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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 December 2024 (26.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/263566 A2

(51) International Patent Classification:
A61K 9/14 (2006.01) *A61K 31/46* (2006.01)

(21) International Application Number:
PCT/US2024/034477

(22) International Filing Date:
18 June 2024 (18.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/521,897 20 June 2023 (20.06.2023) US

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

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

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

(54) Title: DRY POWDER COMPOSITIONS FOR RAPID RECONSTITUTION AND PARENTERAL DELIVERY

(57) Abstract: A dry powder atropine composition for parenteral administration after being reconstituted includes solid particles of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.8 mg and 3.2 mg. The dry powder atropine composition is formulated to be reconstituted in less than 10 seconds after first being mixed with an aqueous solvent having a volume of between 1 mL and 3 mL to form an aqueous solution for parenteral administration. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine base ($C_{17}H_{23}NO_3$).

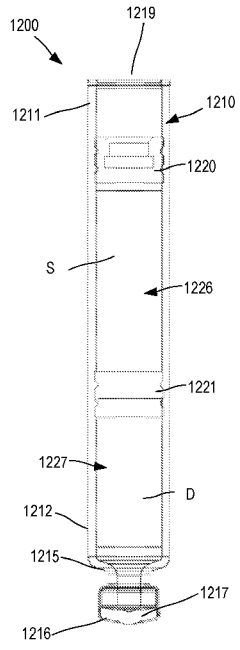

FIG. 1

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DRY POWDER COMPOSITIONS FOR RAPID RECONSTITUTION AND PARENTERAL DELIVERY

Cross-Reference to Related Applications

[1001] This application claims benefit of priority to U.S. Provisional Application No. 63/521,897, entitled "Dry Powder Compositions for Rapid Reconstitution and Parenteral Delivery," filed June 20, 2023, which is incorporated herein by reference in its entirety.

Background

[1002] The embodiments described herein relate generally to dry powder pharmaceutical compositions, methods of making dry powder compositions, and medicament containers for reconstituting the dry powder compositions. More particularly, the embodiments described herein relate to formulations of atropine for rapid reconstitution in a medicament delivery device.

[1003] Exposure to certain substances, such as, for example, peanuts, shellfish, bee venom, certain drugs, toxins, and the like, can cause allergic reactions in some individuals. Such allergic reactions can, at times, lead to anaphylactic shock, which can cause a sharp drop in blood pressure, hives, and/or severe airway constriction. Similarly, certain medical conditions, such as diabetes, can result in rapid changes or reductions in blood glucose levels, resulting in an emergency condition requiring immediate treatment. As another example, exposure to toxins or nerve agents (e.g., sarin or other organophosphorus compounds) requires immediate treatment. Accordingly, responding rapidly to mitigate the effects from such conditions or exposures is important to prevent injury and/or death. For example, in certain situations, an injection of epinephrine (i.e., adrenaline) can provide substantial and/or complete relief from the allergic reaction. In other situations, for example, an injection of an antidote to a toxin, such as atropine, pralidoxime and midazolam, can greatly reduce and/or eliminate the harm potentially caused by the exposure. Similarly, an injection of glucagon can reduce and/or eliminate the harm potentially caused by reduced blood glucose levels in individuals experiencing a hypoglycemic emergency.

[1004] Because emergency medical facilities are not always available when an individual is suffering from such emergencies or medical conditions, some individuals carry an auto-injector, a rescue inhaler, or the like to rapidly self-administer a medicament in response to

such emergency medical conditions. Some known auto-injectors include a vial containing a liquid medicament and a spring-loaded needle to automatically penetrate the user's skin and inject the medicament. The storage of certain medicaments in a liquid form, however, can result in a shorter shelf life and/or an unstable medicament. Accordingly, some known auto-injectors include a vial containing a first medicament that is separated from a second medicament. Such auto-injectors are often referred to as "wet / dry" auto-injectors, because one substance is often a liquid (e.g., water or another solvent) and the other substance can be substantially solid or dry (e.g., lyophilized glucagon powder). In use, the first medicament and the second medicament must be mixed prior to injection.

[1005] Some known wet / dry injectors, however, require multiple steps to reconstitute the dry medicament and are therefore not suited for rapid deployment. For example, the operation of some known wet/dry delivery systems includes manually inserting the needle into the skin prior to activation and subsequent medicament delivery. The operation of such configurations may also include separately attaching a needle to prepare the device for injection, resulting in a delay in delivery of the medicament. Such configurations can be complicated, making them difficult for a user to operate during an emergency by an individual without medical training. As another example, some known wet / dry injectors require that the user manually actuate a mixing mechanism and/or manually shake the device prior to injection. Such configurations can, however, result in incomplete mixing and/or injection of the substance that is only partially reconstituted. In such instances, the partially reconstituted substance can cause clogging of the needle, which further reduces the effectiveness of the delivery.

[1006] Additionally, many known dry powder formulations can have reconstitution times that are not suited for rapid deployment. For example, some known dry powder formulations have variations of particle size, moisture content, and other characteristics that can cause the reconstitution time to be too great for use in rapid deployment situations. In addition to limitations of known formulations, some known wet / dry injectors require that a user manually vent and/or purge a portion of air included in the medicament container (e.g., mixed with or a part of the glucagon powder). In some instances, such known injectors are generally oriented in a predetermined manner (e.g., with the needle end facing upward) during the mixing process and/or prior to injection to facilitate the venting process (also referred to as "priming"). Although the inclusion of air within the medicament container can possibly improve the mixing and reduce the reconstitution time, the use of injectors that require priming may not be practical

in certain emergency situations, such as, for example, in a combat setting where personnel may have multiple types of autoinjectors and it is preferable for all injectors to have the same use instructions to avoid treatment delay or error.

[1007] Thus, a need exists for improved dry powder pharmaceutical compositions, methods of making dry powder compositions, and medicament containers for rapidly reconstituting the dry powder compositions. Specifically, a need exists for an improved dry powder formulations of atropine for rapid reconstitution in a medicament delivery device.

Summary

[1008] Dry powder compositions, methods of making dry powder compositions, and medicament containers for reconstituting the dry powder compositions are described herein. In some embodiments, a dry powder atropine composition for parenteral administration after being reconstituted includes solid particles of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.8 mg and 3.2 mg. The dry powder atropine composition is formulated to be reconstituted in less than 10 seconds after first being mixed with an aqueous solvent having a volume of between 1 mL and 3 mL to form an aqueous solution for parenteral administration. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate monohydrate [$(C_{17}H_{23}NO_3)_2*H_2SO_4*H_2O$]. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate anhydrous [$C_{34}H_{48}N_2O_{10}S$]. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine base ($C_{17}H_{23}NO_3$).

[1009] In some embodiments, the dry powder atropine composition is formulated to be reconstituted in less than 2 seconds after first being mixed with the aqueous solvent having a volume of between 1.75 mL and 2 mL. In some embodiments, the dry powder atropine composition is formulated to be reconstituted within one second after first being mixed with the aqueous solvent having a volume of between 1.75 mL and 2 mL.

[1010] In some embodiments, the dry powder atropine composition has an average particle size of between about 2 microns and about 100 microns. In some embodiments, the dry powder atropine composition has an average particle size of between about 2 microns and about 30 microns.

[1011] In some embodiments, the dry powder atropine composition includes solid particles of at least one of a bulking agent, a preservative, or a cosolvent. In some embodiments, the dry powder atropine composition includes solid particles of a bulking agent. A ratio of the mass of the bulking agent to the mass of the atropine or the pharmaceutically acceptable salt of atropine is between about 4:1 and about 6:1.

[1012] In some embodiments, the dry powder atropine composition includes a cosolvent. A ratio of the mass of the cosolvent to the mass of the atropine or the pharmaceutically acceptable salt of atropine is between about 5:1 and about 7:1.

[1013] In some embodiments, the dry powder atropine composition has a moisture content of less than 5 percent. In some embodiments, the dry powder atropine composition has a moisture content of between 0.5 percent and 3 percent.

[1014] In some embodiments, the dry powder atropine composition has a purity of at least 90%, as determined by high-performance liquid chromatography (HPLC). In some embodiments, the dry powder atropine composition has a purity of at least 95%, as determined by HPLC.

[1015] In some embodiments, the dry powder atropine composition is produced by any of lyophilization, spray-drying, or milling.

[1016] In some embodiments, a method for producing a dry powder composition for parenteral administration after being reconstituted includes conveying A) a feed stock comprising atropine or a pharmaceutically acceptable salt of atropine and B) an atomizing gas into a spray-drying chamber via a spray nozzle to produce droplets containing the atropine or a pharmaceutically acceptable salt of atropine. The droplets are dried to form solid particles of the atropine or the pharmaceutically acceptable salt of atropine. The solid particles of the atropine or the pharmaceutically acceptable salt of atropine are then separated from the atomizing gas within a vortex separator to produce the dry powder composition. The resulting dry powder composition has an average particle size of between about 2 microns and about 100 microns and a purity of at least 95%, as determined by HPLC.

[1017] In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine base.

[1018] In some embodiments, the feed stock further comprises a bulking agent. A ratio of the mass of the bulking agent to the mass of the atropine or the pharmaceutically acceptable salt of atropine being between about 4:1 and about 6:1. In some embodiments, the feed stock further comprises a cosolvent. A ratio of the mass of the cosolvent to the mass of the atropine or the pharmaceutically acceptable salt of atropine being between about 5:1 and about 7:1.

[1019] In some embodiments, a medicament container assembly includes a container body, a first elastomeric member, a second elastomeric member, and a distal seal. The first elastomeric member is disposed within a proximal end portion of the container body and the second elastomeric member is disposed within the container body distally from the first elastomeric member. The first elastomeric member, the second elastomeric member, and a portion of the container body define a first volume that contains an aqueous solvent. The second elastomeric member and a distal end portion of the container body define a second volume that contains a dry powder atropine composition. The dry powder atropine composition includes solid particles of atropine or a pharmaceutically acceptable salt of atropine having a mass of atropine between about 0.25 mg and 3.2. The dry powder atropine composition is formulated to be reconstituted within the second volume in less than 10 seconds without requiring agitation or other physical mixing steps to be performed by the user after first being combined with the aqueous solvent to form an aqueous solution for parenteral administration.

[1020] In some embodiments, the first volume contains between about 1.75 mL and about 2 mL of the aqueous solvent and the dry powder atropine composition is formulated to be reconstituted in less than 2 seconds after first being mixed with the aqueous solvent.

[1021] In some embodiments, the container body defines a bypass channel configured to fluidically couple the first volume and the second volume on a condition that the second elastomeric member is at least partially aligned with the bypass. The dry powder atropine composition is mixed with the aqueous solvent in response to at least the second elastomeric member being moved distally to at least partially align the second elastomeric member with the bypass channel. In some embodiments, the dry powder atropine composition is mixed with the aqueous solvent solely in response to at least the second elastomeric member being moved distally. In some embodiments, the dry powder atropine composition is mixed with the aqueous solvent without any action extrinsic to the medicament container assembly.

Brief Description of the Drawings

[1022] FIG. 1 is a cross-sectional view of a medicament container assembly containing a medicament according to an embodiment.

[1023] FIG. 2 is a front perspective view of a medicament delivery device according to an embodiment in a first (storage) configuration.

[1024] FIG. 3 is a side view of the medicament delivery device shown in FIG. 2 in the first (storage) configuration.

[1025] FIG. 4 is a front view of the medicament delivery device shown in FIG. 2 with the outer casing removed.

[1026] FIG. 5 is a top perspective view of a housing of the medicament delivery device shown in FIG. 2.

[1027] FIGS. 6 and 7 are a front perspective view (FIG. 6) and a bottom perspective view (FIG. 7) of a top cap of the medicament delivery device shown in FIG. 2.

[1028] FIG. 8 is a cross-sectional view of the medicament delivery device shown in FIG. 2 taken along line X-X in FIG. 3, the medicament delivery device being in the first (storage) configuration.

[1029] FIG. 9 is a front perspective view of a cover (also referred to as a case) of the medicament delivery device shown in FIG. 2.

[1030] FIG. 10 is a top perspective view of a safety lock of the medicament delivery device shown in FIG. 2.

[1031] FIG. 11 is a top perspective view of a base (which functions as an actuator) of the medicament delivery device shown in FIG. 2.

[1032] FIGS. 12 and 13 are cross-sectional views of a distal portion (FIG. 12) and a proximal portion (FIG. 13) of a carrier and medicament container assembly the medicament delivery device shown in FIG. 2.

[1033] FIG. 14 is a cross-sectional view of the medicament delivery device shown in FIG. 2 taken along line X-X in FIG. 3, the medicament delivery device being in a second configuration (with the cover and safety lock removed).

[1034] FIG. 15 is a cross-sectional view of the medicament delivery device shown in FIG. 2 taken along line X-X in FIG. 3, the medicament delivery device being in a third configuration (after being activated).

[1035] FIG. 16 is a cross-sectional view of the medicament delivery device shown in FIG. 2 taken along line X-X in FIG. 3, the medicament delivery device being in a fourth configuration (with the bypass flow being initiated).

[1036] FIG. 17 is a cross-sectional view of the medicament delivery device shown in FIG. 2 taken along line X-X in FIG. 3, the medicament delivery device being in a fifth configuration (with the bypass flow being completed).

[1037] FIG. 18 is a cross-sectional view of the medicament delivery device shown in FIG. 2 taken along line X-X in FIG. 3, the medicament delivery device being in a sixth configuration (with the injection being completed).

[1038] FIG. 19 is a cross-sectional view of the medicament delivery device shown in FIG. 2 taken along line X-X in FIG. 3, the medicament delivery device being in a seventh configuration (with the retraction completed).

[1039] FIG. 20 is a flow chart of a method of producing an atropine composition, according to an embodiment.

[1040] FIG. 21 is a schematic illustration of a spray-drying system that can implement a method of producing an atropine composition, according to an embodiment.

Detailed Description

[1041] Dry powder compositions, methods of making dry powder compositions, and medicament containers for reconstituting the dry powder compositions are described herein. The dry powder compositions described herein can be included within any of the medicament container assemblies and medicament delivery devices described herein, and are formulated to be rapidly reconstituted. By increasing the rate of reconstitution of the dry powder

compositions (i.e., by reducing the time needed for reconstitution), the compositions described herein can be used in a wide variety of delivery devices for rapid response. For example, in some embodiments, the dry powder compositions described herein can be used in a medicament delivery device that does not require external steps (e.g., shaking or tilting) to reconstitute the composition for delivery. Additionally, the medicament container assemblies described herein include features (e.g., shaped bypass channels) and are configured to be manipulated (e.g., via the desired force exerted on the plungers) such that the dry medicament is reconstituted rapidly (quasi-instantaneously) by the flow of the solvent into the dry medicament without requiring additional steps (e.g., shaking, inverting the device, or the like). In some embodiments, the dry powder compositions and/or medicament container assemblies described herein can be used within devices (as described herein) that do not require a separate priming step to allow the excess gas to be bled from the reconstituted drug prior to delivery, while still maintaining the desired dose accuracy. In some embodiments, the dry powder compositions and/or medicament container assemblies described herein can be used within devices (as described herein) that do not require a separate priming step to allow the excess gas to be bled from the reconstituted drug prior to delivery, while still maintaining the desired dose accuracy.

[1042] In some embodiments, the dry powder compositions and/or medicament container assemblies described herein can be used within any of the devices shown and described in U.S. Patent No. 10,695,495, entitled "Devices and Methods for Delivering a Lyophilized Medicament," filed on September 20, 2017, U.S. Patent No. 10,576,206, entitled "Auto-Injectors for Administration of a Medicament Within a Prefilled Syringe," filed December 19, 2017 ("the '206 Patent") and International Patent Publication No. WO2020/140040, entitled "Devices and Methods for Delivery of Substances Within a Prefilled Syringe," filed December 27, 2019 ("the '0040 PCT"), each of which is incorporated herein by reference in its entirety

[1043] Accordingly, the dry powder compositions and medicament container assemblies described herein are suitable for use in a variety delivery devices for emergency situations where more complex, multi-step procedures are not desirable. Such situations can include, for example, drug delivery in a decentralized setting, in a battlefield setting, in a mass delivery setting (vaccinations, delivery of antidote for nerve agents, or the like).

[1044] Additionally, compositions, medicament container assemblies, and medicament delivery devices that are well suited to be stored for long durations (up to 2 years, up to 5 years,

up to 10 years) in rugged environments are described herein. The medicament delivery devices described herein are configured with multiple different levels of safety to prevent premature actuation or inadvertent piercing of the medicament container (e.g., due to being dropped, shaken, stored in environments with changing ambient conditions, etc.).

[1045] The method of producing dry powder compositions described herein can be used to produce a variety of compositions for rapid reconstitution and parenteral delivery. The methods described herein produce a composition having the desired particle size distribution that facilitates rapid reconstitution, while not so small (e.g., less than 1 micron) that the powder is difficult for filling and handling. The methods described herein can include spray drying, milling, and lyophilization.

[1046] As used in this specification, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, the term "a member" is intended to mean a single member or a combination of members, "a material" is intended to mean one or more materials, or a combination thereof.

[1047] As used herein, the term "medicament" includes any constituent of a therapeutic substance. A medicament can include such constituents regardless of their state of matter (e.g., solid, liquid or gas). Moreover, a medicament can include the multiple constituents that can be included in a therapeutic substance in a mixed state, in an unmixed state and/or in a partially mixed state. A medicament can include both the active constituents and inert constituents of a therapeutic substance. Accordingly, as used herein, a medicament can include non-active constituents such as, water, colorant or the like.

