

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2013273277 B2**

(54) Title
Method of manufacturing a propellant container and syringe comprising a propellant container

(51) International Patent Classification(s)
B65B 31/04 (2006.01) **B65B 51/30** (2006.01)
B65B 51/26 (2006.01)

(21) Application No: **2013273277** (22) Date of Filing: **2013.06.07**

(87) WIPO No: **WO13/182859**

(30) Priority Data

(31)	Number	(32)	Date	(33)	Country
	1210082.2		2012.06.07		GB

(43) Publication Date: **2013.12.12**

(44) Accepted Journal Date: **2016.12.01**

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(56) Related Art
US 4769974 A
US 2160367 A



(43) International Publication Date
12 December 2013 (12.12.2013)

- (51) **International Patent Classification:**
B65B 31/04 (2006.01) **B65B 51/30** (2006.01)
B65B 51/26 (2006.01)
- (21) **International Application Number:**
PCT/GB2013/051510
- (22) **International Filing Date:**
7 June 2013 (07.06.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
1210082.2 7 June 2012 (07.06.2012) GB
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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, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, 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, 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 non-prejudicial disclosures or exceptions to lack of novelty (Rule 4.17(v))*

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: METHOD OF MANUFACTURING A PROPELLANT CONTAINER AND SYRINGE COMPRISING A PROPELLANT CONTAINER

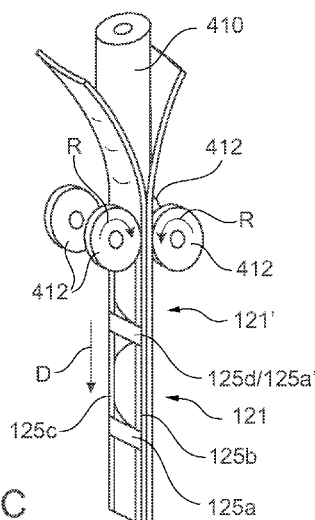


Fig. 14C

(57) Abstract: A method of manufacturing a container containing propellant comprising the steps of: i) sealing a first sheet of rupturable material to a second sheet of rupturable material to form a lower seal and two side seals; ii) placing a propellant dispensing apparatus in fluid communication with a central volume defined by said lower seal, said two side seals and a seal between the propellant dispensing apparatus and the first and second sheets; iii) depositing propellant in the central volume using said propellant dispensing apparatus; and iv) sealing the first sheet to the second sheet to form an upper seal to form a container where the propellant is contained between said upper seal, said lower seal, and said two side seals.

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METHOD OF MANUFACTURING A PROPELLANT CONTAINER AND SYRINGE COMPRISING A PROPELLANT CONTAINER

[0001] This invention relates to a method of manufacturing a container, and in particular to a method of manufacturing a container containing propellant.

5 BACKGROUND

[0002] Automatically actuable syringes are known and include a power source, such as a spring or a compressed gas to deliver a dose of medicament to a patient. Typically, a syringe has a barrel defining a chamber for containing a dose of medicament and a moveable stopper connected to a plunger rod for compressing the medicament to force it out of an opening in the barrel. In more complex devices, additional features are provided that are actuated in a sequence determined by the axial position of the plunger rod or the drive spring, for example. In such devices, the axial position of the plunger rod or the like is indicative of the stage of medicament delivery. Examples of such features include movement of the needle out of or into the device, and movement of a needle shroud between a needle-protecting and a needle-exposing position.

[0003] A self-contained pressurized injection device used for administering very viscous dermal filler material is described in WO-A-2009/086250 (Aesthetic Sciences Corporation). The described device includes an actuator assembly having a pressurized fluid container, a regulator and a bias member. The pressurized fluid container is configured to move between a first closed position and a second open position to selectively activate the device. The bias member biases the pressurized fluid container towards the first closed position.

[0004] It is an object of the present invention to provide a method of manufacturing a container containing propellant.

[0004A] Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

[0004B] As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude other additives, components, integers or steps.

BRIEF SUMMARY OF THE DISCLOSURE

[0005] The present invention is defined in the appended claims.

[0006] In one aspect of the present invention there is provided a method of manufacturing a container containing propellant comprising the steps of:

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- i) providing a container having an opening;
- ii) placing a propellant dispensing apparatus in fluid communication with the opening;
- iii) depositing liquid propellant in the container using said propellant dispensing apparatus;
- iv) temporarily clamping the container to itself so as to substantially fluidly isolate a volume of dispensed liquid propellant in a central volume defined by the temporary clamp;
- v) sealing the container to itself at a location that is not across the central volume; and
- vi) removing the temporary clamp so as to leave propellant sealed in the container.

