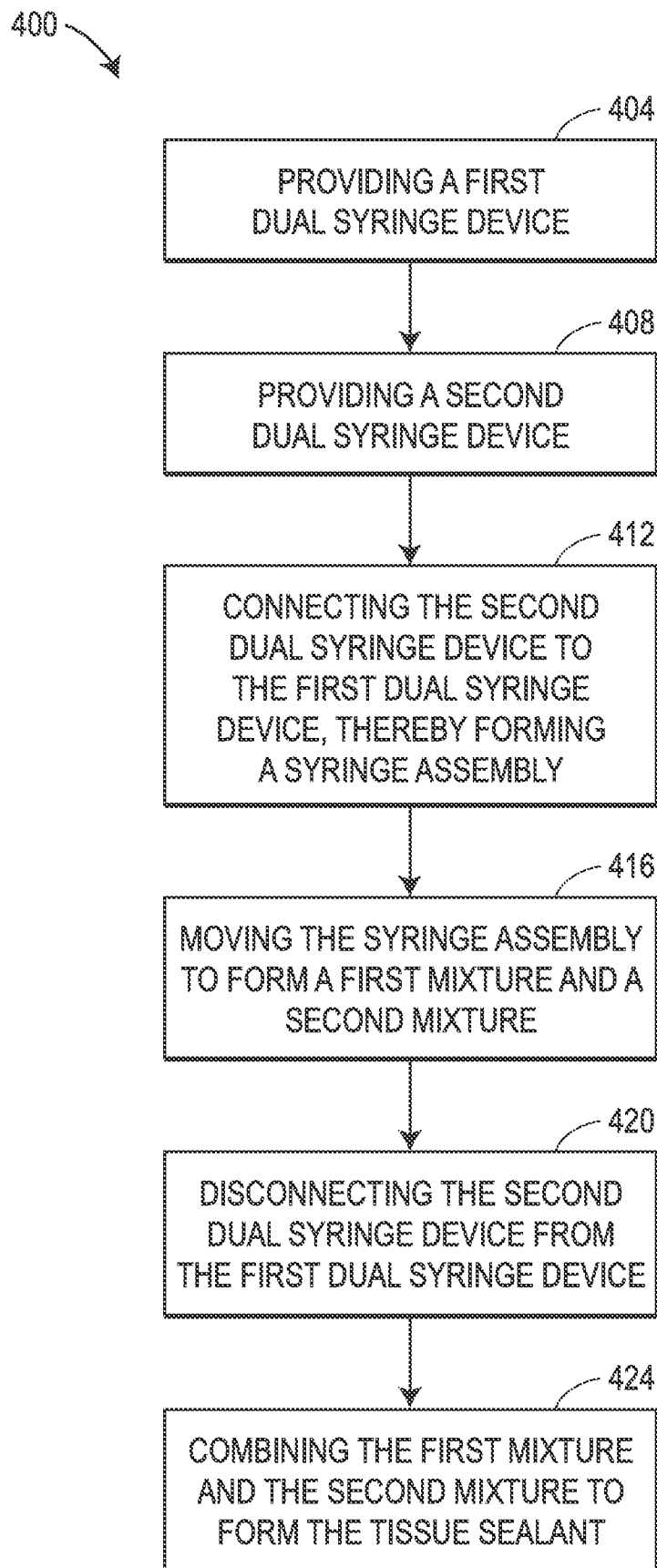


FIG. 3

**FIG. 4**

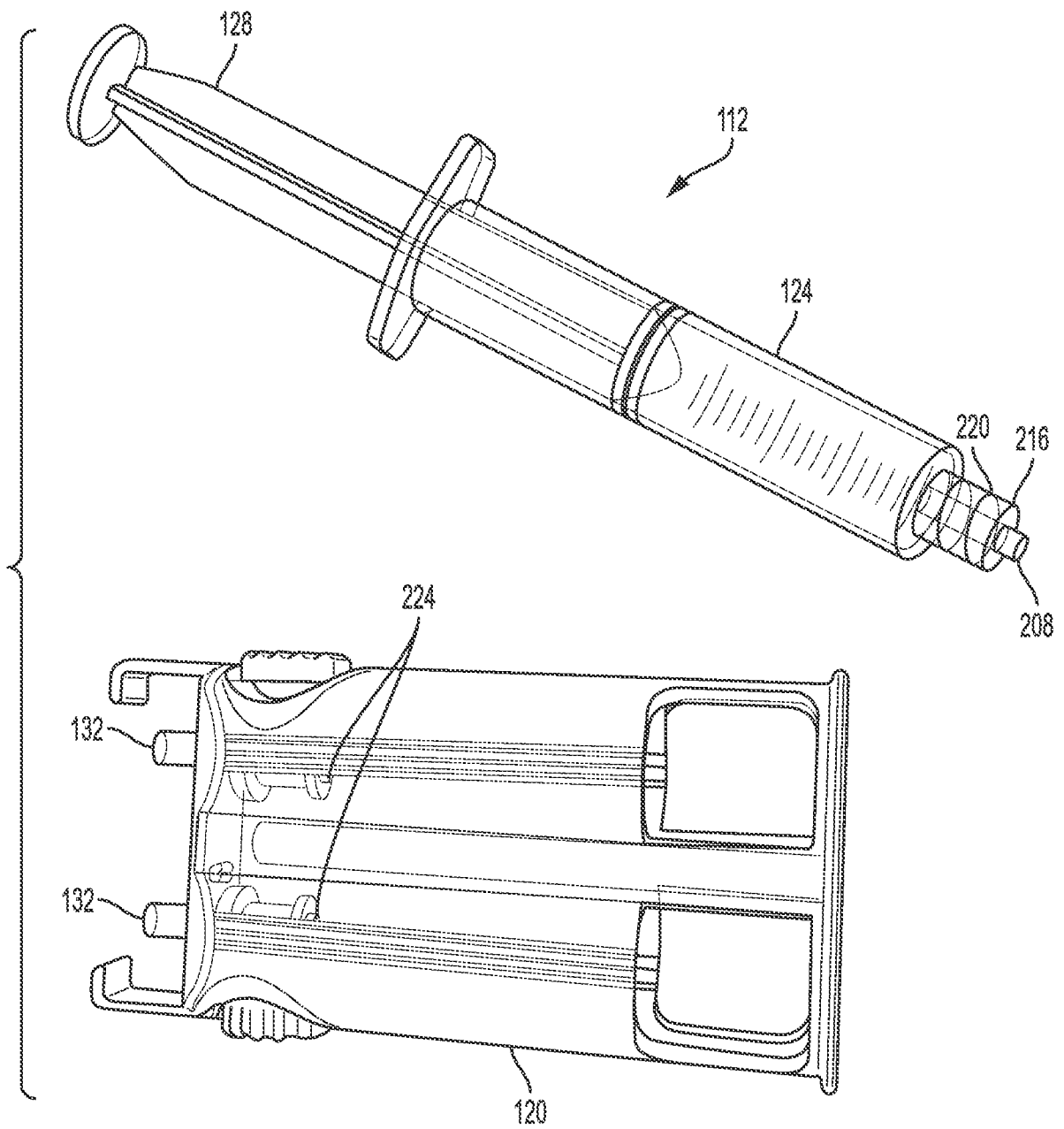


FIG. 5

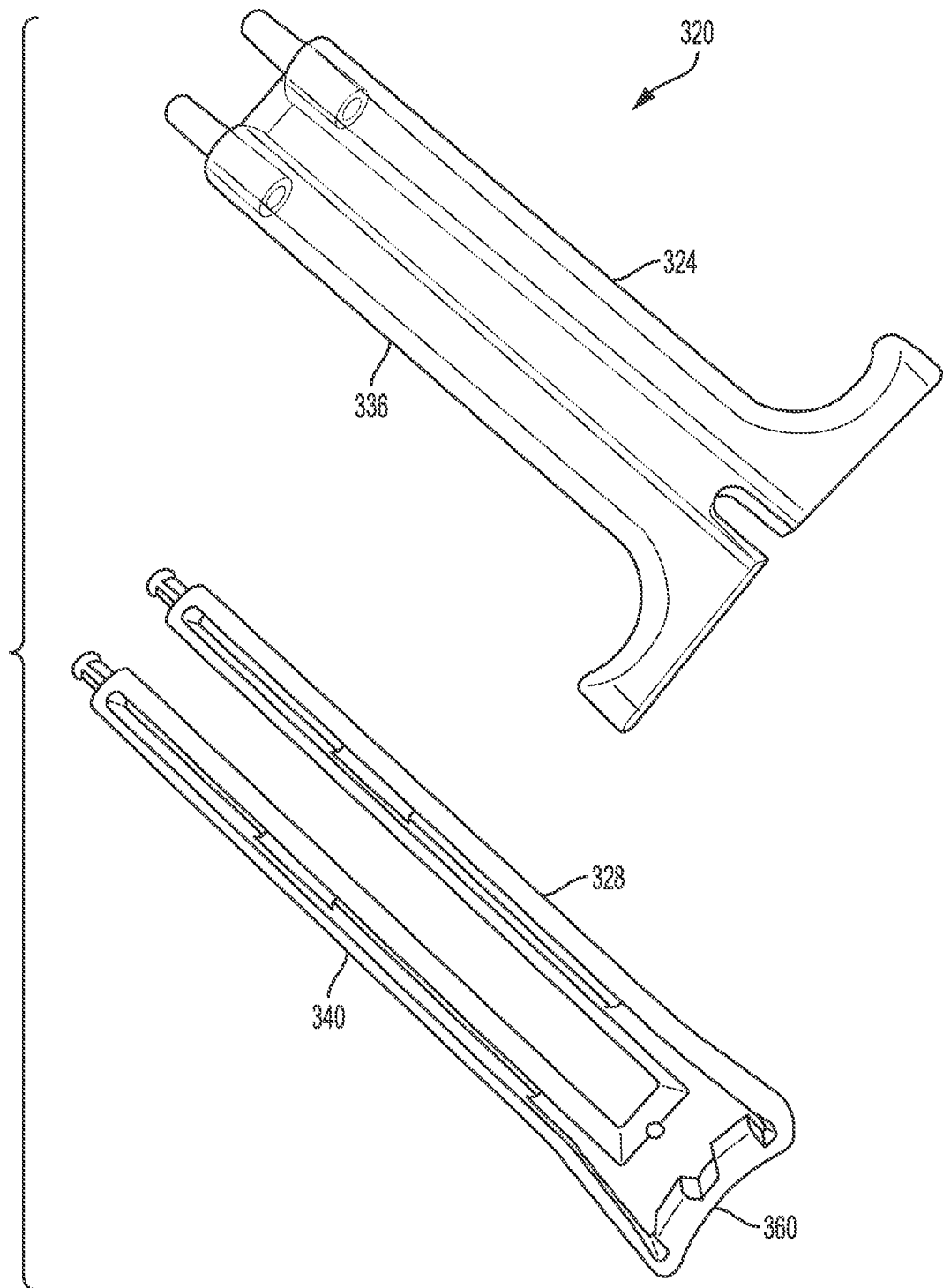


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/050975

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/19
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)
A61M A61B

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)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"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

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Date of the actual completion of the international search

2 May 2018

Date of mailing of the international search report

14/05/2018

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

Chopinaud, Marjorie

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/050975

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International application No

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