[1048] The term "about" when used in connection with a referenced numeric indication means the referenced numeric indication plus or minus up to 10 percent of that referenced numeric indication. For example, "about 100" means from 90 to 110.

[1049] As used herein, the words "proximal" and "distal" refer to direction closer to and away from, respectively, an operator of the medical device. Thus, for example, the end of the medicament delivery device contacting the patient's body would be the distal end of the medicament delivery device, while the end opposite the distal end would be the proximal end of the medicament delivery device. As another example, the distal end portion of a medical injector is the end from which a needle or delivery member extends during the delivery event.

[1050] FIG. 1 shows a medicament container assembly 1200 according to an embodiment. The medicament container assembly contain a solvent S within a solvent volume 1226 and a dry medicament D within a dry medicament volume 1227. More specifically, the medicament container assembly 1200 includes a container body 1210 having a proximal end portion 1211, a distal end portion 1212, and defining a proximal end opening 1219 and a distal end opening. The distal end portion 1212 of the container body 1210 includes a neck 1215 and a distal cap 1216 including a seal member 1217. The distal end portion 1212 is configured to be at least partially disposed within a retention portion 1284 of the carrier 1260, as described below. The distal cap 1216 can be, for example, a crimp seal or cap disposed about the distal end portion 1212 of the container body 1210. The seal member 1217 can be any suitable member, such as, for example, a septum, a valve, a frangible seal, and/or the like. In this manner, the seal member 1217 is configured to engage a surface of the container body 1210 and an inner surface of the distal cap 1216 to define a fluidic seal.

[1051] The proximal end opening 1219 of the container body 1210 allows the inner volume to receive a first elastomeric member 1220 and a second elastomeric member 1221. The first elastomeric member 1220 and the second elastomeric member 1221 are placed within the container body 1210 during the fill / finish process to define the solvent volume 1226 and the dry medicament volume 1227. Said another way, the solvent volume 1226 is a volume disposed within the container body 1210 defined between the first elastomeric member 1220 and the second elastomeric member 1221. The dry medicament volume 1227 is a volume disposed within container body 1210 defined between the second elastomeric member 1220 and the seal member 1217 disposed at the distal end portion 1212 of the container body 1210. As shown in FIG. 1, the solvent volume 1226 and the dry medicament volume 1227 are defined by the positions of the first elastomeric member 1220 and the second elastomeric member 1221 relative to and/or within the container body 1210. In some embodiments, the solvent volume 1226 can contain a medicament solvent S, such as, for example, any of aqueous solvents described herein. In other embodiments, the solvent S includes an alcohol or a miscible organic solvent suitable for parenteral delivery. In some embodiments, the solvent S includes any of the constituents described herein, such as a buffering agent, a bulking agent, a surfactant, or any other suitable constituents.

[1052] In some embodiments, the dry medicament volume 1227 can contain any of the dry powder compositions described herein. The dry powder composition D can include any of the

constituents described herein, such as a bulking agent, a preservative, a co-solvent, or any other suitable constituents. Moreover, the dry powder composition D and the medicament container assembly 1200 can be produced by any of the methods described herein and in U.S. Patent Publication No. 2024/0058538, entitled "Devices and Methods for Delivering Reconstituted Medicaments," filed on July 28, 2023, which is incorporated herein by reference in its entirety.

[1053] The first elastomeric member 1220 and the second elastomeric member 1221 can be of any design or formulation suitable for contact with the medicament (e.g., the solvent contained in the solvent volume 1226 and/or the dry powder composition D contained in the dry medicament volume 1227). For example, the elastomeric members 1220 and 1221 can be formulated to minimize any reduction in the efficacy of the medicament that may result from contact (either direct or indirect) between the elastomeric members 1220 and 1221 and the medicament. In some embodiments, the elastomeric members 1220 and 1221 can be made from and/or can include butyl rubber, such as chlorobutyl rubber, bromobutyl rubber, and/or the like. In some embodiments, the first elastomeric member 1220 and the second elastomeric member 1221 can be formulated to minimize any leaching or out-gassing of compositions that may have an undesired effect on the medicament. In other embodiments, the elastomeric members 1220 and 1221 can be formulated to maintain its chemical stability, flexibility and/or sealing properties when in contact (either direct or indirect) with the medicament over a long period of time (e.g., for up to six months, one year, two years, five years or longer).

[1054] As shown in FIGS. 4 and 17, the container body also includes one or more bypass channels 1214. The bypass channels 1214 are configured to facilitate the mixing and reconstitution of the dry powder composition D contained within the container body 1210, as described in further detail herein. In particular, the bypass 1214 is configured to place the dry medicament volume 1227 and the solvent volume 1226 in fluid communication with each other. Although shown as being a series of channels, in other embodiments, the bypass 1214 can be a singular channel bypass. Although the bypass 1214 is shown as being an internal bypass, in other embodiments, the bypass 1214 can be an external bypass (e.g., a portion that protrudes from the outer surface of the container body. Said another way, in some embodiments a bypass can be configured such that the outer diameter of the container body 1210 is substantially constant.

[1055] FIGS. 2-19 show various views of a medical injector 1000 according to an embodiment in various different configurations (or stages of operation). FIGS. 2 is a perspective view and

FIG. 8 is cross-sectional view of the medical injector 1000 (also referred to herein as "medicament delivery device" or "drug product") in a first configuration (i.e., prior to use). FIG. 14 is a cross-sectional view of the medicament delivery device in a second configuration (with the cover and safety lock removed). FIG. 15 is a cross-sectional view of the medicament delivery device in a third configuration (after being activated). FIG. 16 is a cross-sectional view of the medicament delivery device in a fourth configuration (with the bypass flow being initiated). FIG. 17 is a cross-sectional view of the medicament delivery device in a fifth configuration (with the bypass flow being completed). FIG. 18 is a cross-sectional view of the medicament delivery device in a sixth configuration (with the injection being completed). FIG. 19 is a cross-sectional view of the medicament delivery device in a seventh configuration (with the retraction completed). The medical injector 1000 can contain any of the dry powder compositions described herein (including, but not limited to, the dry powder atropine compositions).

[1056] The medical injector 1000 includes a cover 1180 (see FIG. 9), a housing 1100 (see FIG. 5), a system actuation assembly, a medicament container assembly 1200 (see, e.g., FIG. 1), a base 1510 (or actuator, see FIG. 11); and a safety lock 1700 (see FIG. 10). As shown, the housing 1100 has a proximal end portion 1101 and a distal end portion 1102. The housing 1100 defines a pair of status indicator apertures 1130 disposed on a front side and a rear side of the housing 1100 (e.g., opposite sides of the housing 1100), which are configured to allow a patient to monitor the status and/or contents of the medicament container 1200 contained within the housing 1100. For example, by visually inspecting the status indicator apertures 1130, a patient can determine whether the medicament container assembly 1200 contains a medicament and/or whether the medicament has been dispensed. In some embodiments, the container assembly 1200 can be positioned such that the dry medicament volume 1227 and/or the dry medicament therein are at least partially shielded. In this manner, if the dry medicament is deformed or broken apart by the methods described herein, the user will not improperly interpret such non-uniformities as being indicative of a defective drug product.

[1057] As shown in FIG. 5, the inner surface of the housing 1100 defines a gas cavity 1151, a medicament cavity 1139, and a side cavity 1132. The gas cavity 1151 is configured to receive a set of retention members 1163 included in a proximal cap 1160, a gas container 1580, and a portion of the system actuator assembly 1500 (e.g., a release member 1550 and a spring 1565, as shown in FIG. 8). The gas cavity 1151 is at least partially separated from the medicament

cavity 1139. The gas cavity 1151 is in fluid communication with the medicament cavity 1139 to allow flow of pressurized gas via a gas passageway (not identified).

[1058] The medicament cavity 1139 is configured to receive the medicament container assembly 1200 and the carrier 1260. An inner surface of the housing 1100 includes and/or forms a sidewall that separates the medicament cavity 1139 from the gas cavity 1151, and a sidewall that separates at least a portion of the medicament cavity 1139 from the side cavity 1132. The carrier 1260 and the medicament container assembly 1200 are movable within the medicament cavity 1139 in the proximal direction and in the distal direction. Moreover, the carrier 1260 includes a seal member 1270 configured to form a substantially fluid tight seal with the inner surface of the housing 1100 defining the medicament cavity 1139. The seal member 1270 also seals the carrier 1260 and the container body 1210. Thus, the proximal portion of the medicament cavity 1139 forms a gas chamber that is substantially fluidically isolated by the seal member 1270. Specifically, the seal member 1270 has two sealing portions: one that forms a seal against the container body 1210 and the other that forms a seal against the inner surface of the housing 1100. In use, the pressurized gas applies an actuation force in a distal direction against the seal member 1270. The actuation force urges the two sealing portions outward (i.e., one sealing portion outward towards the container body 1210 and the other outward towards the housing 1100), which further enhances sealing. In other embodiments, however, the carrier 1260 can include multiple separate seals (e.g., O-rings) that form a fluid-tight seal with the housing 1100 and the container body 1210.

[1059] In some embodiments, the proximal portion of the medicament cavity can include a protrusion or stepped feature that limits movement of a retention portion 1284 of the carrier 1260. Referring to FIG. 12, when the medical injector 1000 is in the first configuration, the distal end portion 1212 of the container body 1210 is secured within a retention portion 1284 of the carrier 1260. Thus, the distal end portion of the medicament container assembly 1200 is within the coupling volume 1283 but spaced apart from the proximal tip of the needle 1290. As shown in FIG. 15, when the device is actuated, the carrier moves distally, and the gas pressure exerted causes the medicament container assembly 1200 to be pushed distally and released from the retention portion 1284 by an outward deformation of the retention portion (see the arrows AA in FIG. 12). The optional proximal safety protrusion can contact the carrier in a manner to prevent inadvertent outward deformation of the retention portion 1284 when the device is in the first configuration. Similarly stated, in some embodiments, the inner wall of

the housing 1100 that defines the medicament cavity can include a stepped portion that engages the carrier 1260 near the retention portion 1284. This arrangement limits the likelihood that retention portion 1284 will inadvertently be deformed outward when the device 1000 is in the storage configuration. This additional safety feature can be helpful to prevent the seal of the medicament container assembly 1200 from being punctured by the needle during conditions when the device 1000 may be subjected to high external forces (e.g., vibratory forces, impact forces due to being dropped, etc.).

[1060] The distal end portion 1102 of the housing 1100 defines a lock rod opening, a needle opening, and a system activation opening. The lock rod opening receives a portion of the safety lock 1700 when the safety lock 1700 is coupled to the housing 1100. The needle opening is the opening through which the needle 1290 is disposed (see e.g., FIGS. 15-18) when the medical injector 1000 is actuated. The system activation opening receives a portion of the rod 1550 and allows the system actuator 1500 to be moved in a proximal direction relative to the housing 1100. As described above, the proximal end portion 1101 of the housing 1100 includes and/or is otherwise coupled to a proximal cap 1160 (see e.g., FIGS. 6-7). The proximal cap 1160 includes the retention members 1163. The proximal cap 1160 is coupled to the proximal surface of the housing 1100. In some embodiments, the proximal cap 1103 is fixedly coupled to the proximal surface via, for example, ultrasonic welding, adhesive, fasteners, and/or the like or a combination thereof. Moreover, a seal member can be disposed in a seal recess to form a substantially fluid tight seal between the proximal cap 1160 and the proximal surface of the housing 1100.

[1061] The retention members 1163 of the proximal cap 1160 are configured to receive and/or retain the gas container 1580 that contains a pressurized gas. When the medical injector 1000 is actuated, pressurized gas from the gas container 1580 is conveyed from the gas cavity 1151 to the medicament cavity 1139 via the gas passageway.

[1062] FIG.9 shows the cover 1180 of the medical injector 1000. The cover 1180 can be any suitable configuration and can include any suitable feature to house, contain and/or protect portions of the medical injector 1000. The cover 1180 includes a proximal end portion 1181 and a distal end portion 1182, and defines a cavity and a set of status windows 1183. The cavity of the cover 1180 is configured to receive at least a portion of the housing 1100. The status windows 1183 are disposed on opposite sides of the cover 1180 and are configured such that, when the portion of the housing 1100 is disposed within the cover 1180, the status

windows 1183 of the cover 1180 are at least partially aligned with the corresponding status indicator aperture 1130 of the housing 1100. Thus, a user can visually inspect a portion of the medicament container assembly 1200 via the status windows 1183 of the cover 1180 and the status indicator apertures 1130 of the housing 1100. The cover 1180 also functions as a safety mechanism by preventing movement of the safety guard 1700 and by preventing inward movement of the base 1510.

[1063] FIG. 10 shows the safety lock 1700 of the medical injector. The safety lock has similar structure and function as the safety locks shown in U.S. Patent No. 10,576,206, entitled "Auto-Injectors for Administration of a Medicament Within a Prefilled Syringe" ("the '206 Patent") and International Patent Publication No. WO2020/140040, entitled "Devices and Methods for Delivery of Substances Within a Prefilled Syringe," filed December 27, 2019 ("the '0040 PCT"), each of which is incorporated herein by reference in its entirety.

[1064] FIG. 11 shows the base 1510 (which functions as an actuator) of the medical injector. The base has similar structure and function as the safety locks shown in the '206 Patent and the '0040 PCT, each of which is incorporated herein by reference in its entirety.

[1065] FIG. 13 shows the gas release assembly 1310 of the medical injector. The gas release assembly 1310 expands as the first elastomeric member 1220 moves distally and serves to release a gas vent when the end of the injector stroke is reached. The gas release assembly 1310 a has similar structure and function as the gas release (or expandable) assemblies shown in the '206 Patent and the '0040 PCT, each of which is incorporated herein by reference in its entirety. In some embodiments the side cavity 1132 of the housing can receive the vented gas. In some embodiments, the side cavity 1132 can include an acoustic structure to produce an audible indicator (e.g., a whistling sound) when the gas is released.

[1066] FIGS. 14-19 show the medical injector in its various states of delivery.

[1067] After the cover 1180 is removed from the housing 1100, the medical injector 1000, the safety lock 1700 is exposed and can be removed. FIG. 14 shows the medical injector in the second configuration with the cover 1180 and the safety lock 1700 both removed.

[1068] Referring to FIG. 15, the medical injector 1000 can then be activated by moving the base 1510 from a first position to a second position to place the medical injector 1000 in the third configuration. Similarly stated, the medical injector 1000 can be activated by the system

actuator assembly 1500 by moving the base 1510 proximally relative to the housing 1100. The base 1510 is moved from its first position to its second position by placing the medical injector 1000 against a target surface (e.g., the body of the patient) and moving the base 1510 with respect to the housing 1100 in the proximal direction.

[1069] The proximal movement of the base 1510 from its first position to its second position actuates and/or otherwise releases the release member 1550. As such, the spring 1565 is allowed to transition from a first configuration (e.g., a compressed configuration) to a second configuration (e.g., a non-compressed configuration), thereby moving the release member 1550 within the gas cavity 1151. Proximal movement of the release member 1550 causes the puncturer 1575 to puncture and/or pierce a portion of the gas container 1580 (e.g., a frangible seal or the like). After the gas container 1580 has been punctured, an actuating portion of a compressed gas flows from the gas container 1580 and into the gas cavity 1151. Moreover, with a seal of the release member 1550 forming a substantially fluid tight seal with the inner surface defining the gas cavity 1151, the actuating portion of the compressed gas fills the gas cavity 1151 and is forced through the gas passageway and into the medicament cavity 1139.

[1070] As the gas flows into the medicament cavity 1141, the gas applies gas pressure to the upper portion of the carrier 1260 (including the carrier seal 1270) and the first elastomeric member 1220 within the medicament container 1210. This gas force (the insertion force) causes the medicament container 1210, the carrier 1240 and the needle 1290 to contemporaneously move within the housing 1100 in the distal direction. The movement of the needle 1290 in a distal direction causes the distal end portion of the needle 1290 to exit the housing 1100 and enter the body of a patient prior to administering the medicament.

[1071] Referring to FIG. 16, after the needle 1290 is inserted the continued build-up of gas pressure moves the first elastomeric member 1220 and the second elastomeric member 1221 distally to a position where the bypass 1214 is aligned with the second elastomeric member 1221. In this embodiment, the bypass 1214 can extend along a length of the medicament container 1210 that is greater that a length along which each elastomeric member 1220 and 1221 extends. Thus, when the bypass 1214 is substantially aligned with the second elastomeric member 1221, the increased pressure within the solvent volume 1226 urges a flow of the liquid solvent through the bypass 1214 and around the second elastomeric member 1221 to be transferred into the dry medicament volume 1227. In this manner, the solvent can mix with the dry powder composition D disposed within the dry medicament volume 1227 to reconstitute

the medicament for injection. As described above, the bypass channels 1214 and the pressure exerted by the movement of the elastomeric members can produce sufficient fluidic mixing within the dry medicament volume 1227 to eliminate the need for shaking, inverting the injector, or any other steps. FIG. 17 shows the medical injector at the end of the movement the elastomeric members (just prior to injection of the reconstituted drug).