[0007] Preferably, prior to step v), propellant present in the container that is not in the central volume is allowed to disperse. Heating may be applied to encourage dispersal of propellant present in the container that is not in the central volume. Alternatively, a vacuum may be applied to remove propellant present in the container that is not in the central volume. Additionally or alternatively, a predetermined period of time is allowed to elapse between performing steps iv) and v) so as to allow dispersal of propellant present in the container that is not in the central volume.

[0008] Said propellant may include a hydrofluoroalkane (HFA) which may be HFA 134a.

[0009] In one or more embodiments the container is one that is suitable for use as a power source in a syringe.

[0010] There is also disclosed herein a method of manufacturing a container containing propellant comprising the steps of:

- i) sealing a first sheet of rupturable material to a second sheet of rupturable material to form a lower seal and two side seals;
- ii) placing a propellant dispensing apparatus in fluid communication with a central volume defined by said lower seal, said two side seals and a seal between the propellant dispensing apparatus and the first and second sheets;
- iii) depositing propellant in the central volume using said propellant dispensing apparatus; and

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- iv) sealing the first sheet to the second sheet to form an upper seal to form a container where the propellant is contained between said upper seal, said lower seal, and said two side seals.

5 [0011] The first and second sheets may move relative to the propellant dispensing apparatus so that the upper seal of the container becomes a lower seal of a subsequent container, where steps i) to iv) are repeated to form said subsequent container. Rollers may be provided to move the first and second sheets relative to the propellant dispensing apparatus, said rollers bringing said first sheet and said second sheet together along their respective edges for formation of said two side seals. Said rollers may be configured to also form said two side seals, two pairs of separate rollers may be provided.

10 [0012] Said lower seal and said upper seal may be severed to form a discrete container.

[0013] After step iii) and prior to step iv) the first sheet and second sheet may be temporarily clamped together between the lower seal and the seal made between the propellant dispensing apparatus and the first and second sheets;

15 wherein step iv) comprises forming the upper seal at a position that is not between the temporary clamp and the lower seal; and

the temporary clamp is removed following formation of the upper seal.

20 [0014] The step of temporarily clamping the first sheet to the second sheet may be achieved by using a force sufficient to substantially prevent propellant from escaping through the clamped area, but not of a magnitude that structurally damages the first and second sheets.

[0015] Any or each of said lower seal, said upper seal and said two side seals may be a heat seal, a sonic weld, or an adhesive seal.

[0016] There is further disclosed herein a method of manufacturing a container containing propellant comprising the steps of:

- 25 i) providing a tube of rupturable material;
- ii) sealing a lower end of the tube to form a lower seal;
- iii) sealing an upper end of the tube to form a first upper seal and defining internal volume between the first upper seal and the lower seal;
- iv) forming an opening in the tube;
- 30 v) depositing propellant in the internal volume through the opening; and
- vi) sealing the tube to form a second upper seal that is between the first upper seal and the lower seal, wherein the opening is between the first upper seal and the second upper seal.

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[0017] The method may further comprise the step of cutting the tube through the second upper seal to form the container and/or further comprise the step of cutting the tube through the lower seal to form the container.

[0018] Step iv) may be performed prior to performing step iii).

[0019] The step of depositing propellant in the internal volume through the opening may comprise bringing a propellant dispenser into fluid communication with the opening and where the propellant dispenser forms a sealing arrangement around the opening.

[0020] The tube of rupturable material may be an extruded tube.

[0021] At least steps i) to vi) may be performed when said extruded tube has not been cut from the extrusion line.

[0022] Said first upper seal may become the lower seal of a tube extending above thereof such that the method may be repeated for said tube extending above thereof.

[0023] Any or each of said lower seal, said first upper seal and said second upper seal may be a heat seal, a sonic weld, or an adhesive seal.

[0024] The step of forming an opening in the tube preferably produces substantially no loose material.

[0025] Still further disclosed herein is a syringe having a barrel, a stopper axially moveable within the barrel and a container, wherein the container comprises a chamber containing a propellant that boils at a predetermined temperature, and one or more seals sealing the chamber, wherein the container is formed of a flexible rupturable material substantially impermeable to said propellant and said one or more seals are formed between two like materials, wherein said container is a power source for actuating the syringe and causing the stopper to move axially in the barrel.

[0026] Said one or more seals may be formed by heat sealing, sonic welding, or adhesives.