[1072] As shown in FIGS. 17 and 18, the first elastomeric member 1220 can be in contact with the second elastomeric member 1221 such that the gas pressure exerts a force sufficient to move both the elastomeric members 1220 and 1221 in the distal direction. The distal movement of the elastomeric members 1220 and 1221 generates a pressure upon the medicament contained within the container body 1210, thereby allowing at least a portion of the medicament to flow out of the container body 1210 via the needle 1290, as shown in FIG. 18. Furthermore, when the elastomeric members 1220 and 1221 are disposed in a distal position within the medicament container 1210, the medical injector 1000 has delivered a dose of the reconstituted medicament.

[1073] FIG. 19 shows the medical injector in its retracted position. The retraction of the carrier 1260 and the needle occurs in response to the pressurized gas within the gas chamber of the housing being vented by the expansion of the gas release assembly 1310. Specifically, when the first elastomeric member 1220 reaches the desired position (i.e., its distal-most position corresponding to the end of injection), the gas release assembly 1310 actuates a valve to release the gas. Operation of the gas release assembly 1310 can be similar to that shown in the '206 Patent and the '0040 PCT, each of which is incorporated herein by reference in its entirety. After the gas pressure within the gas chamber is reduced, a retraction spring (not shown) urges the carrier 1260 proximally.

[1074] In some embodiments, the delivery sequence is devoid of any separate priming operation (also referred to as a gas venting operation). The dry medicament is formulated to be reconstituted quickly, and the limited amount of gas present within the medicament container assembly 1200 obviates the need for additional time (for reconstitution) or gas venting.

Compositions

[1075] Any of the devices and/or medicament containers shown and described herein can include any suitable medicament or therapeutic agent. For example, although the medical

injectors described above are shown and described as including a multi-chamber medicament container (e.g., medicament container 1210) that includes a substantially dry medicament (e.g., contained within the dry medicament volume 1227) and a solvent (e.g., contained within the solvent volume 1226), in other embodiments, any of the medicament delivery devices disclosed herein can include a multi-chamber container that is filled with any suitable substances. For example, in some embodiments, any of the medicament delivery devices disclosed herein can include a medicament container (e.g., a cartridge) that separately stores and mixes, upon actuation, two liquid substances. For example, in some embodiments, any of the devices shown and described herein can include a medicament container filled with (in separate chambers) any of the dry powder medicaments D and solvents S described herein and in U.S. Patent Publication No. 2024/0058538, entitled "Devices and Methods for Delivering Reconstituted Medicaments," filed on July 28, 2023, which is incorporated herein by reference in its entirety.

[1076] In some embodiments, any of the devices and/or medicament containers shown and described herein can include a dry powder medicament composition that includes an effective amount of atropine or a pharmaceutically acceptable salt of atropine. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate monohydrate [$(C_{17}H_{23}NO_3)_2*H_2SO_4*H_2O$]. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate anhydrous [$C_{34}H_{48}N_2O_{10}S$]. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine base ($C_{17}H_{23}NO_3$). As used herein, an "effective amount" is an amount sufficient to provide a desired therapeutic effect. For example, as described herein, the present atropine compositions may be useful in treating indications associated with nerve agent toxicity. Accordingly, an effective amount of atropine in the present compositions may be an amount sufficient to provide the desired blocking of receptors in response to exposure to a nerve agent (e.g., sarin (GB), soman (GD), tabun (GA) and VX). The present atropine compositions typically include a dose of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.25 mg and 3.2 mg. In some embodiments, a dry medicament composition can include a dose of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.8 mg and 3.2 mg. In some embodiments, a dry medicament composition can include a dose of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.25 mg and 2.0 mg. In some embodiments, a dry medicament composition can include a dose of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.25 mg and 1.0 mg. In some embodiments, a dry

medicament composition can include a dose of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.25 mg and 0.5 mg. In other embodiments, a dry medicament composition can include a dose of atropine base ($C_{17}H_{23}NO_3$). In some embodiments, the dry power composition can be included in a medicament container with or mixed with a sufficient amount of solvent to produce a single dose of between about 1.75 mL and 2.25 mL of drug solution. In some embodiments, the single dose of reconstituted atropine is about 2 mL of drug solution.

[1077] The medicament containers and/or medicament delivery devices disclosed herein can contain any suitable amount of any medicament. For example, in some embodiments, a medicament delivery device as shown herein can be a single-dose device containing an amount of medicament to be delivered of approximately 0.25 mg, 0.4 mg, 0.5 mg, 0.8 mg, 1 mg, 1.6 mg or 2 mg. As described above, the fill volume can be such that the ratio of the delivery volume to the fill volume is any suitable value (e.g., 0.4, 0.6 or the like).

[1078] In some embodiments, the dry powder compositions described herein may exclusively comprise one or more active or bioactive agents (i.e., 100% w/w). In other embodiments, however, the dried material may incorporate much less bioactive agent depending on the activity thereof. Accordingly, for highly active materials the dried material may incorporate as little as 0.001% by weight, although a concentration of greater than about 0.1% w/w is preferred. Other embodiments of the dry powder compositions may comprise greater than about 5%, 10%, 15%, 20%, 25%, 30% or even 40% w/w active or bioactive agent. In yet other embodiments, the dried material may comprise greater than about 50%, 60%, 70%, 75%, 80% or even 90% w/w active or bioactive agent. The precise amount of active or bioactive agent incorporated in the present invention is dependent upon the agent of choice, the required dose, and the form of the agent actually used for incorporation.

[1079] The dry powder compositions produced according to the methods described herein are formulated to rapidly and thoroughly be reconstituted in a solvent in a manner to facilitate the injection methods described herein. More particularly, the dry powder medicaments described herein can be included within a medical injector (e.g., the medical injector 1000 described herein), which can be actuated by a single operation to initiate reconstitution, needle insertion, and drug delivery. The medical injector can include a medicament container within which the dry powder medicament and a liquid solvent are contained. The dry powder compositions described herein are formulated to be rapidly reconstituted (quasi-instantaneously) by the flow

of the solvent into the dry medicament without requiring additional steps (e.g., shaking, inverting the device, or the like). In this manner, an accurate dose of the reconstituted medicament can be delivered via a single operation (i.e., without requiring separate mixing and/or priming steps prior to commencing injection). In some embodiments, the reconstituted medicament can be delivered through a needle (e.g., a needle having a size of between 22 gauge and 29 gauge).

[1080] In some embodiments, the dry powder compositions described herein are formulated to include between 1 mg and 3 mg active pharmaceutical ingredient (API) that is reconstituted in less than 2 mL aqueous solvent in less than 10 seconds. In some embodiments, the dry powder medicaments include an atropine composition formulated to be reconstituted in less than 2 seconds after first being mixed with the aqueous solvent having a volume of between 1.75 mL and 2 mL. In some embodiments, the dry powder atropine composition is formulated to be reconstituted within one second after first being mixed with the aqueous solvent having a volume of between 1.75 mL and 2 mL. Dissolution of the reconstituted composition is measured using pharmaceutically accepted methods, such as those described in the United States Pharmacopeia or other international standards.

[1081] In some embodiments, a dry powder composition has an average particle size of between about 2 microns and about 100 microns. In some embodiments, the dry powder composition has an average particle size of between about 2 microns and about 30 microns.

[1082] The dry powder compositions herein will have a moisture content that allows the dry powder to remain chemically and physically stable during storage at ambient temperature and easily dispersible. As such, the moisture content of the microparticles is typically less than 6% by weight, and preferably less 3% by weight. In some instances, the moisture content will be as low as 1% by weight. In some embodiments, the final lyophilized cake will have a moisture of between 0.5-3%. Of course, it will be appreciated that the moisture content is, at least in part, dictated by the formulation and is controlled by the process conditions employed, e.g., inlet temperature, feed concentration, pump rate, and blowing agent type, concentration and post drying.

[1083] In some embodiments, a dry powder composition D and a solvent S can include any suitable excipients and/or material which possesses physical and chemical characteristics that are compatible with the active ingredients. In some embodiments, such additives can include

any inactive ingredients that are known to those skilled in the art for lyophilization, spray drying, fluid bed drying, pan granulation, extrusion, dry blending, spray coating, and other similar techniques. These can include bulking agents, buffering agents, chelating agents, co-solvents, isotonicity agents, preservatives, and surfactants.

[1084] In some embodiments any of the dry powder compositions described herein can include a bulking agent. Bulking agents form the bulk volume of the dry powder and provide structure to the powder in the form of a cake, aggregate, or free flowing powder. Such bulking agents can include but are not limited sugar like molecules such as mannitol, lactose, trehalose, sugar, sorbitol, and dextrose; amino acids such as arginine, glycine, histidine, and lysine; cellulosic materials such as carboxymethylcellulose, croscarmellose, methylcellulose; polymeric materials such as crospovidone, Dl-Lactide and glycolide copolymer, Poloxamer 188, Polyethylene glycol 300, Polyethylene glycol 400, Polyethylene glycol 3350, Polyethylene glycol 4000, polylactide, Povidone, Povidone K12, Povidone K17, Povidone K30; other substances including ascorbic acid, creatinine, gelatin, lactic acid, maleic acid, methionine, niacinamide, sodium ascorbate, tartaric acid, and zinc oxide.

[1085] In some embodiments, certain bulking agents can be used to improve the stability, solubility and/or efficacy of the composition when reconstituted in any of the devices shown and described herein. Specifically, bulking agents may also be added to the reconstitution solution to aid in the rapid rehydration of the dried active ingredient. In some embodiments, the rapid rehydration of an active ingredient can be enhanced by the appropriate ratios of bulking agent in the reconstitution solution. In some embodiments, a dry powder atropine composition includes solid particles of a bulking agent. A ratio of the mass of the bulking agent to the mass of the atropine or the pharmaceutically acceptable salt of atropine is between about 4:1 and about 6:1. In some embodiments, certain bulking agents can be used to produce a visual indicia when the composition is reconstituted (e.g., such agents can allow the reconstituted medicament to be more easily detected by the user). It should also be understood that combinations of different bulking agents in both the dry powder composition D and/or the solvent S are covered by the scope the embodiments described herein.

[1086] Additionally, the solubility of atropine can be increased with changes in the pH. In certain embodiments, the atropine compositions, prior to being formed as a dry powder and/or after reconstitution, have a pH of less than about pH 6.5, including less than about pH 5.5, less than about pH 4.5, less than about pH 4.0, less than about pH 3.5. In other embodiments of the

invention, the atropine formulations, prior to being formed as a dry powder and/or after reconstitution, have a pH range of about pH 4.0 to about pH 5.0, inclusive of all ranges and subranges therebetween, e.g., about 4.4 to about 4.6; about 4.3 to about 4.7; about 4.2 to about 4.8; about 4.1 to about 4.9. In other embodiments of the invention, the atropine formulations, prior to being formed as a dry powder and/or after reconstitution, have a pH range of about pH 3.0 to about pH 4.0, inclusive of all ranges and subranges therebetween, e.g., about 3.4 to about 3.6; about 3.3 to about 3.7; about 3.2 to about 3.8; about 3.1 to about 3.9. In certain embodiments, the pH of the atropine composition is adjusted prior to being formed as a dry powder by the addition of a suitable acid, such as hydrochloric acid or citric acid.

[1087] In some embodiments, any of the compositions described herein can include buffering agents. Buffering agents are used to maintain the optimal pH of the dried active ingredient and/or the reconstitution solution. These agents can provide additional stability to the active ingredient during storage. These agents can also aid in the rapid rehydration of the dried active by maintaining a pH for reconstitution in the optimal solubilization range. In some embodiments, a buffering agent may comprise an organic and/or inorganic acid or salt thereof (e.g., alkali metal salts [Li, Na, K, etc.], alkaline earth metal [e.g., Ca, Mg, etc.] salts, ammonium salts, etc.). In other embodiments, the buffering agent includes mixtures of one or more acids and one or more salts thereof. For example, buffering agents can include but are not limited to acetic acid, adipic acid, ammonia, ammonium acetate, benzoic acid, citric acid, hydrochloric acid, methanesulfonic acid, phosphoric acid, potassium phosphate dibasic, potassium phosphate monobasic, sodium acetate, sodium bicarbonate, sodium bisulfate, sodium bisulfite, sodium carbonate, sodium hydroxide, sodium phosphate dibasic, sodium phosphate monobasic, sodium phosphate tribasic, succinic acid, sulfuric acid, trisodium citrate, and tromethamine.

[1088] In some embodiments, any of the compositions described herein can include isotonicity agents. Such isotonicity agents can be added to the dried active ingredient and/or the reconstitution solution to maintain an appropriate osmotic pressure for injection. Isotonicity agents can improve the storage stability of the active. Isotonicity agents can also reduce rehydration times. These components can include but are not limited to calcium chloride, potassium chloride, potassium sulfate, and sodium chloride.

[1089] In some embodiments, any of the compositions described herein can include chelating agents. Such chelating agents are used to remove dissolved ions in solution. Removing these

dissolved ions can improve the stability of the dried active ingredient. Chelating agents included in any of the compositions described herein can include, but are not limited to, betadex sulfobutyl ether, EDETATE calcium or sodium salt and hydroxypropyl Betadex.

[1090] In some embodiments, any of the compositions described herein can include preservatives. Such preservatives can be added to the dried active ingredient and/or the reconstitution solution to eliminate microbial or fungal contamination. Preservatives can include but are not limited to benzyl benzoate, chlorobutanol, methylparaben, miripirium chloride, phenol, phenylethyl alcohol, propylparaben, sodium benzoate, sodium metabisulfite, sodium sulfite, triethylene glycol, and zinc chloride.

[1091] In some embodiments, any of the compositions described herein can include cosolvents. Such co-solvents can be added to an aqueous solution to improve the solubility or reduce the reconstitution time of an active ingredient. Cosolvents can also be used to improve the processing parameters such as reducing lyopholization time. These can include but are not limited to alcohol (ethanol), tert-butanol, benzyl alcohol, dimethyl sulfoxide, glycerin, medium chain triglycerides, methylpyrrolidone, and propylene glycol. In some embodiments, a dry powder atropine compositions includes a cosolvent, where a ratio of a mass of the cosolvent to the mass of the atropine or the pharmaceutically acceptable salt of atropine is between about 5:1 and about 7:1.

[1092] In some embodiments, any of the compositions described herein can include surfactants. Such surfactants are surface active agents that can be used to modify the surface of particles, emulsify materials, and alter surface energies. Surfactants that can be included in the embodiments described herein include, but are not limited to, benzalkonium chloride, benzethonium chloride, sodium docusate, lecithin, polyoxyl 35 castor oil, polysorbate 20, polysorbate 80, sodium tartrate, and stearic acid.

[1093] In addition to those excipients discussed above, it will further be appreciated that a wide range of excipients may optionally be used in conjunction with any of the compositions described herein. For example, it may be desirable to add other excipients to a formulation to improve particle rigidity, production yield, delivery efficiency and deposition, shelf-life and patient acceptance. Such optional excipients include, but are not limited to: coloring agents, desiccants, lyophilization aids, viscosity modifiers, disintegrants, hygroscopic agents, antioxidants, and chemical stabilizers. Further, various excipients may be incorporated in, or

added to, the particulate matrix to provide structure and form the microstructures required for optimal rehydration.

[1094] The powder compositions described herein may be reconstituted by any suitable solvent or combination of solvent, including, but not limited to, water, sterile water, glycerin, or hydrochloric acid.

Examples

[1095] In some embodiments, an atropine composition can include a formulation with minimal excipients. For example, in some embodiments, a dry powder formulation can include an effective amount of atropine or a pharmaceutically acceptable salt of atropine having a concentration of about 0.1% w/w. The dry powder atropine composition is formulated to be mixed with an aqueous solvent that includes an isotonicity agent (of the types described herein) of between about 0.1 – 1%. Table 1 provides an example formulation with minimal excipients.

Dried Cake:	mg	g/mol	wt%	mM
Atropene Sulfate (monohydrate)	2.00	694.83	0.10%	1.4392
Reconstitution Solution:				
Sodium Chloride	18.00	58.4425	0.90%	153.9975
Water	1980.00	18.02	99.00%	
Total = 2.0 mL	2000.00		100.00%	

Table 1: Minimal Excipients

[1096] In some embodiments, an atropine composition can include a formulation that is reconstituted with a buffered solution. For example, in some embodiments, a dry powder formulation can include an effective amount of atropine or a pharmaceutically acceptable salt of atropine having a concentration of about 0.1% w/w. The dry powder atropine composition is formulated to be mixed with an aqueous solvent that includes a buffering agent (of the types described herein) of between about 0.05-5%. The aqueous solvent can optionally include a secondary buffering agent of between about 0.05-5%. Table 2 provides an example formulation with a buffered solution.

Dried Cake:	mg	g/mol	wt%	mM
Atropene Sulfate (monohydrate)	2.00	694.83	0.10%	1.4392

Reconstitution Solution:				
Citric Acid (Monohydrate)	3.43	210.14	0.17%	8.1612
Sodium Citrate (anhydrous)	2.89	258.06	0.14%	5.5995
Water	1991.68	18.02	99.58%	
Total = 2.0 mL	2000.00		100.00%	

Table 2: Buffered Solution

[1097] In some embodiments, an atropine composition can include, in addition to any of the excipients described herein, a bulking agent. For example, in some embodiments, a dry powder formulation can include an effective amount of atropine or a pharmaceutically acceptable salt of atropine having a concentration of about 0.1% w/w. The dry powder atropine composition can further include a bulking agent (of the types described herein) having a concentration of between about 0.1-10% w/w. The dry powder atropine composition is formulated to be mixed with an aqueous solvent that includes a bulking agent (of the types described herein) of between about 0.1-10%. The aqueous solvent can also optionally include a buffering agent (of the types described herein) of between about 0.05-5%. The aqueous solvent can optionally include a secondary buffering agent of between about 0.05-5%. Table 3 provides an example formulation with a bulking agent.

Dried Cake:	mg	g/mol	wt%	mM
Atropene Sulfate (monohydrate)	2.00	694.83	0.10%	1.4392
Mannitol	10.00	182.17	0.50%	
Reconstitution Solution:				
Mannitol	60.00	182.17	3.00%	164.6813
Citric Acid (Monohydrate)	3.43	210.14	0.17%	8.1612
Sodium Citrate (anhydrous)	2.89	258.06	0.14%	5.5995
Water	1921.68	18.02	96.08%	
Total = 2.0 mL	2000.00		100.00%	

Table 3: Bulking Agent

[1098] In some embodiments, an atropine composition can include, in addition to any of the excipients described herein, one or more preservatives. For example, in some embodiments, a dry powder formulation can include an effective amount of atropine or a pharmaceutically acceptable salt of atropine having a concentration of about 0.1% w/w. The dry powder atropine composition can further include a bulking agent (of the types described herein) having a concentration of between about 0.1-10% w/w. The dry powder atropine composition can

further include a preservative (of the types described herein) having a concentration of between about 0.01-2% w/w. The dry powder atropine composition is formulated to be mixed with an aqueous solvent that includes a bulking agent (of the types described herein) of between about 0.1-10%. The aqueous solvent can also optionally include a buffering agent (of the types described herein) of between about 0.05-5%. The aqueous solvent can optionally include a secondary buffering agent of between about 0.05-5%. Table 4 provides an example formulation with a bulking agent.

Dried Cake:	mg	g/mol	wt%	mM
Atropene Sulfate (monohydrate)	2.00	694.83	0.10%	1.4392
Mannitol	10.00	182.17	0.50%	27.4469
Phenol	2.80	94.113	0.14%	14.8757
Reconstitution Solution:				
Mannitol	60.00	182.17	3.00%	164.6813
Citric Acid (Monohydrate)	3.43	210.14	0.17%	8.1612
Sodium Citrate (anhydrous)	2.89	258.06	0.14%	5.5995
Water	1918.88	18.02	95.94%	
Total = 2.0 mL	2000.00		100.00%	

Table 4: Preservative

[1099] In some embodiments, an atropine composition can include, in addition to any of the excipients described herein, one or more of a cosolvent or a surfactant. For example, in some embodiments, a dry powder formulation can include an effective amount of atropine or a pharmaceutically acceptable salt of atropine having a concentration of about 0.1% w/w. The dry powder atropine composition can further include a bulking agent (of the types described herein) having a concentration of between about 0.1-10% w/w. The dry powder atropine composition can further include a preservative (of the types described herein) having a concentration of between about 0.01-2% w/w. The dry powder atropine composition can further include a cosolvent (of the types described herein) having a concentration of between about 0.05-5% w/w. The dry powder atropine composition is formulated to be mixed with an aqueous solvent that includes a bulking agent (of the types described herein) of between about 0.1-10%. The aqueous solvent can also include a surfactant (of the types described herein) of between about 0.05-2%. The aqueous solvent can also optionally include a buffering agent (of the types described herein) of between about 0.05-5%. The aqueous solvent can optionally

include a secondary buffering agent of between about 0.05-5%. Table 5 provides an example formulation with a cosolvent and surfactant.

Dried Cake:	mg	g/mol	wt%	mM
Atropene Sulfate (monohydrate)	2.00	694.83	0.10%	1.4392
Mannitol	10.00	182.17	0.50%	27.4469
Phenol	2.80	94.113	0.14%	14.8757
Glycerin	12.47	92.094	0.62%	67.7026
Reconstitution Solution:				
Mannitol	60.00	182.17	3.00%	164.6813
Polysorbate 20	10.00	1228	0.50%	4.0717
Citric Acid (Monohydrate)	3.43	210.14	0.17%	8.1612
Sodium Citrate (anhydrous)	2.89	258.06	0.14%	5.5995
Water	1896.41	18.02	94.82%	
Total = 2.0 mL	2000.00		100.00%	

Table 5: Cosolvent / Surfactant

[1100] In some embodiments, any of the dry powder atropine compositions described herein can be produced by any of lyophilization, spray-drying, or milling. For example, FIG. 20 is a flow chart of a method 10 of producing a dry powder composition for parenteral administration after being reconstituted via spray-draying. The method 10 can be performed using any suitable spray-drying system, such as the system 100 shown in FIG. 21. The system 100 includes a spray nozzle 110 that receives a liquid or slurry feed stock. In some embodiments, the spray nozzle 110 can be a high-pressure nozzle that atomizes the feed stock into the spray drying chamber 120. In other embodiments, the nozzle 110 can be a gas-atomizing nozzle (which can operate at lower pressures) that receives both the feedstock and an atomizing gas to produce an atomized flow into the spray drying chamber 120. In yet other embodiments, the nozzle 110 can be a rotary atomizer. In some embodiments, the system 100 can have both a gas input (e.g., inert gas, such as nitrogen, not shown) to the nozzle 110 and a flow of dry gas into the chamber that removes the moisture from the feedstock. The dried particles are then conveyed into a separator 130 to produce the dried particle output.

[1101] Referring to FIG. 20, the method 10 includes conveying A) a feed stock comprising atropine or a pharmaceutically acceptable salt of atropine and B) an atomizing gas into a spray-drying chamber via a spray nozzle to produce droplets containing the atropine or a pharmaceutically acceptable salt of atropine, at 12. The droplets are dried to form solid

particles of the atropine or the pharmaceutically acceptable salt of atropine, at 13. The solid particles of the atropine or the pharmaceutically acceptable salt of atropine are then separated from the atomizing gas within a vortex separator to produce the dry powder composition, at 14. The resulting dry powder composition has an average particle size of between about 2 microns and about 100 microns and a purity of at least 95%, as determined by HPLC, at 15.

[1102] In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate. In some embodiments, the atropine or the pharmaceutically acceptable salt of atropine comprises atropine base.

[1103] In some embodiments, the composition can include any of the excipients described herein. For example, in some embodiments, a spray drying excipient can include Mannitol, as it possesses many advantageous properties. Specifically, Mannitol will readily dry in a crystalline state, is water soluble and is considered non-hygroscopic as it picks up less than 1% moisture at relative humidity as high as 70% (Handbook of Pharmaceutical Excipients, 6th Edition, R. C. Rowe). In addition, it can pick up 10% of mass in water at humidity's >70% RH.

[1104] In other embodiments, the composition can include trehalose. Specifically, trehalose (α-D-glucopyranosyl-α-D-glucopyranoside) is a naturally occurring, non-reducing disaccharide which was initially found to be associated with the prevention of desiccation damage in certain plants and animals which can dry out without damage and can revive when rehydrated. Trehalose, however, does not spray dry completely crystalline and will instead form an amorphous matrix. This amorphous matrix is hygroscopic and will readily absorb water.

[1105] While various embodiments have been described above, it should be understood that they have been presented by way of example only, and not limitation. Where schematics and/or embodiments described above indicate certain components arranged in certain orientations or positions, the arrangement of components may be modified. While the embodiments have been particularly shown and described, it will be understood that various changes in form and details may be made. Although various embodiments have been described as having particular features and/or combinations of components, other embodiments are possible having a combination of any features and/or components from any of embodiments as discussed above.

[1106] Where methods and/or events described above indicate certain events and/or procedures occurring in certain order, the ordering of certain events and/or procedures may be modified. Additionally, certain events and/or procedures may be performed concurrently in a parallel process when possible, as well as performed sequentially as described above.

[1107] All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

[1108] Although the medicament delivery devices are shown and described herein as being medical injectors having a medicament container divided into two portions (see e.g., the medical injector 1000), in other embodiments, any of the components, methods and/or formulations described herein can be used in any suitable medicament delivery device. In some embodiments, the medicament delivery device can include a medicament container having any number of plungers and/or defining any number of volumes therein.

[1109] Although the medicament container 1210 is shown as being initially spaced apart from and/or fluidically isolated from the needle 1290, in other embodiments, a medical injector 1000 can include a medicament container that has a staked needle. For example, in some embodiments, a medical injector 1000 includes a prefilled syringe in which the needle is in fluid communication with the medicament container. In such embodiments, the mixing operation need not, therefore, place the container in fluid communication with the needle.

[1110] Any of the medicament containers described herein can be any container suitable for storing the compositions disclosed herein. In some embodiments, the medicament container can be a pre-filled syringe, a pre-filled cartridge, a vial, or the like. In some embodiments, for example, any of the devices shown and described herein can include components and/or mechanisms to accommodate a pre-filled syringe, similar to the embodiments shown and described in U.S. Patent Publication No. 2013/0023825 entitled, "Medicament Delivery Devices for Administration of Medicament within a Prefilled Syringe," filed January 25, 2012

the disclosure of which is incorporated herein by reference in its entirety. In other embodiments, the medicament containers described here can be a container having a flexible wall, such as, for example, a bladder.

[1111] Any of the devices and/or medicament containers shown and described herein can be included in a kit (not shown), which can include fungible components and reusable components. For example, in some embodiments, at least a housing of a medical injector can be reusable without the need for sterilization, as described in detail above. In some embodiments, such as with the medical injector 1000, the proximal cap 1160 can be removed from the housing 1100 to allow access to and removal of the used components disposed within the housing 1100. In addition, the removal of the proximal cap 1160 from the housing 1100 can allow for any suitable portion of the medical injector 1000 to be reset to, for example, a pre-activated or pre-actuated configuration, as described above.

What is claimed is:

1. A dry powder atropine composition for parenteral administration after being reconstituted, comprising:

solid particles of atropine or a pharmaceutically acceptable salt of atropine having a mass of between about 0.8 mg and 3.2 mg, the dry powder atropine composition formulated to be reconstituted in less than 10 seconds after first being mixed with an aqueous solvent having a volume of between 1 mL and 3 mL to form an aqueous solution for parenteral administration.

2. The dry powder atropine composition of claim 1, wherein:

the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate.

3. The dry powder atropine composition of claim 1, wherein:

the dry powder atropine composition is formulated to be reconstituted in less than 5 seconds after first being mixed with the aqueous solvent having a volume of between 1 mL and 2 mL.

4. The dry powder atropine composition of claim 1, wherein:

the dry powder atropine composition is formulated to be reconstituted in less than 2 seconds after first being mixed with the aqueous solvent having a volume of between 1.75 mL and 2 mL.

5. The dry powder atropine composition of claim 1, wherein:

the dry powder atropine composition is formulated to be reconstituted in less than 1 second after first being mixed with the aqueous solvent having a volume of between 1.75 mL and 2 mL.

6. The dry powder atropine composition of claim 5, wherein:

the dry powder atropine composition has an average particle size of between about 2 microns and about 30 microns.

7. The dry powder atropine composition of any of claims 3-6, wherein the dry powder atropine composition is mixed with the aqueous solvent within a medicament container assembly that defines a first volume that contains the aqueous solvent and a second volume that contains the dry powder atropine composition.

8. The dry powder atropine composition of any of claims 1-6, further comprising:
solid particles of at least one of a bulking agent, a preservative, or a cosolvent.

9. The dry powder atropine composition of any of claims 1-6, further comprising:
solid particles of a bulking agent, a ratio of a mass of the bulking agent to the mass of the atropine or the pharmaceutically acceptable salt of atropine being between about 4:1 and about 6:1.

10. The dry powder atropine composition of claim 9, further comprising:
a cosolvent, a ratio of a mass of the cosolvent to the mass of the atropine or the pharmaceutically acceptable salt of atropine being between about 5:1 and about 7:1.

11. The dry powder atropine composition of any of claims 1-6, wherein the dry powder atropine composition has a moisture content of less than 5 percent.

12. The dry powder atropine composition of any of claims 1-6, wherein the dry powder atropine composition has a moisture content of between 0.5 percent and 3 percent.

13. The dry powder atropine composition of any of claims 1-6, wherein the dry powder atropine composition has a purity of at least 90%, as determined by high-performance liquid chromatography (HPLC).

14. The dry powder atropine composition of claim 11, wherein the dry powder atropine composition has a purity of at least 95%, as determined by HPLC.

15. The dry powder atropine composition of any of claims 1-6, wherein the dry powder atropine composition is produced by any of lyophilization, spray-drying, or milling.

16. A medicament container assembly, comprising:

a container body;

a first elastomeric member;

a second elastomeric member; and

a distal seal,

wherein the first elastomeric member is disposed within a proximal end portion of the container body and the second elastomeric member is disposed within the container body distally from the first elastomeric member,

wherein the first elastomeric member, the second elastomeric member, and a portion of the container body define a first volume that contains an aqueous solvent, and

wherein the second elastomeric member and a distal end portion of the container body define a second volume that contains the dry powder atropine composition of any of claims 1-6.

17. A method of producing the dry powder atropine composition of any of claims 1-6, comprising:

conveying a feed stock comprising atropine sulfate and an atomizing gas into a spray-drying chamber via a spray nozzle to produce droplets containing the atropine sulfate;

drying the droplets to form the solid particles of atropine sulfate; and

separating the solid particles of atropine sulfate from the atomizing gas within a vortex separator to produce the dry powder atropine composition.

18. A method of producing the dry powder atropine composition of any of claims 1-6, comprising:

conveying particles of atropine sulfate into a milling apparatus; and

producing collisions of the particle of atropine sulfate to form the dry powder composition.

19. A method for producing a dry powder composition for parenteral administration after being reconstituted, comprising:

conveying A) a feed stock comprising atropine or a pharmaceutically acceptable salt of atropine and B) an atomizing gas into a spray-drying chamber via a spray nozzle to produce droplets containing the atropine or a pharmaceutically acceptable salt of atropine;

drying the droplets to form solid particles of the atropine or the pharmaceutically acceptable salt of atropine; and

separating the solid particles of the atropine or a pharmaceutically acceptable salt of atropine from the atomizing gas within a vortex separator to produce the dry powder composition,

wherein the dry powder composition has an average particle size of between about 2 microns and about 100 microns and a purity of at least 95%, as determined by HPLC.

20. The method of claim 19, wherein the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate.

21. The method of claim 19, wherein the atropine or the pharmaceutically acceptable salt of atropine comprises atropine base.

22. The method of claim 19, wherein:

the dry powder atropine composition has an average particle size of between about 2 microns and about 30 microns.

23. The method of claim 19, wherein:

the feed stock further comprises a bulking agent, a ratio of a mass of the bulking agent to the mass of the atropine or the pharmaceutically acceptable salt of atropine being between about 4:1 and about 6:1.

24. The method of claim 19, wherein:

the feed stock further comprises a cosolvent, a ratio of a mass of the cosolvent to the mass of the atropine or the pharmaceutically acceptable salt of atropine being between about 5:1 and about 7:1.

25. A medicament container assembly, comprising:

a container body;

a first elastomeric member;

a second elastomeric member; and

a distal seal,

wherein the first elastomeric member is disposed within a proximal end portion of the container body and the second elastomeric member is disposed within the container body distally from the first elastomeric member,

wherein the first elastomeric member, the second elastomeric member, and a portion of the container body define a first volume that contains an aqueous solvent, and

wherein the second elastomeric member and a distal end portion of the container body define a second volume that contains a dry powder atropine composition comprising solid particles of atropine or a pharmaceutically acceptable salt of atropine, the atropine or the pharmaceutically acceptable salt of atropine having a mass of between about 0.8 mg and 3.2 and formulated to be reconstituted within the second volume in less than 10 seconds after first being mixed with the aqueous solvent to form an aqueous solution for parenteral administration.

26. The medicament container assembly of claim 25, wherein:

the first volume contains between about 1.75 mL and about 2 mL of the aqueous solvent; and

the dry powder atropine composition is formulated to be reconstituted in less than 2 seconds after first being mixed with the aqueous solvent.

27. The medicament container assembly of claim 26, wherein:

the container body defines a bypass channel configured to fluidically couple the first volume and the second volume on a condition that the second elastomeric member is at least partially aligned with the bypass channel; and

the dry powder atropine composition is mixed with the aqueous solvent in response to at least the second elastomeric member being moved distally to at least partially align the second elastomeric member with the bypass channel.

28. The medicament container assembly of claim 27, wherein the dry powder atropine composition is mixed with the aqueous solvent solely in response to at least the second elastomeric member being moved distally.

29. The medicament container assembly of claim 27, wherein the dry powder atropine composition is mixed with the aqueous solvent without any action extrinsic to the medicament container assembly.