Said material may have a gas permeability of 0.365 g/(m².day). Said material may include polyethylene, or a polyamide. Said material may include nylon and may consist substantially of nylon. Said material may comprise a laminate of polyethylene and a polyamide. Said material may comprise a laminate of polyethylene and a metal. Said metal may be a metallic foil. The container may be formed from two sheets of said material, wherein said chamber is defined by an area where the two sheets are not bonded to one another and said one or more seals are defined by one or more areas where the two sheets are bonded to one another. The container may be formed from a substantially cylindrical piece of said material initially having two open ends, wherein said two open ends are pinched closed to form two sealed ends. Said propellant may include a hydrofluoroalkane (HFA) and may be HFA 134a.

[0027] All non-mutually exclusive combinations of features disclosed in the present application are within the scope of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which:

Figure 1A is a schematic cross sectional view of a syringe according to an embodiment of the present invention comprising a self-contained rupturable container of propellant;

Figure 1 B is a schematic cross sectional view of a syringe according to an alternative embodiment of the present invention comprising a propellant chamber containing a self-contained rupturable container of propellant;

Figure 1C is a schematic cross sectional view of the syringe of Figure 1 B additionally comprising a fluid conduit extending into the propellant chamber;

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Figure 2 shows an embodiment of a container for containing propellant in accordance with the present invention;

Figure 3 shows an alternative embodiment of a container for containing propellant in accordance with the present invention;

Figure 4 shows a rupturing portion in accordance with an embodiment of the present invention;

Figure 5 shows an alternative rupturing portion in accordance with an embodiment of the present invention;

Figure 6A shows a time-dependent gas volume profile of a compressed gas powered syringe in accordance with the prior art where the compressed gas reservoir is large relative to the internal volume of the system, and Figure 6B shows the corresponding time-dependent pressure profile;

Figure 7A shows a time-dependent gas volume profile of a compressed gas powered syringe in accordance with the prior art where the compressed gas reservoir is small relative to the internal volume of the system, and Figure 7B shows the corresponding time-dependent pressure profile;

Figure 8A shows a time-dependent gas volume profile of a propellant powered syringe in accordance with an embodiment of the present invention, and Figure 8B shows the corresponding time-dependent pressure profile;

Figure 9 shows a pressure profile of vapour pressure vs. time for propellant in the second chamber of a syringe in accordance with the present invention where liquid propellant is introduced into the second chamber;

Figure 10 shows a pressure profile of vapour pressure vs. time for propellant in the second chamber of a syringe in accordance with the present invention where gaseous and liquid propellant is introduced into the second chamber;

Figure 11 shows a pressure profile of vapour pressure vs. time for propellant in the second chamber of a syringe in accordance with the present invention where only gaseous propellant is introduced into the second chamber;

Figure 12 shows a pressure profile of vapour pressure vs. time for propellant in the second chamber of a syringe in accordance with the present invention where the propellant in the second chamber has been actively cooled during delivery;

Figures 13A to 13D are schematic cross sectional views representing a method of filling a propellant container in accordance with an embodiment of the present invention;

Figures 14A and 14B are schematic cross sectional views representing a method of filling a propellant container in accordance with an alternative embodiment of the present invention, and Figure 14C is a schematic perspective view of a further step of the method represented by Figures 14A and 14B;

and

Figures 15A to 15E show various stages of a method of manufacturing a propellant filled container in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION

[0029] A syringe 10 according to an embodiment of the present invention is shown in Figure 1A. The syringe 10 has a barrel 12 having an outlet 14 at a forward end and a stopper 16 disposed in the barrel 12. The stopper 16 is axially moveable within the barrel 12 when subjected to a sufficient axial force. The barrel 12 has a finger flange 12a at a rear end, however some syringes within the scope of the present invention may not comprises finger flanges. The stopper 16 defines and separates a first chamber 18 and a second chamber 20 where the first chamber 18 is axially forwards of the stopper 16 and is configured for containing a substance such as a medicament, and in particular, a liquid medicament. Hereinafter, the first chamber 18 will be considered to be initially containing medicament, although the skilled person will appreciate that other alternative substances may be present. The second chamber 20 is axially rearwards of the stopper 16 and is configured to receive propellant from a propellant source. In the syringe of Figure 1A, the propellant source is a container 21 which comprises a rupturable wall 24 defining a third chamber 22 containing propellant.

[0030] The syringe 10 additionally has a rupturing portion (not shown) configured to rupture the rupturable wall 24 to irreversibly fluidly connect the third chamber 22 and the second chamber 20 so that propellant enters the second chamber 20. That is, the rupturable wall 24 is frangible or breakable such that once it has been broken or opened, it cannot be reclosed or resealed without additional means for doing such. The rupturable wall 24 is preferably flexible at least in part so that the shape of the container 21 is changeable.

[0031] According to certain embodiments of the present invention, once a fluid connection is established between the third chamber 22 and the second chamber 20, the fluid connection is maintained and not closed or sealed. This is necessary for the desired thermodynamic properties of the syringe 10 in accordance with the present invention, as is described in more detail below. Depending on the nature of the third chamber 22, the rupturing portion may be a needle or other suitable element configured to slice, rupture, break, pierce or otherwise create an opening in the rupturable wall 24 (or, in other embodiments, a similar rupturable element defining at least a part of the third chamber 22) and establish a fluid connection between the third chamber 22 and the second chamber 20. In the case where the rupturing portion is a needle or similar piercing element, it is preferable that it is either hooked, or hollow in configuration or otherwise shaped so that upon rupturing, breaking, or piercing the rupturable wall 24, the rupturing portion itself does not entirely block the newly formed fluid passageway

between the third chamber 22 and the second chamber 20. In the case where the rupturing portion has a hollow configuration, the propellant may flow through the hollow portion from the third chamber 22 to the second chamber 20. In other embodiments, the rupturing portion may comprise apparatus for rupturing the rupturable wall 24 by a bursting mechanism. That is, the rupturing portion acts to exert a force on the container 21 so that that the pressure in the third chamber 22 increases so that the rupturable wall 24 is caused to rupture, thereby establishing a fluid connection between the third chamber 22 and the second chamber 20. In some embodiments, the rupturing portion may be moved towards the third chamber 22 to rupture the third chamber 22. In other embodiments, the third chamber 22 may be moved towards the rupturing portion to cause rupturing of the third chamber 22. Figure 4 shows an example of a rupturing portion 510 in accordance with an embodiment of the present invention for establishing a permanent fluid connection between the third chamber 22 and the second chamber 20. The rupturing portion 510 includes a conical element 512 that has a cut-out portion 512a and a bore 512b running therethrough. The conical element 512 projects from a base 514 through which the bore 512b passes. In use, the conical element 512 pierces a hole in a rupturable wall of the third chamber 22 requiring only a relatively low force to establish a fluid connection between the third chamber 22 and the second chamber 20 via the bore 512b. The tapered profile of the conical element 512 means that as the rupturing portion 510 is advanced further towards the rupturable wall, the conical element 512 will enlarge the hole created and ensure that the fluid path between the third chamber 22 and second chamber 20 is not obstructed. The cut-out portion 512a ensures that the hole is created effectively and minimizes the risk of the rupturing portion 510 itself sealing the hole it creates. Fluid egress from the third chamber 22 is therefore maximized. The presence of the bore 512b facilitates direct and efficient passage of both liquid and gaseous propellant between the third chamber 22 and second chamber 20.

[0032] The rupturing portion 510 may be shaped (e.g. the shape of the base 514) so that multiple rupturing portions can be arranged in close proximity to act on the same rupturable wall. As an example, Figure 5 shows two identical rupturing portions 510 in suitably close arrangement for acting on a single rupturable wall. The use of multiple rupturing portions (in general) will facilitate greater transfer of fluid from the third chamber 22 to the second chamber 20. The one or more rupturing portions may rupture the third chamber 22 from any direction and in any orientation. Depending on the specific syringe, it may be preferable to rupture the third chamber 22 at a particular point or in a particular direction to maximize or otherwise control the release of propellant from the third chamber 22.

[0033] Other non-conical but tapered elements may be used to form the rupturing portion of the present invention. In such cases, it is still preferable for the tapered element to include a

cut-out portion to improve fluid flow and minimize the risk of the rupturing element sealing newly created hole in the rupturable wall. Additionally or alternatively, it is preferable for the rupturing portion to include a through-bore for channeling fluid from the third chamber 22 to the second chamber 20.

[0034] The propellant is one that boils at a predetermined temperature which in all cases must be below the local operating temperature of the system during use. A particularly preferable propellant is or includes a hydrofluoroalkane (HFA) as this provides a suitable pressure for use with aqueous solution in a fine bore needle syringe. HFA 134a boils at -26.4°C which is able to provide sufficient pressure even when the medicament that is to be delivered is chilled. In other embodiments a propellant may have a lower boiling point which provides an increased pressure is use, which is especially useful for the delivery of highly viscous drugs. For example HFA 422d has a boiling point between -46.2°C and -41.5°C. Similarly, HFA 507c has a boiling point of -46.9°C. In alternative embodiments, the propellant may boil at a higher temperature such that it cannot generate sufficient pressure to drive the medicament without additional energy from an external source such as the patient or another heat source. For example HFA 123 boils at +27.9°C. Similarly, HFA 245fa has a boiling point of +15.3°C.