30. The medicament container assembly of any of claims 25-29, wherein:

the atropine or the pharmaceutically acceptable salt of atropine comprises atropine sulfate present in the aqueous solution in an amount between 0.05 wt % and 0.15 wt %;

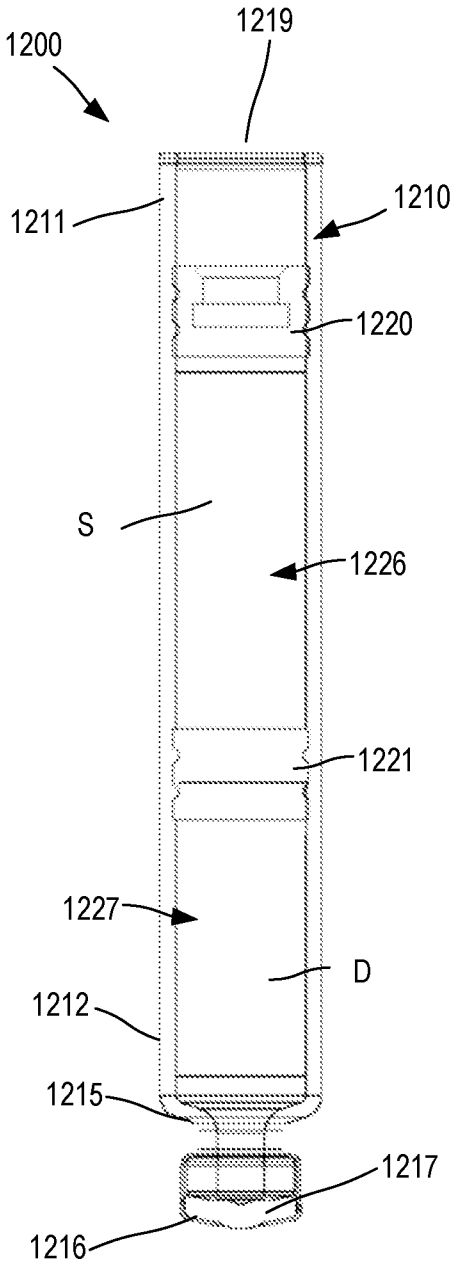
the dry powder atropine composition includes a bulking agent and a cosolvent, a ratio of a mass of the bulking agent to the mass of the atropine sulfate being between about 4:1 and about 6:1, a ratio of a mass of the cosolvent to the mass of the atropine sulfate being between about 5:1 and about 7:1.

31. The medicament container assembly of claim 30, wherein:

the aqueous solvent includes a bulking agent present in the aqueous solution in an amount between 0.05 wt % and 12 wt %.

32. The medicament container assembly of claim 31, wherein:

the aqueous solvent includes a buffering agent present in the aqueous solution in an amount between 0.05 wt % and 10 wt %.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1216