[0035] When the third chamber 22 is in fluid communication with the second chamber 20, propellant is released into the second chamber 20. At the predetermined temperature, the propellant released into the second chamber 20 is initially in its liquid phase. Additionally or alternatively, some of the propellant may be initially in its liquid phase due to the confines of the volume in which it resides, even if the propellant is at a temperature above the predetermined temperature.

[0036] Some of this liquid propellant will evaporate due to the heat that the propellant is exposed to (e.g. ambient heat), thereby providing gas phase propellant to the second chamber 20. Since the vaporization of propellant requires the absorption of latent heat from the liquid propellant, the process of evaporation cools the remaining liquid propellant. This cooling results in the vapour pressure immediately above the liquid propellant being lower than it is at its initial starting (i.e. ambient) temperature. Nevertheless, the pressure in the second chamber 20 begins to increase enough so that the stopper 16 moves axially forwardly in the barrel 12, thereby reducing the volume of the first chamber 18 and pressurizing the medicament held therein. The pressurized medicament exits the barrel 12 through the outlet 14, which may be fluidly connected to a needle or other applicator, for entry into an injection site such as subcutaneous tissue.

[0037] In the case where a propellant is used that boils at a temperature higher than ambient temperature, the ambient temperature will not be sufficient to boil the propellant and thus the stopper 16 will not move as a consequence. In these embodiments, an additional heat source

must be provided to boil the propellant and begin movement of the stopper 16. For example, the heat source could be the user's hand which will be at "body temperature" (approximately 37°C, or 33°C at the surface of the skin). This arrangement may reduce the risk of accidental delivery of medicament if the propellant is inadvertently in fluid communication with the second chamber 20.

[0038] As the stopper 16 moves axially forwards towards the outlet 14 to reduce the volume of the first chamber 18, the second chamber 20 is made larger. Thus, additional volume is continuously created in the second chamber 20 into which the propellant can evaporate into. This further vaporization causes further cooling of the remaining liquid propellant and thus further reduces the observed vapour pressure in the second chamber 20.

[0039] However, the system is not completely adiabatic (nor is it isothermal) so thermal energy is absorbed by the liquid propellant from its immediate environment (e.g. the barrel 12) to counter the reduction in temperature of the liquid propellant and the reduction in vapour pressure in the second chamber 20. Indeed, in the absence of this heat absorption, the propellant would freeze or at least become a stable liquid as the temperature of the liquid propellant continues to drop, and the syringe 10 would cease to operate correctly. This drop in vapour pressure in the second chamber 20 is exhibited throughout delivery of the medicament from the first chamber 18. In particular, since the stopper 16 is moving, the propellant in the second chamber 20 is continuously exposed to "new" sections of the inside of the barrel 12. Since the "new" sections of the inside of the barrel have not previously been in contact with the propellant, its thermal energy will initially be substantially at or near to ambient temperature or a higher temperature if additional heating means are present (unlike the sections of the barrel 12 axially rearward thereof which have already given up thermal energy to the liquid propellant). The "new" sections of barrel that the propellant is exposed to during delivery therefore act as a fresh heat source which is able to provide thermal energy to the propellant in the second chamber 20.

[0040] The stopper 16 continues to move axially forwardly in the barrel 12 until it reaches the forwardmost end of the barrel 12 where further forward axial movement is not possible. At this point, the full dose of medicament in the first chamber 18 has been delivered and the first chamber 18 has been reduced to its smallest volume (i.e. at or near substantially zero, depending on the formation of the front end of the barrel 12). With no further movement of the stopper 16, the temperature of the gas phase propellant, and any remaining liquid propellant, begins to increase as thermal energy is absorbed from the environment. Since, with the stopper 16 stationary in the barrel 12, the second chamber 20 has a constant volume, the increase in temperature of the propellant results in an increase in vapour pressure in the second chamber 20. This increase in vapour pressure tends towards the vapour pressure of the propellant at the

temperature of its immediate environment (e.g. ambient temperature or a higher temperature if additional heating means are still present at this point). Indeed, the vapour pressure in the second chamber 20 will reach the vapour pressure of the propellant at the temperature of its immediate environment given long enough as equilibrium is reached.

[0041] The magnitude of the drop in vapour pressure in the second chamber 20 during delivery from the initial vapour pressure maximum when the propellant is released into the second chamber 20 to when the stopper 16 has reached the front end of the barrel 12 depends on any one or more of i) the thermal properties of the syringe 10, ii) the rate of delivery of propellant into the second chamber 20, and iii) the phase of the propellant entering the second chamber 20 (as will be described in more detail below). With regards to the effects of the thermal properties of the syringe 10, such properties determine the rate of heat transfer into the propellant in the second chamber 20. Similarly, the rate and phase of propellant entering the second chamber 20 affects the thermodynamic processes occurring during delivery with regards to the propellant in the second chamber 20.

[0042] As an example, a 0.5 bar drop in vapour pressure may be exhibited when delivering 1 ml of aqueous solution through a 27 gauge needle attached to the outlet 14 measured from the initial vapour pressure maximum when the propellant is released into the second chamber 20 to when the stopper 16 has reached the front end of the barrel 12.

[0043] The advantages of liquefied gas powered syringes are best understood by comparison with a syringe powered by a compressed gas. In known prior art compressed gas syringes, compressed gas is released from a reservoir into a volume behind a stopper in a syringe barrel where the expanding volume of gas can act on the stopper and cause it to move and expel medicament from the barrel. Figure 6A shows a time-dependent volume profile of a compressed gas syringe in accordance with the prior art. 5 cc of compressed gas is initially contained in a reservoir which is in selective fluid communication with a volume of the syringe rearward of a stopper. As shown in Figure 6A, when the reservoir is opened the compressed gas expands rapidly at 500 as the compressed gas fills the dead volume behind the stopper.

[0044] There is a constant mass of gas which follows the ideal gas law under adiabatic conditions and behaves as $PV=nRT$, where P is the pressure of the gas, V is the volume of the gas, n is the number of moles of gas, T is the temperature of the gas and R is the universal gas constant. Once the dead volume is filled with compressed gas, the expanding gas begins to gas the stopper to move, as indicated at 502 on Figure 6A, and medicament is expelled from the barrel. Once the stopper reaches its forwardmost position in the barrel, the compressed gas ceases to expand further, as indicated at 504 of Figure 6A.

[0045] Since the quantity nRT is constant for adiabatic expansion, the pressure of the gas drops as the volume increases. This is shown in Figure 6B which shows a time-dependent

pressure profile corresponding to the volume profile of Figure 6A. This drop in pressure occurs both as the compressed gas enters the dead volume (i.e. when the compressed gas reservoir is initially opened) and during the time that the stopper is moving forwards and expelling medicament. As shown in Figure 6B, the result is an initially steep drop in pressure, followed by a more gradual drop in pressure. The final pressure of the compressed gas is determined by the volume in which it resides at the end of the delivery, when the stopper is at its forwardmost position in the barrel. Figures 6A and 6B relate to a syringe where the reservoir of compressed gas is large relative to the internal volume of the system. As a consequence of this, the final pressure of compressed gas is maintained at a relatively high level (~5 bar from an initial 10 bar).

[0046] Figures 7A and 7B relate to a syringe where the reservoir of compressed gas is small (0.3 cc) relative to the internal volume of the system. Figure 7A shows the time-dependent volume profile of the compressed gas, and Figure 7B shows the corresponding time-dependent pressure profile of the compressed gas. Again, Figure 7A shows a rapid increase in volume at 500 when the compressed gas reservoir is initially opened and the compressed gas fills the dead volume. This is followed by a more gradual increase in volume at 502 as the stopper begins to move and the volume behind the stopper increases. Finally, when the stopper is in its forwardmost position in the barrel, the volume of the compressed gas ceases to increase as shown at 504 of Figure 7A. The corresponding pressure profile shown in Figure 7B shows that there is a large and initially rapid reduction in pressure as the gas expands, and then a more gradual decrease in pressure as the stopper begins to move.