FIG. 1

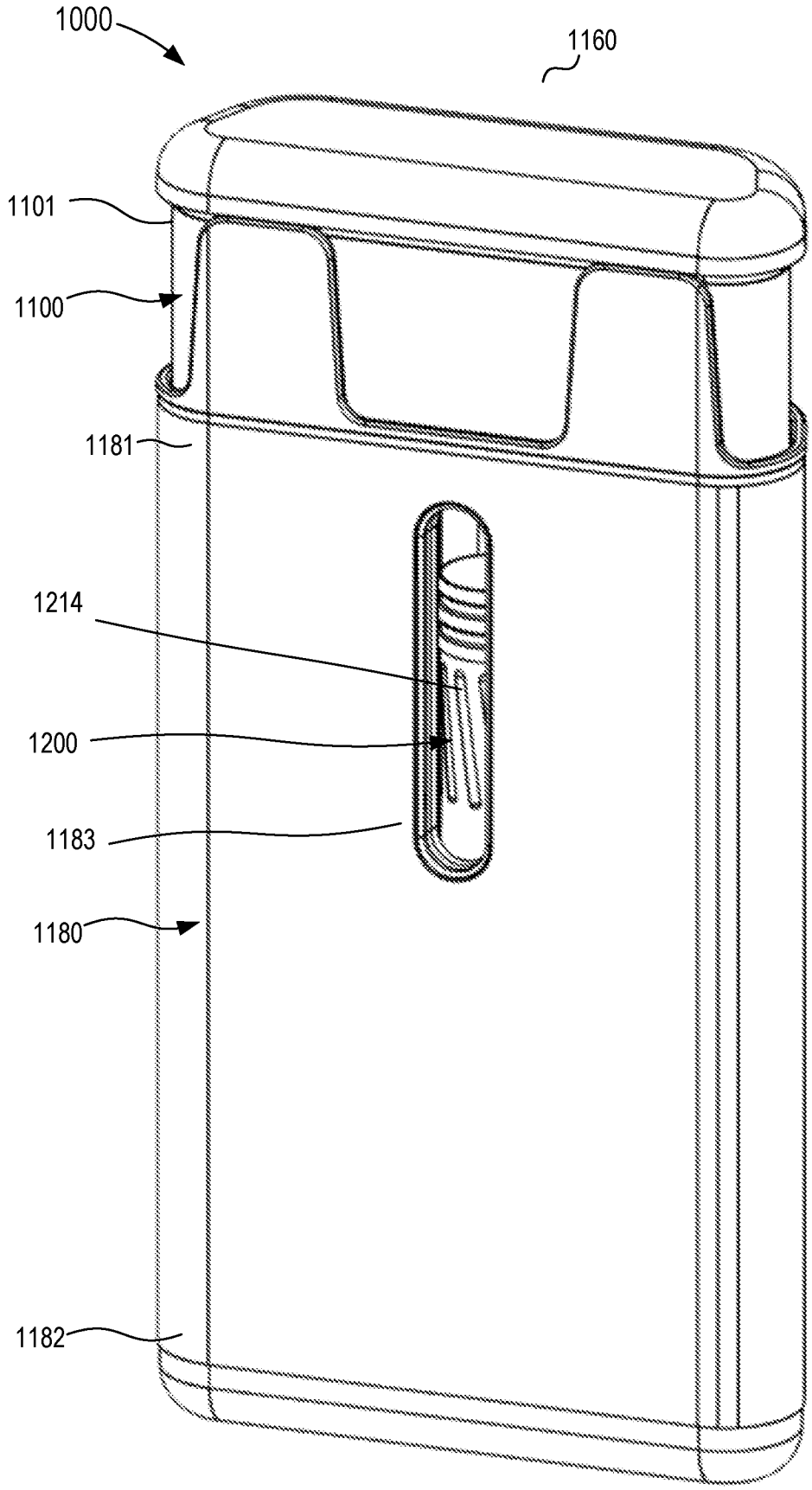


FIG. 2

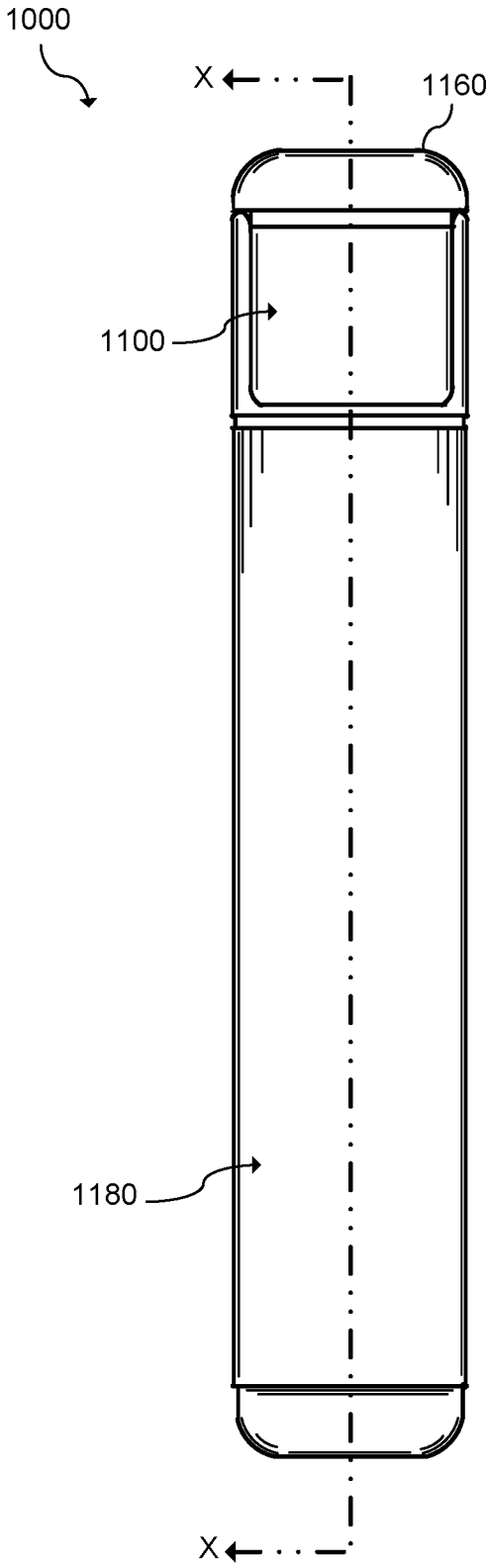


FIG. 3

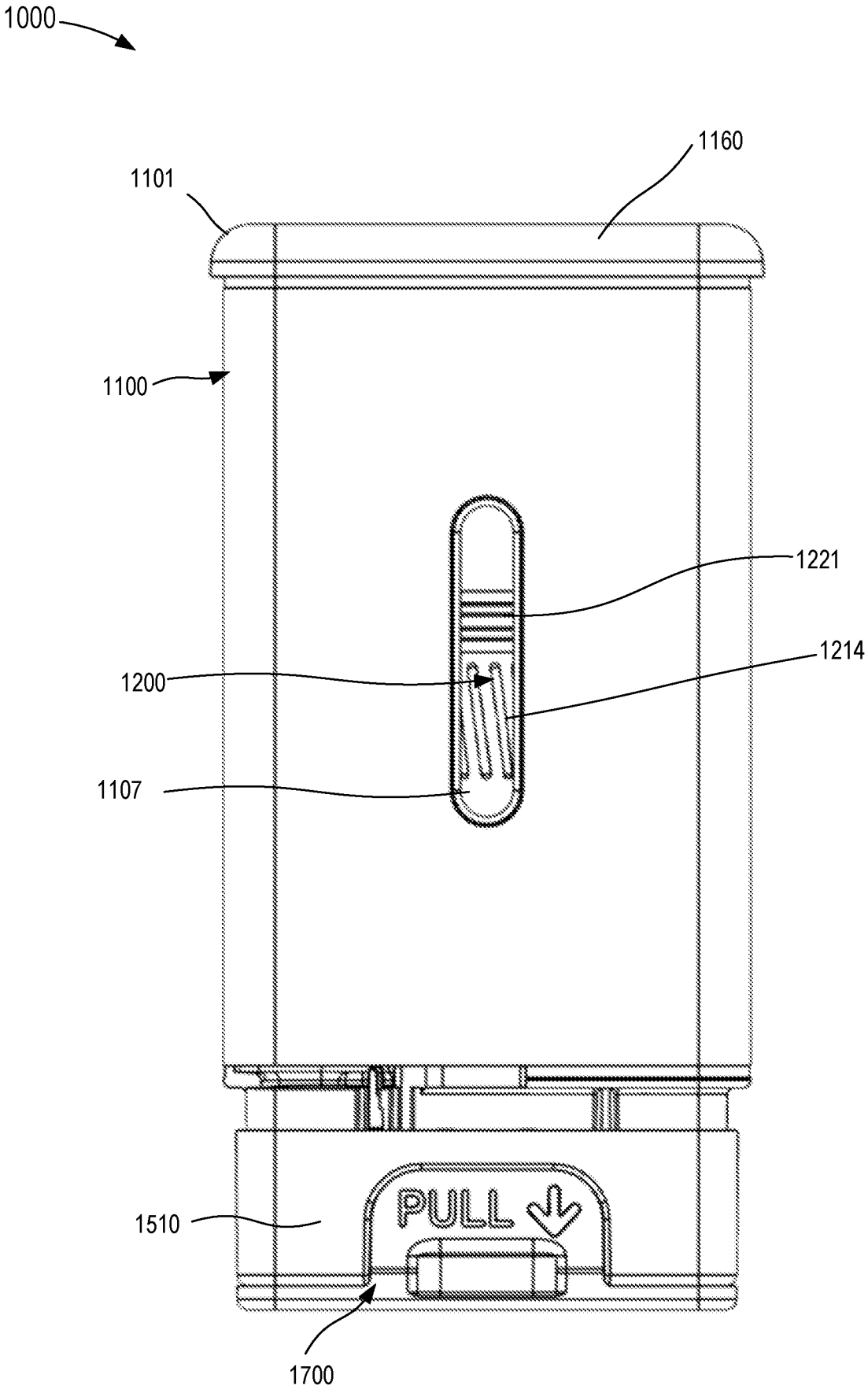


FIG. 4

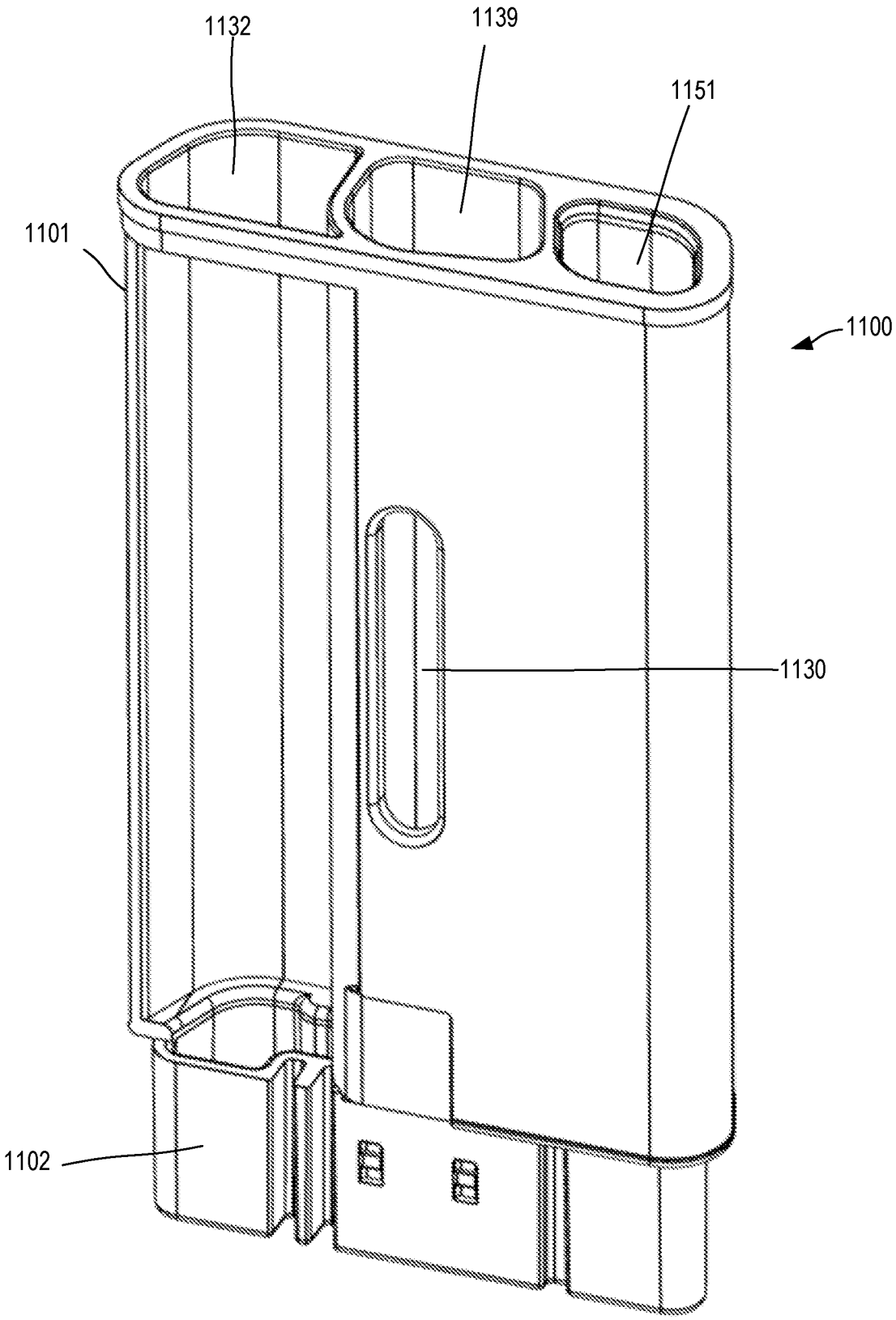


FIG. 5

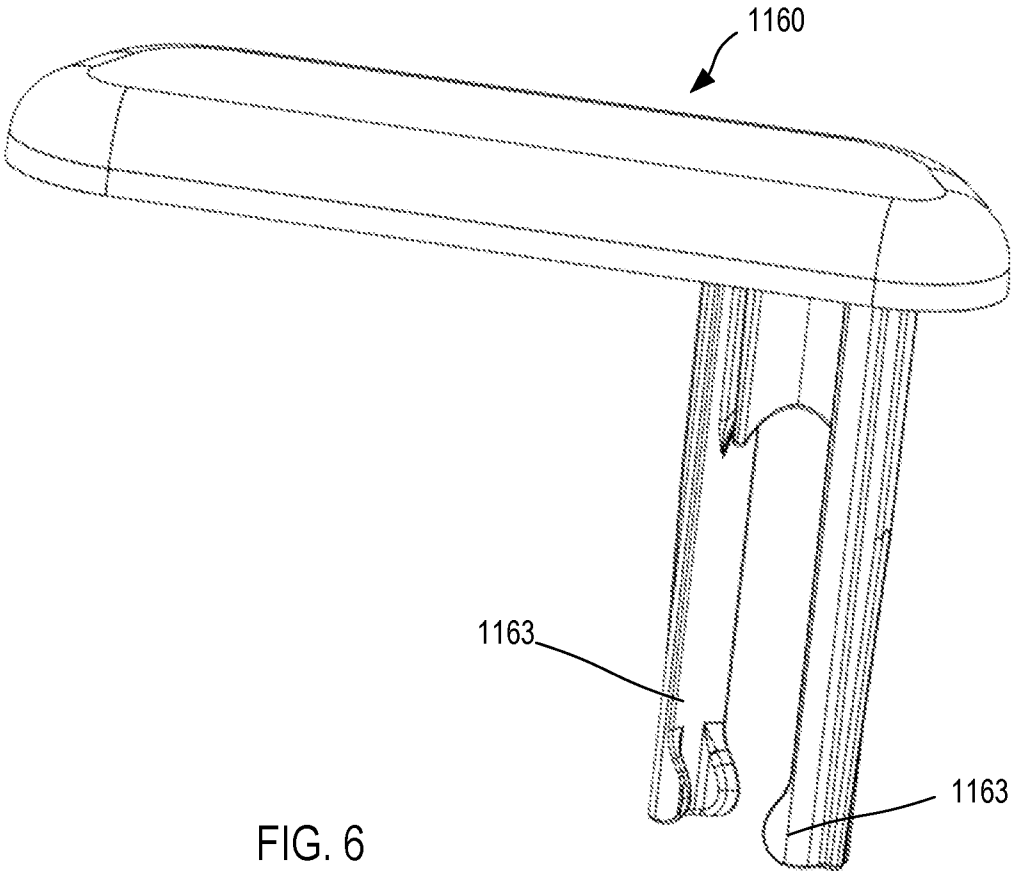


FIG. 6

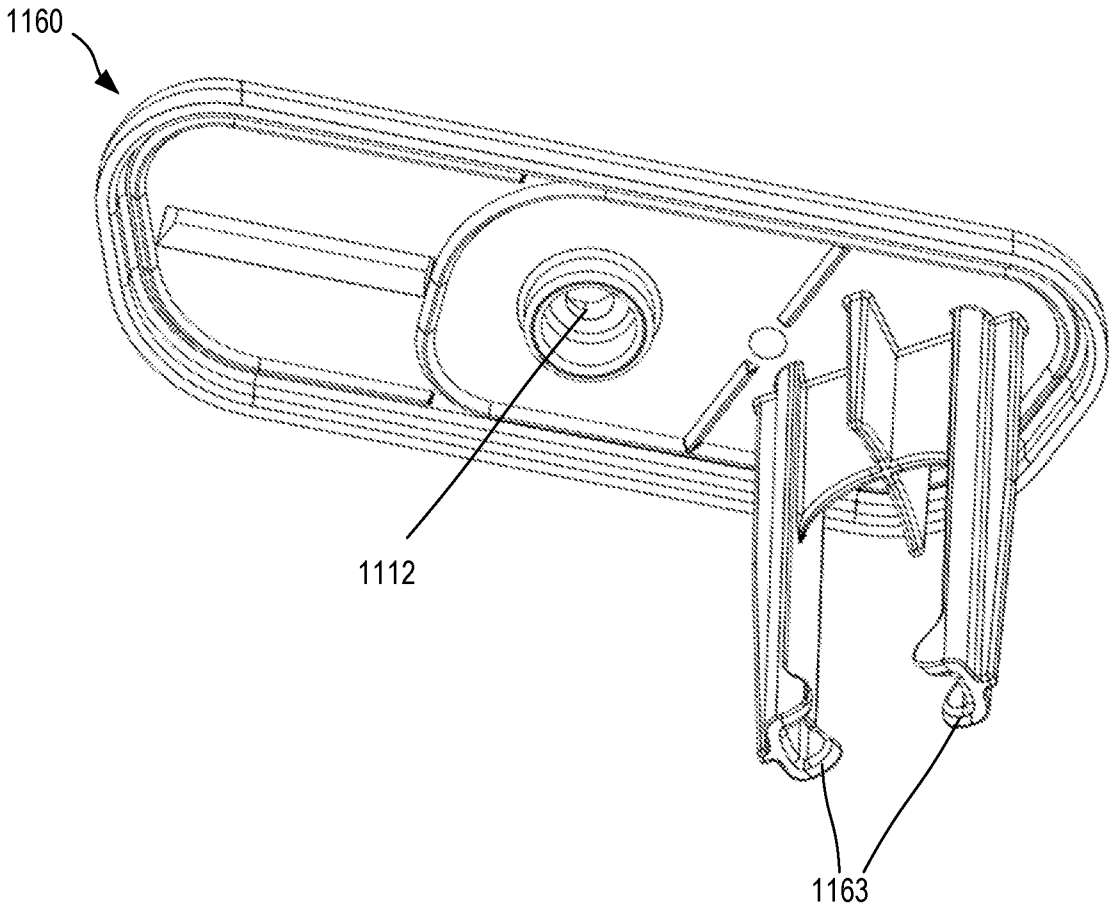
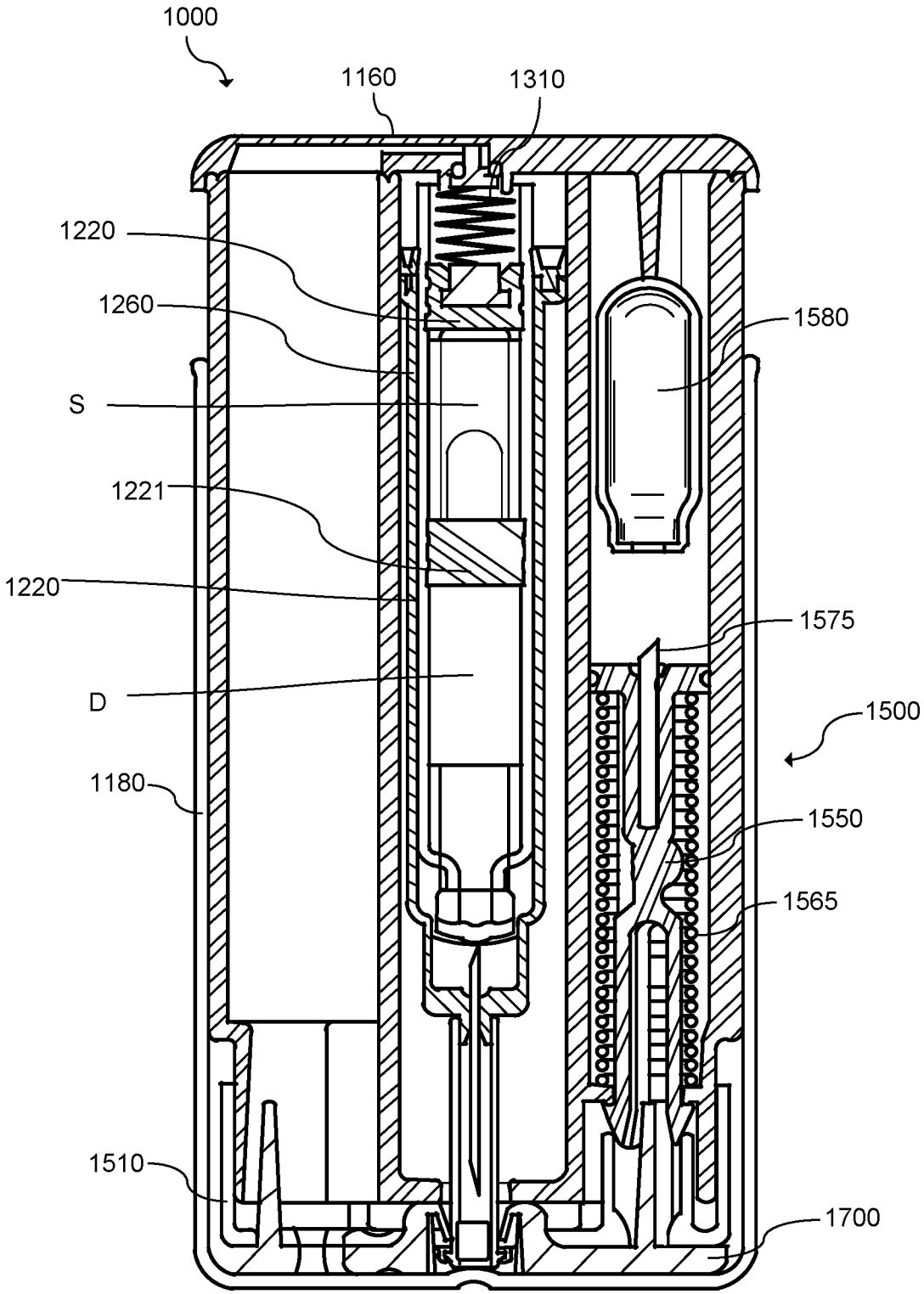


FIG. 7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D
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1580
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1700