[0047] In contrast, if the gas is initially a liquefied gas in accordance with the present invention, the mass of the gas increases as the gas expands as the liquid boils. It is this increasing mass aligned with the increasing volume that provides a more consistent pressure profile. Figure 8A shows a time-dependent volume profile of a syringe powered by 0.3 cc of a liquefied propellant in accordance with an embodiment of the present invention. In the reservoir (e.g. the third chamber) the propellant will be a liquid in equilibrium with a saturated vapour. Once the reservoir is opened and put into fluid communication with the volume behind the stopper, the liquid propellant boils and volume of the gas increases as shown at 500 of Figure 8A. As with the compressed gas, once the stopper begins to move, the volume behind the stopper increases and permits the volume of the gas to increase further as shown at 502. Once the stopper reaches its forwardmost position, the volume of gas plateaus, as shown at 504. At this point there will still be some liquid propellant remaining in fluid communication with the second chamber. However, since the mass of gas increases as the liquid boils, the propellant generates more gas at the vapour pressure and therefore maintains a more constant pressure as shown in Figure 8B. Whilst there is an initial variation in gas pressure as the reservoir is first

put into fluid communication with the volume behind the stopper, there is no significant overall drop in gas pressure as there is with compressed gases, as evidenced by Figures 6B and 7B. Consequently, the present invention offers a much more consistent pressure profile with a very small initial volume of propellant.

[0048] In the syringes associated with each of Figures 6A to 8B, the dead internal volume into which the compressed gas or vapourised propellant initially expands into is ~3 cc.

[0049] Figure 9 shows an example of a pressure profile (i.e. vapour pressure vs. time within the second chamber 20) exhibited by a syringe such as the one described above in relation to Figure 1A during use. Point A indicates the start of propellant release into the second chamber 20 and the subsequent boiling of the propellant which results in a very fast increase in vapour pressure over a first time period (typically of the order of 10-100ms) up to point B. At point B, the vapour pressure in the second chamber 20 is great enough to cause the stopper 16 to move axially forwardly and begin expulsion of medicament from the first chamber 18. In practice, the stopper 16 may start to move just before point B is reached as the pressure in the second chamber 20 is sufficient to overcome the frictional resistance of the stopper 16 in the syringe 10. As described above, the thermodynamics of the syringe 10 dictate that the vapour pressure drops during delivery. This is shown in the pressure profile of Figure 9 as the negative gradient between points B and C over a second time period, where point C is indicative of the instant where axial movement of the stopper 16 ceases to continue (i.e. the end of delivery).

Consequently, the vapour pressure at C is lower than the vapour pressure at B. A third time period between point C and point D represents the vapour increase in the second chamber 20 as the propellant therein absorbs heat from the environment. This increase tends towards the vapour pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature). Indeed, point D represents substantially this vapour pressure. For the pressure profile of Figure 9, the vapour pressure at D is greater than both the vapour pressures at B and C (and of course A). This may be because the stopper 16 began moving axially forwardly before the propellant could reach its vapour pressure at the temperature of its immediate environment. At point D there will still be some liquid propellant remaining in fluid communication with the second chamber.

[0050] The pressure profile of Figure 9 reveals that there is not necessarily a simple constant pressure acting on the stopper 16 (i.e. the vapour pressure in the second chamber 20) during delivery. In accordance with the present invention, this pressure profile may be manipulated so as to provide a more reliable and/or useful device, and/or be more suitable for a particular medicament or application. Indeed, as noted above, the form of the pressure profile is dependent on any one or more of i) the thermal properties of the syringe 10, ii) the rate of delivery of propellant into the second chamber 20, and iii) the phase of the propellant entering

the second chamber.

[0051] Further embodiments of syringes 10 in accordance with the present invention are described below with reference to Figures 1B and 1C. Given the differences in configuration, the various embodiments of syringes 10 will each exhibit a different pressure profile of vapour pressure in the second chamber 20 during use.

[0052] A further embodiment of a syringe in accordance with the present invention is shown in Figure 1B. The syringe 10 of Figure 1B comprises a non-rupturable wall 26 extending across the barrel 12 along an inner circumference of the barrel 12. The non-rupturable wall 26 does not form a continuous disc and has an axial aperture 26a therethrough. The non-rupturable wall 26 defines a fourth chamber 28 which is fluidly connected to the second chamber 20 via aperture 26a which defines a propellant channel. The fourth chamber 28 contains a container 21 as described above in relation to Figure 1A. In use, the rupturable wall 24 of the container ruptures to fluidly connect the third chamber 22 to the fourth chamber 28, and therefore also to the second chamber 20 via the aperture 26a. The extent of the aperture 26a largely determines the flow rate of propellant from the fourth chamber 28 to the second chamber 20 upon rupturing of the rupturable wall 24. The aperture 26a may be a simple hole, or may be any other fluid passageway that connects the fourth chamber 28 to the second chamber 20. For example, in one embodiment, the aperture 26a may be a labyrinth arrangement or a valve arrangement that opens when the fluid pressure acting on it exceeds a predetermined threshold. A baffle arrangement may prevent or minimize the flow of droplets (e.g. a mist) of propellant passing from the fourth chamber 28 to the second chamber 20.