FIG. 8

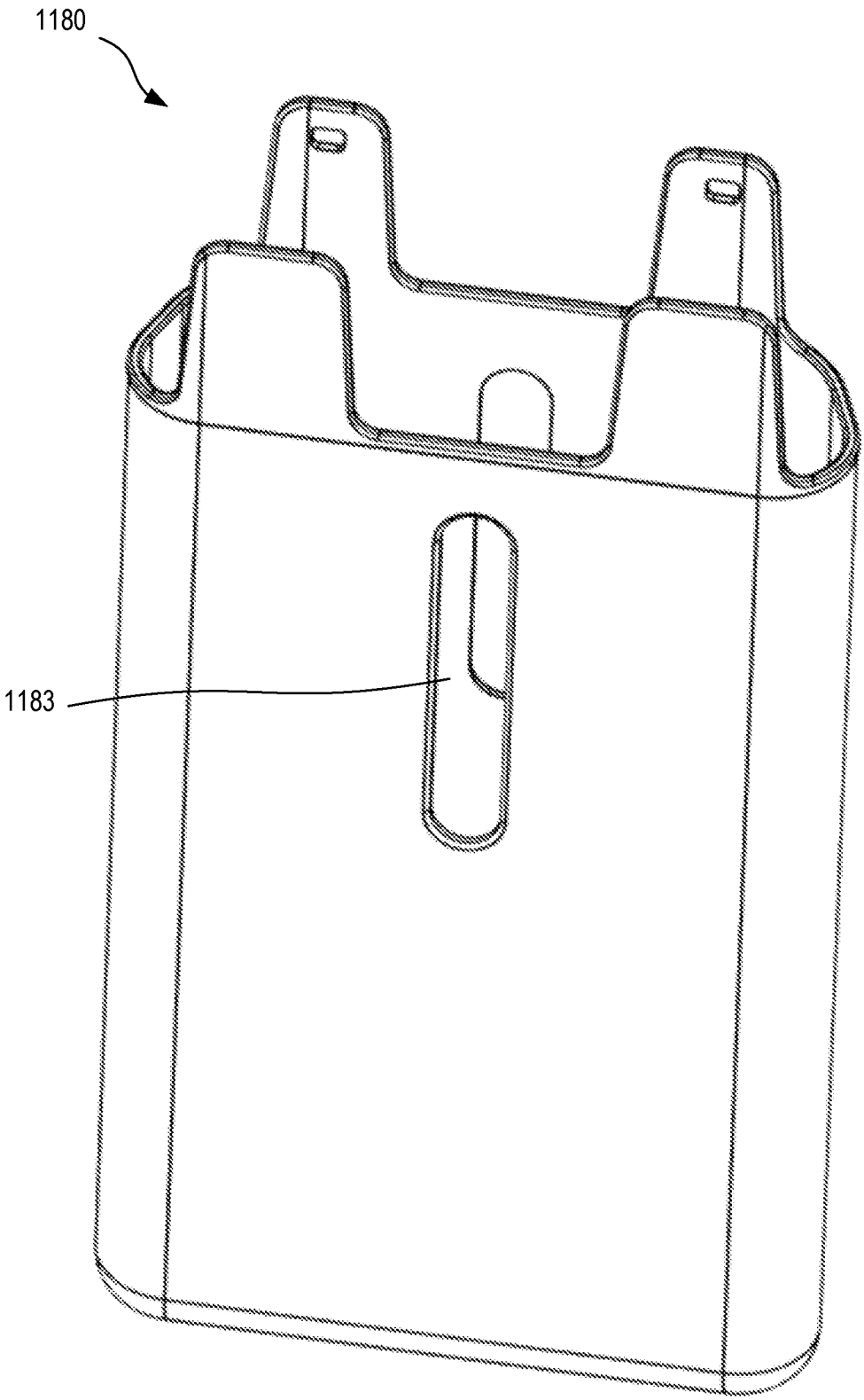

FIG. 9

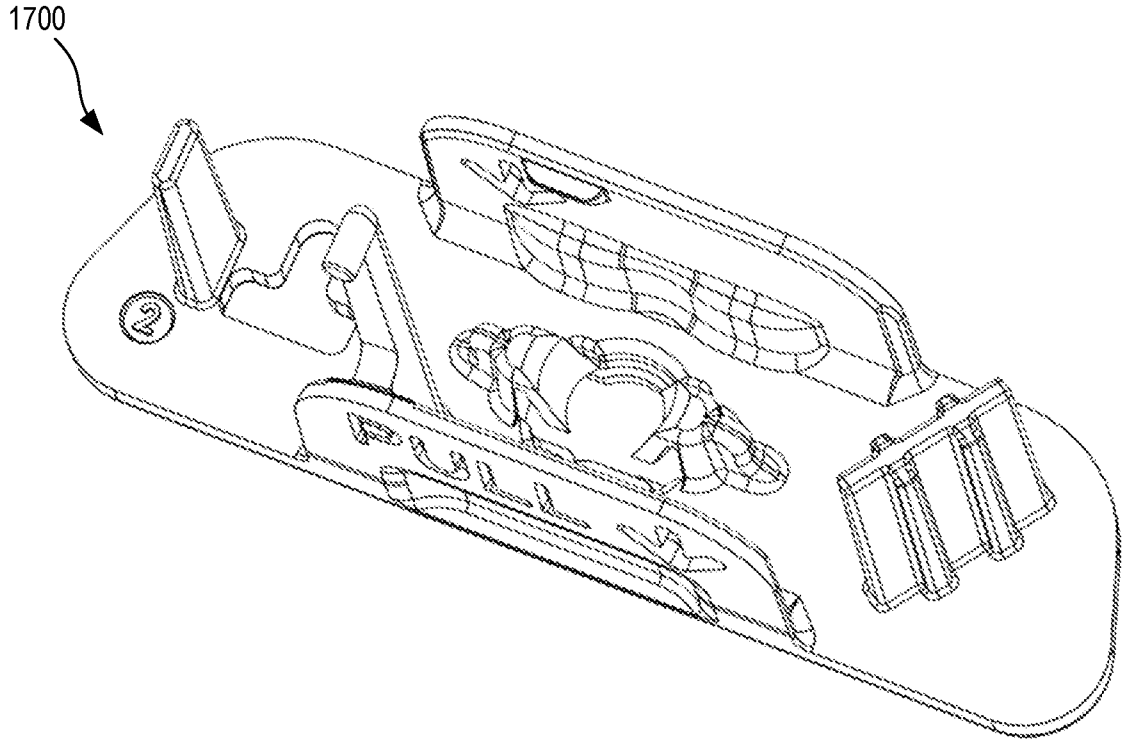

FIG. 10

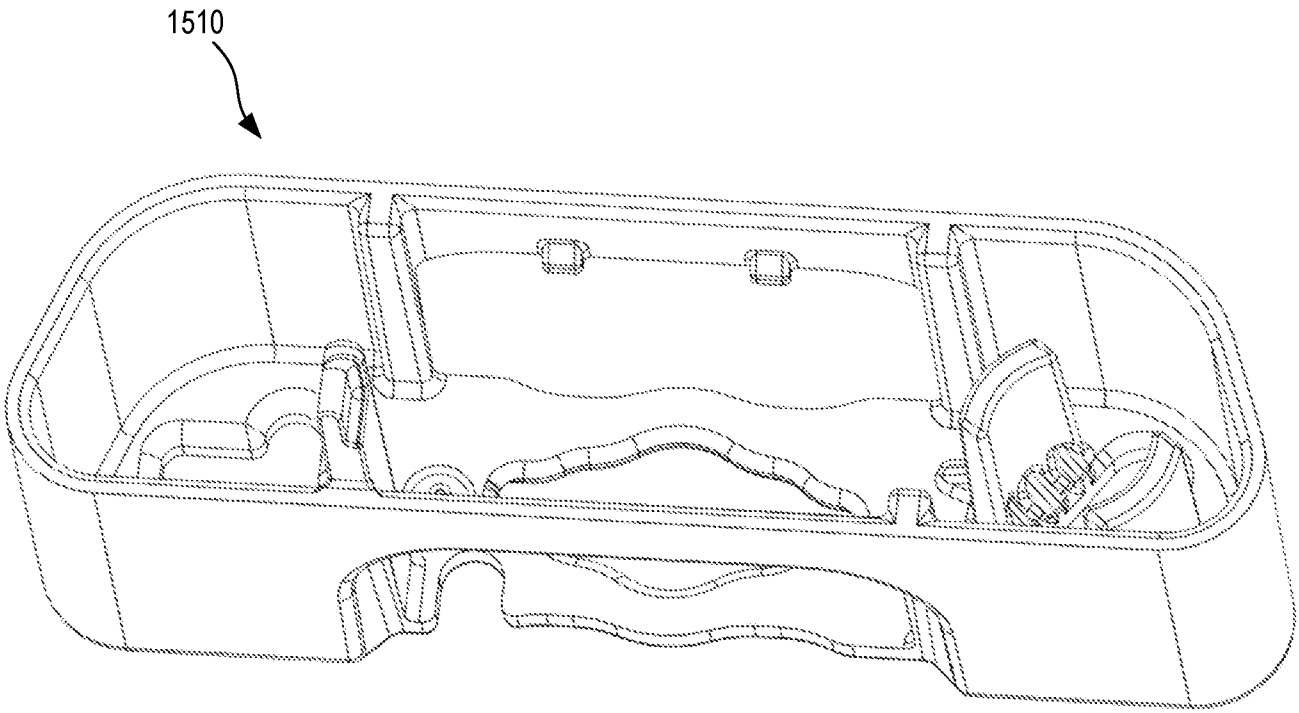

FIG. 11

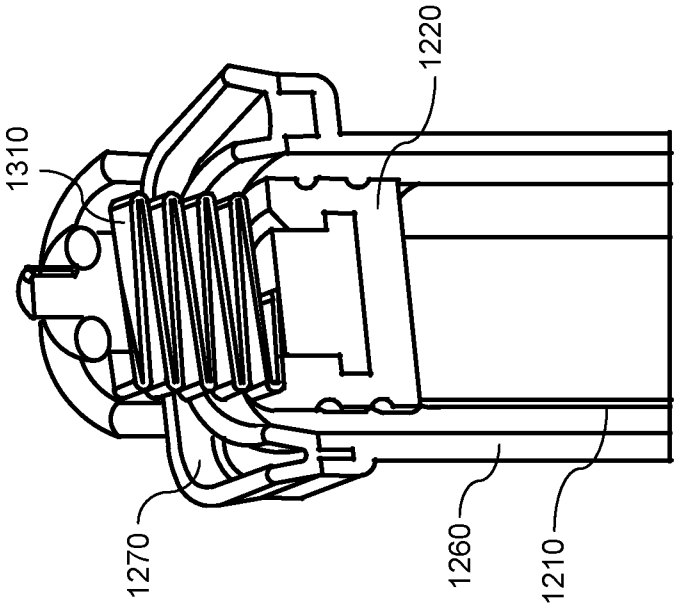

FIG. 13

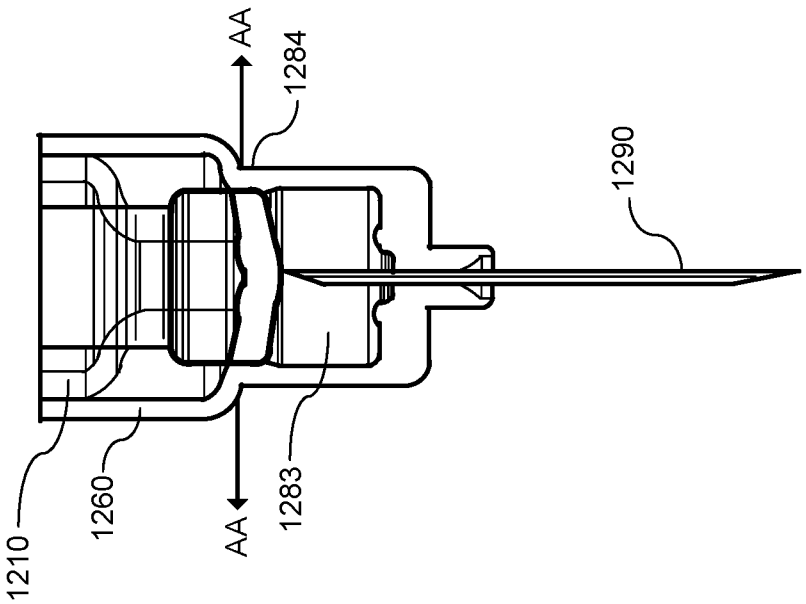

FIG. 12

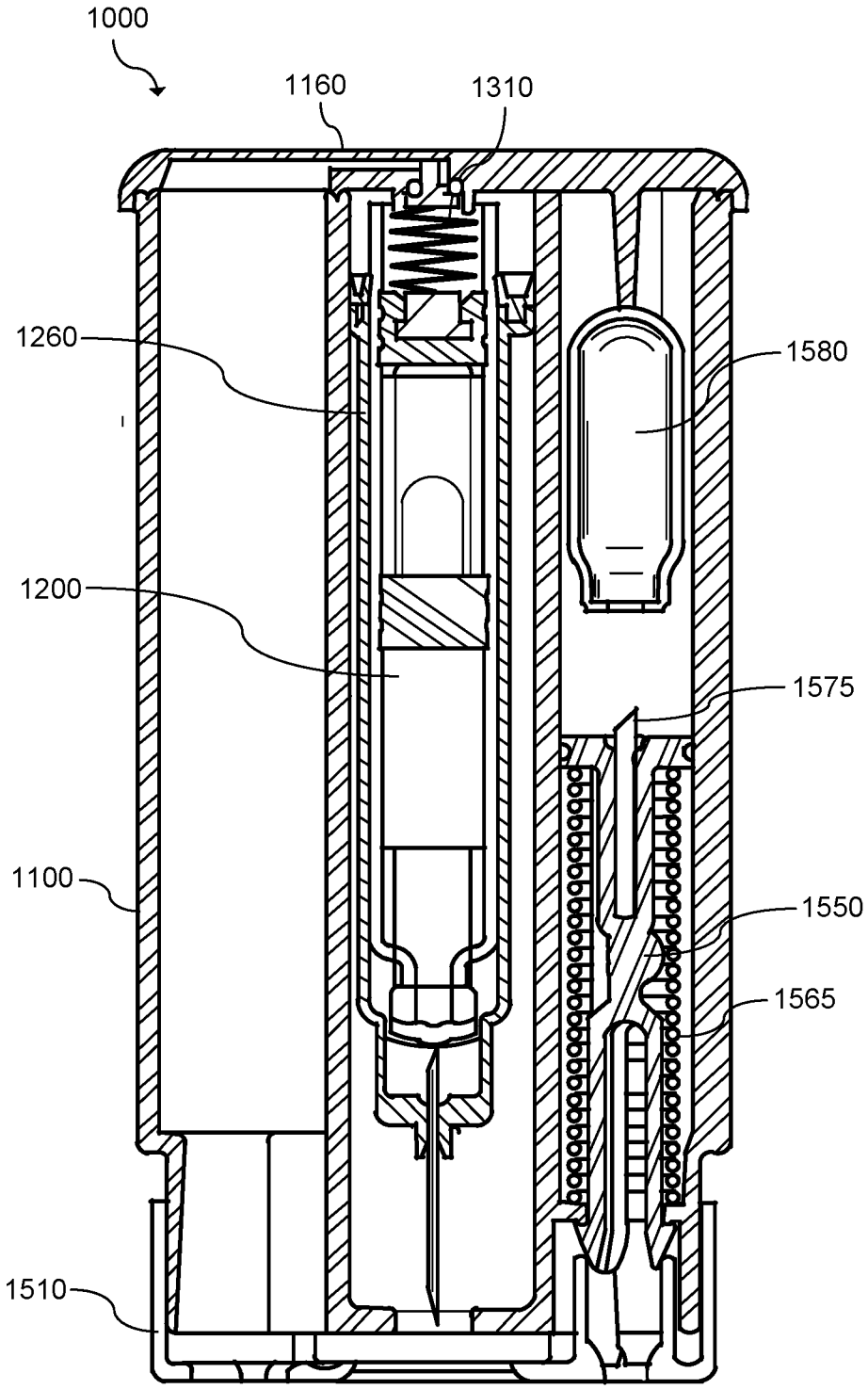

FIG. 14

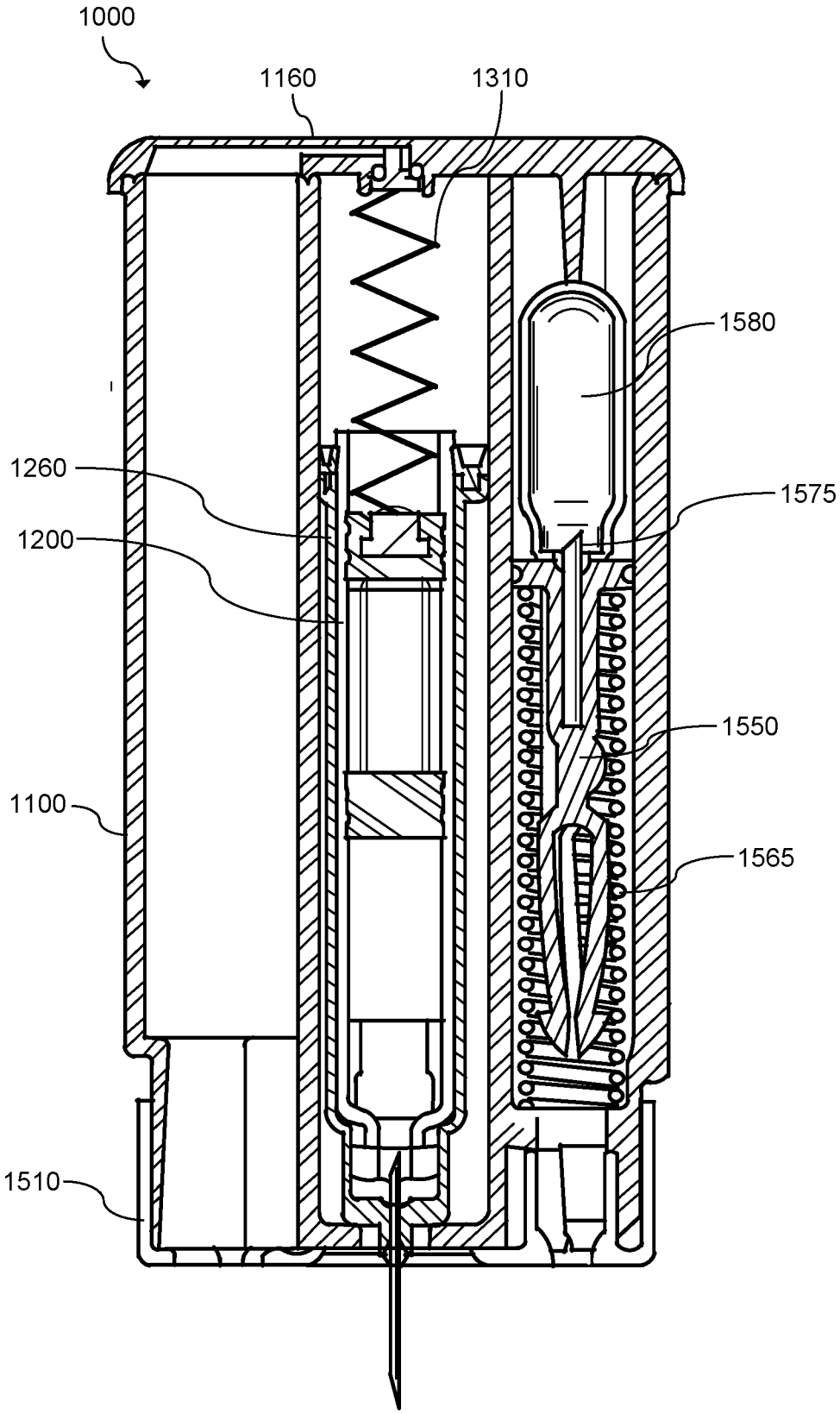

FIG. 15

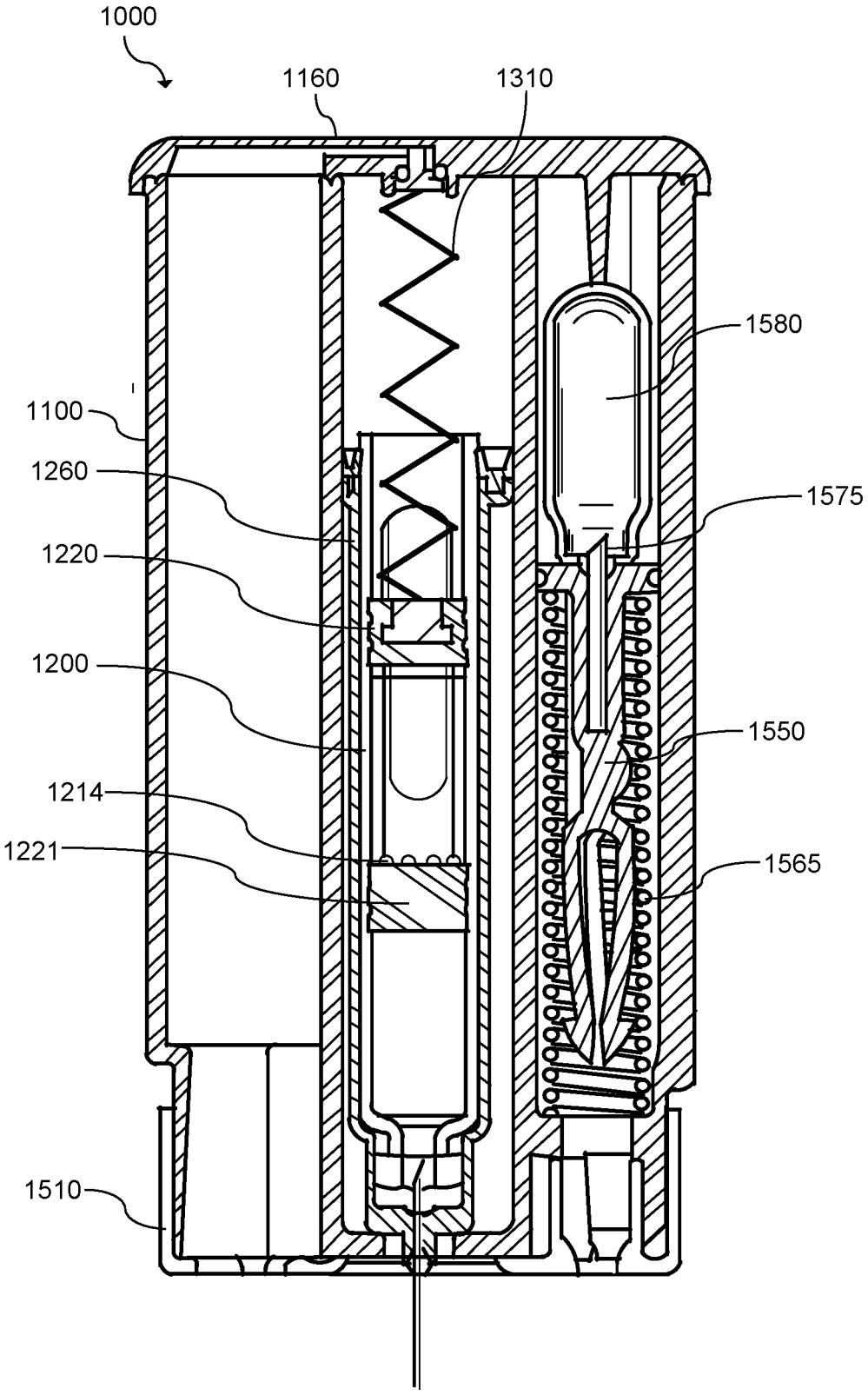
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FIG. 16

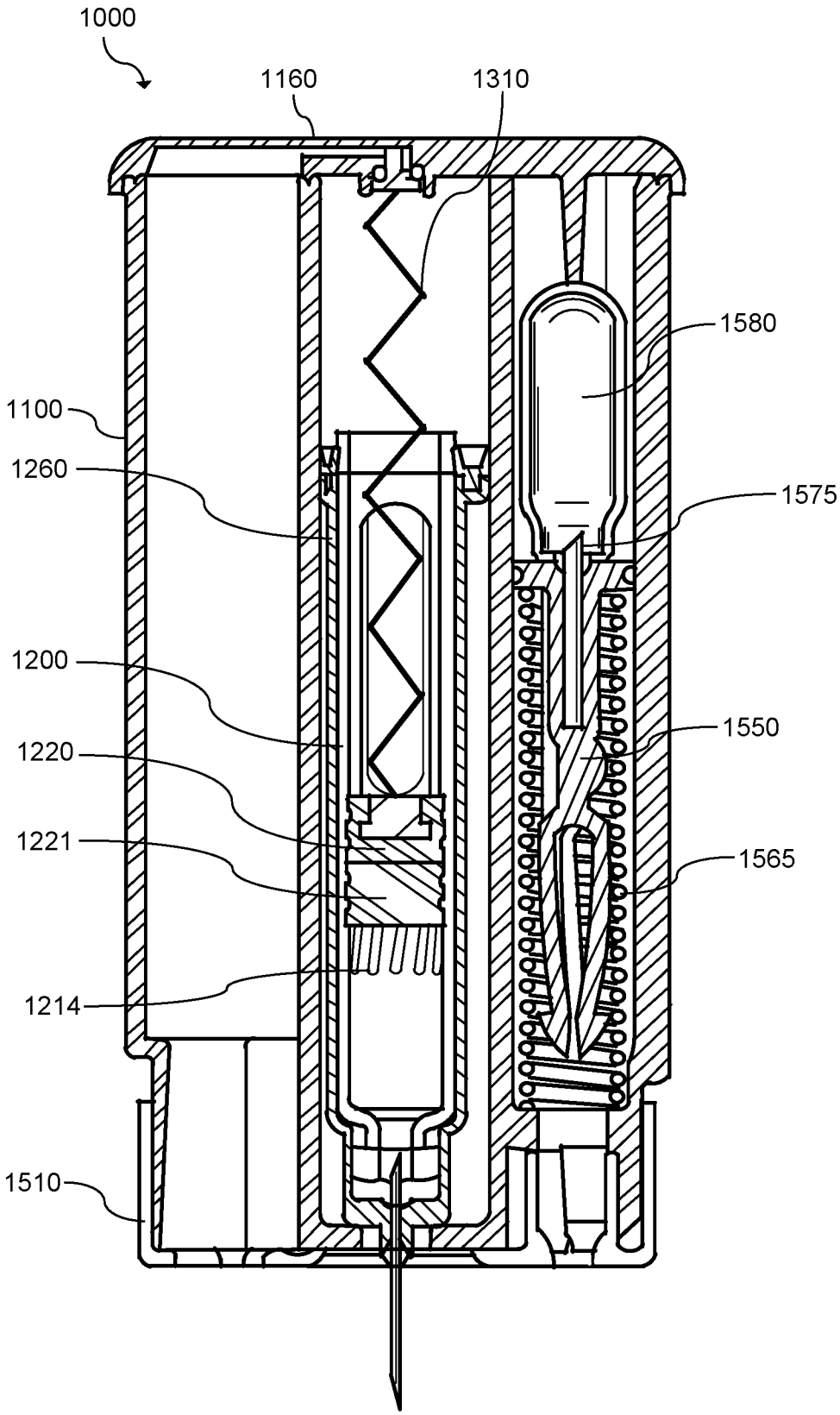
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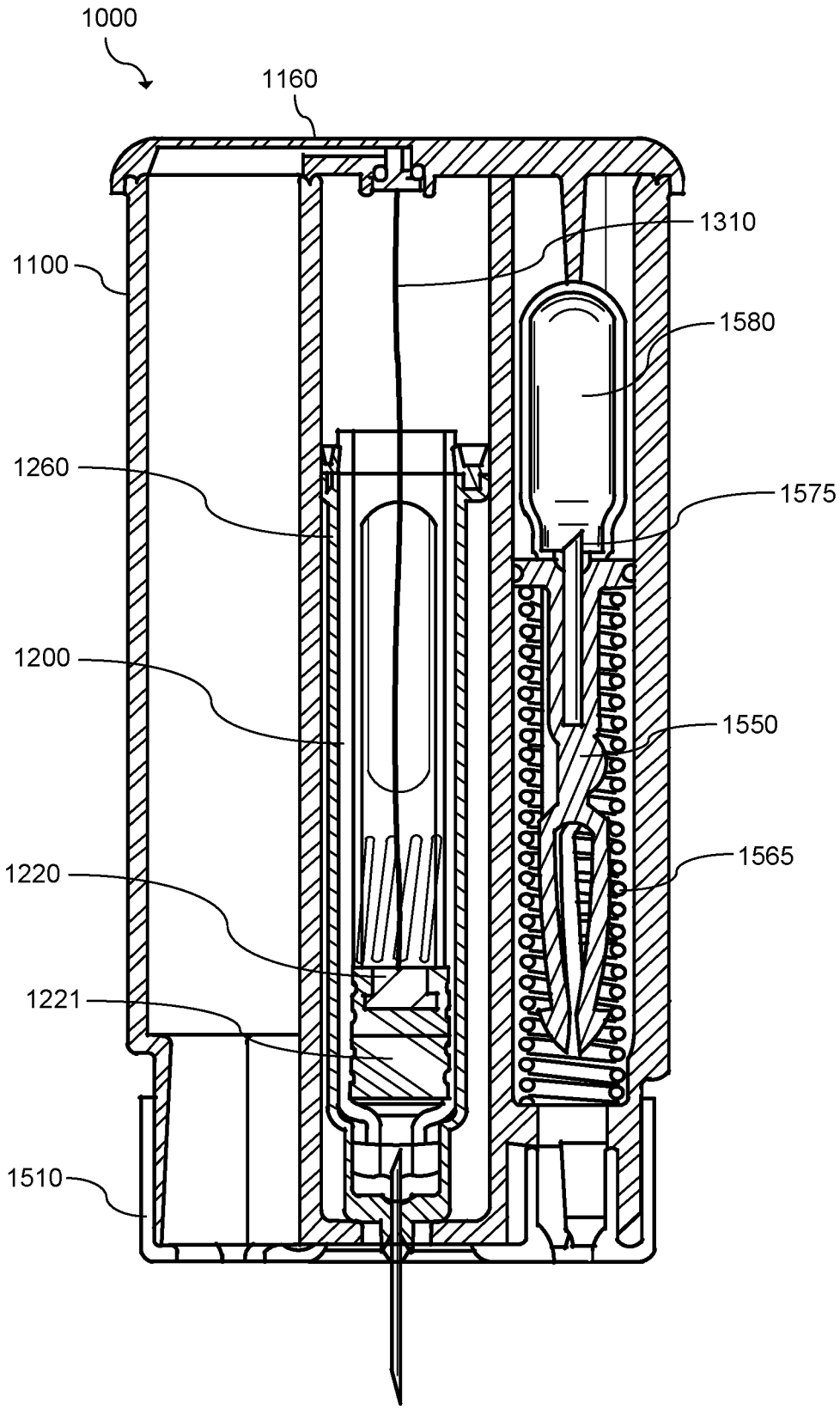
FIG. 17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1221
1510

FIG. 18

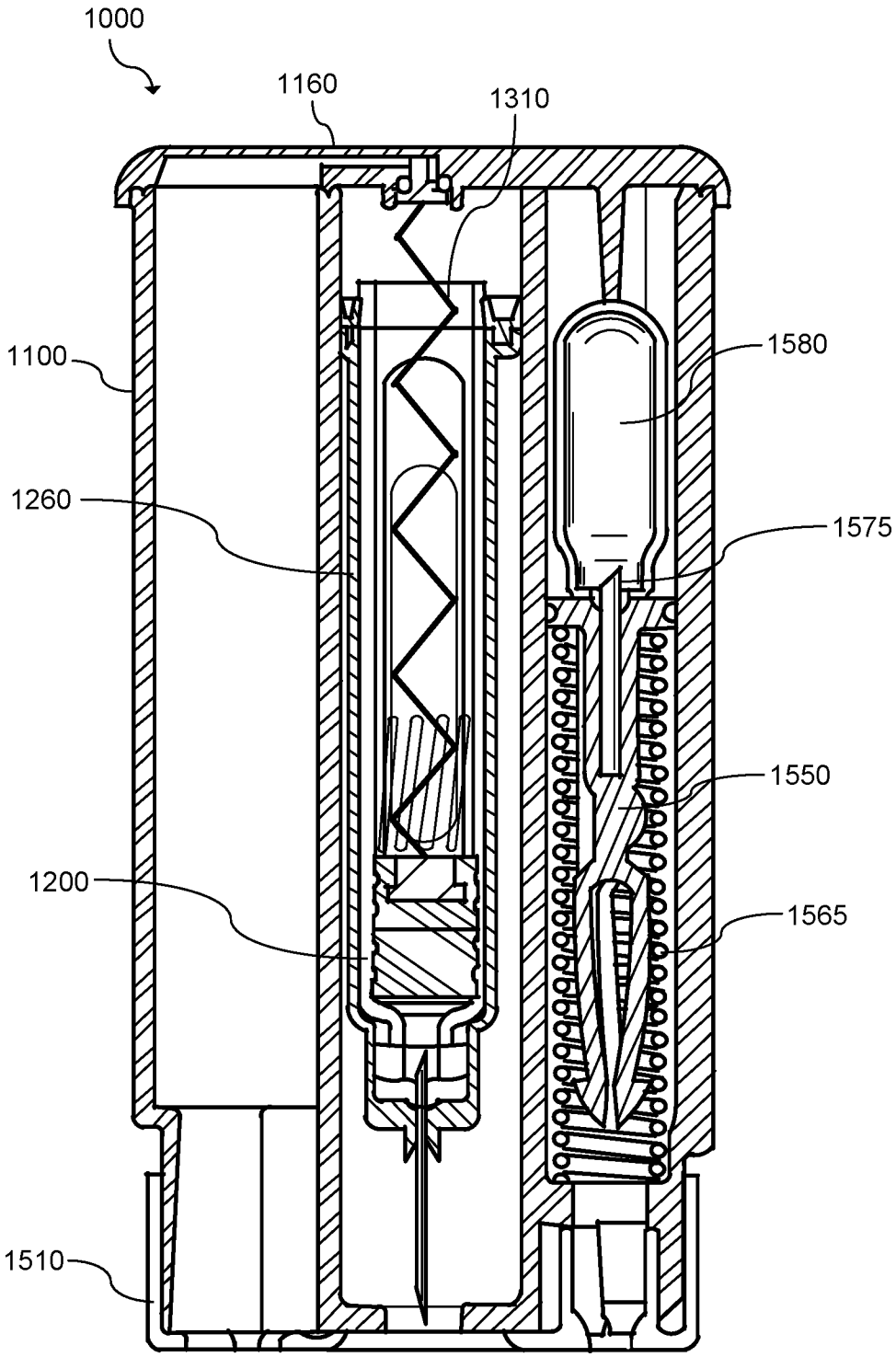

FIG. 19

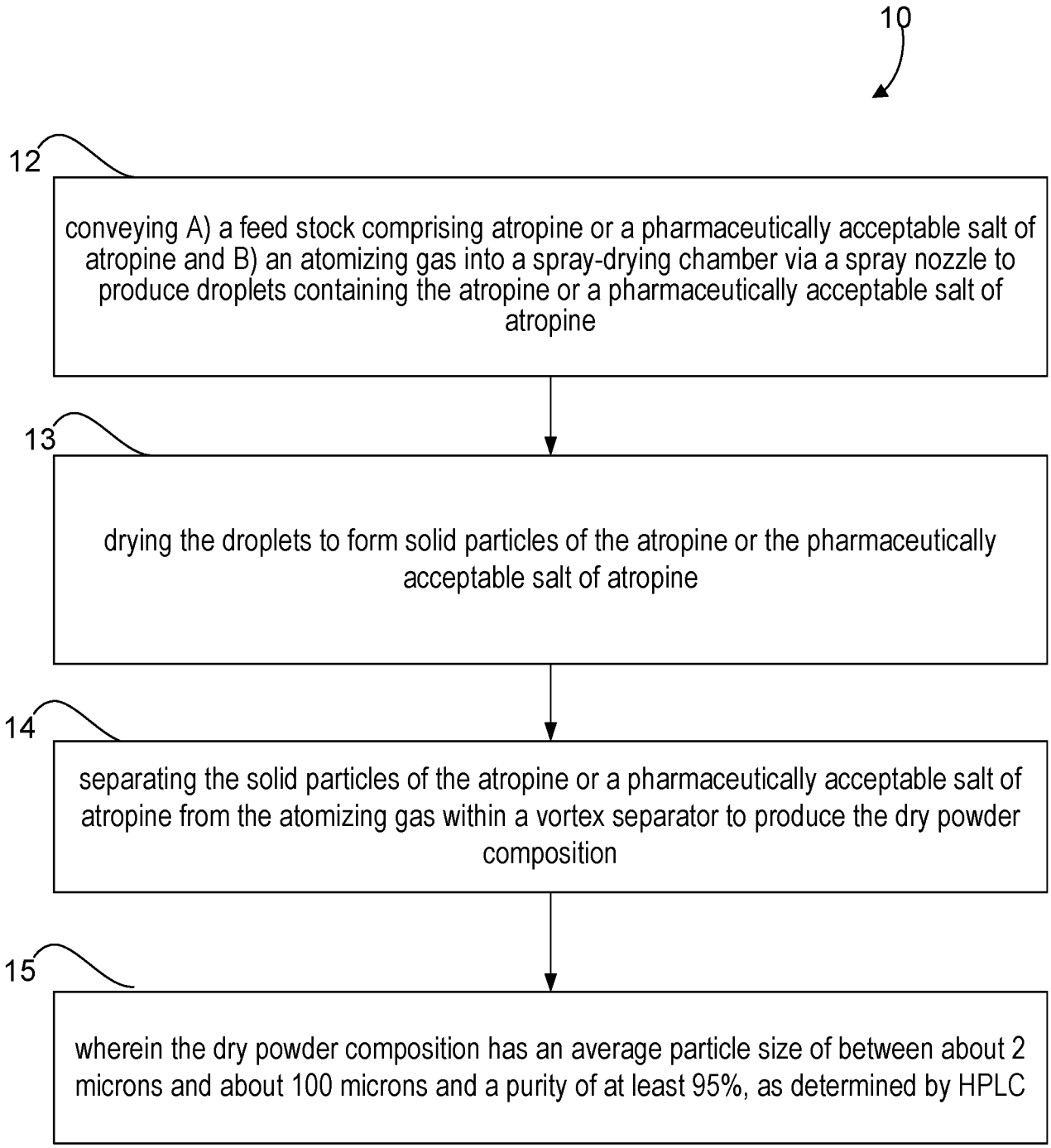
10
12
conveying A) a feed stock comprising atropine or a pharmaceutically acceptable salt of atropine and B) an atomizing gas into a spray-drying chamber via a spray nozzle to produce droplets containing the atropine or a pharmaceutically acceptable salt of atropine
13
drying the droplets to form solid particles of the atropine or the pharmaceutically acceptable salt of atropine
14
separating the solid particles of the atropine or a pharmaceutically acceptable salt of atropine from the atomizing gas within a vortex separator to produce the dry powder composition
15
wherein the dry powder composition has an average particle size of between about 2 microns and about 100 microns and a purity of at least 95%, as determined by HPLC

FIG. 20

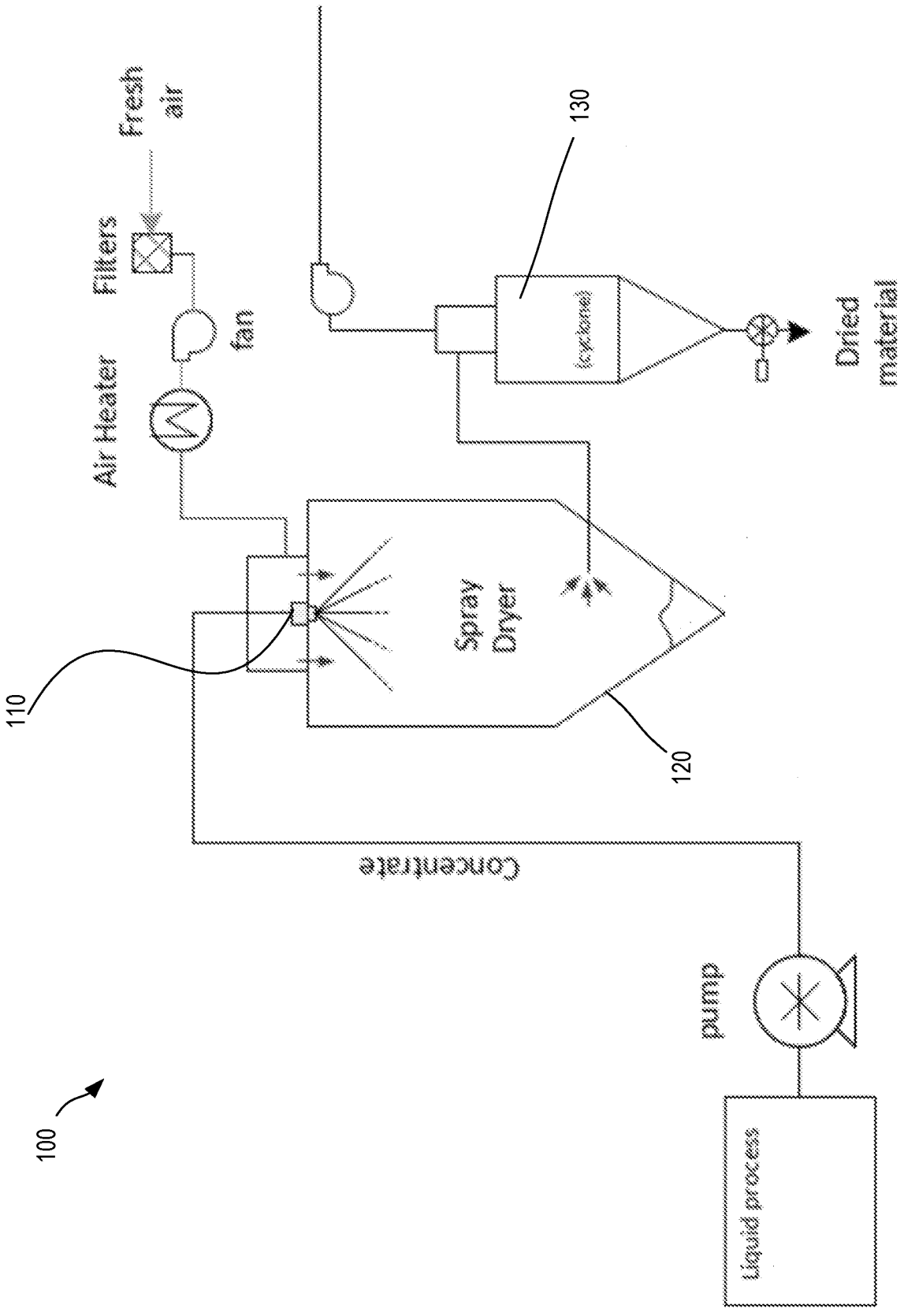
Fresh air
Filters
fan
Air Heater
130
(cyclone)
Dried material
Spray Dryer
110
120
Concentrate
pump
Liquid process
100

FIG. 21