[0053] Yet another embodiment of a syringe 10 in accordance with the present invention is shown in Figure 1C. The syringe 10 of Figure 1C is largely the same as the syringe of Figure 1B but the propellant channel fluidly connecting the third chamber 22 and the fourth chamber 28 is defined by a propellant conduit 30. The propellant conduit 30 has a bore therethrough fluidly connecting the third chamber 22 and the fourth chamber 28, and the bore largely determines the flow rate of propellant from the third chamber 22 to the fourth chamber 28. The propellant conduit 30 extends axially rearwardly into the fourth chamber by distance L. The axially rearwardly extending propellant conduit 30 acts to limit the quantity of liquid propellant passing from the fourth chamber 28 to the second chamber 20 during use of the syringe 10. In particular, during use of the syringe 10, the syringe 10 will be orientated so that the outlet 14 is proximate to an injection site. Usually, the syringe 10 will be orientated so that the longitudinal axis of the syringe is held vertically above the injection site (or at least be inclined with respect to the horizontal). In this orientation, liquid propellant exiting the third chamber 22 (i.e. after rupture of rupturable wall 24) will move under the influence of gravity towards the non-rupturable wall 26. The propellant conduit 30 will then extend above some, if not all, of the

liquid propellant, depending on the magnitude of L and the quantity of propellant present. The propellant conduit 30 acts to limit or prevent entirely the flow of liquid propellant from the fourth chamber 28 to the second chamber 20. The syringe 10 may be used at orientations other than vertical (e.g. horizontal, or indeed any orientation between vertical and horizontal) and so it is preferable for L to be sufficient so that the flow of liquid propellant from the fourth chamber 28 to the second chamber 20 is limited, or further preferably, substantially prevented.

[0054] Modeling the second chamber 20 as a cylinder having radius r and height H , $\pi r^2 H$ should be greater than the maximum volume of liquid propellant in the second chamber 20 for the rear (open) end of the propellant conduit 30 to rise above the propellant liquid level when the syringe 10 is in a vertical orientation. Additionally, $(\pi r^2 H/2)$ should be greater than the maximum volume of liquid propellant in the second chamber 20 for the propellant conduit to remain above the propellant liquid level when the syringe 10 is in a horizontal orientation. In one example, for a 100 μ l volume of propellant in a second chamber 30 of diameter 6.35 mm, the magnitude of L should be 3.158 mm or greater to be above the propellant liquid level. In another example, for a 10 μ l volume of propellant in a second chamber 30 of diameter 6.35 mm, the magnitude of L should be 0.316 mm or greater to be above the propellant liquid level.

[0055] The pressure profile of vapour pressure of propellant in the second chamber 20 during use will be influenced by the phase of propellant entering the second chamber. For example, if a constant or near constant flow of gas-phase (or predominantly gas-phase) propellant is being supplied to the second chamber 20 through the propellant conduit 30, then the stopper 16 will experience a more constant vapour pressure and move axially forwardly at a more constant rate within the barrel 12 and expel medicament from the first chamber 18 at a constant rate. This may be particularly suitable for applications where it is important to deliver medicament at a constant or near constant rate.

[0056] The passage of propellant through the propellant conduit 30 or aperture 26a does not constitute “regulated delivery”. Indeed, passage through the propellant conduit 30 or aperture 26a constitutes bolus delivery of the propellant into the second chamber 20.

[0057] Unless otherwise stated, all described features of the syringe of Figure 1A (excluding the form of the third chamber 22) may be applicable to any one or more of the syringes of Figures 1B and 1C. Indeed, any non-mutually exclusive features of any one or more of the syringes of Figures 1A to 1C may be applicable to any other of the syringes of Figures 1A to 1C.

[0058] Figure 10 shows an example pressure profile of vapour pressure in the second chamber 20 of a syringe 10 where mostly gas propellant is supplied to the second chamber 20. The pressure profile of Figure 10 shows that propellant enters the second chamber 20 at point A and immediately results in an increase of vapour pressure in the second chamber 20 to an

initial maximum vapour pressure and point B. The rate of increase of vapour pressure decreases slightly immediately prior to reaching point B. The change from point A to point B occurs over a first time period. The vapour pressure then decreases slightly over a second time period as the stopper 16 begins to move axially forwardly to deliver medicament until point C is reached. During the second time period, the little liquid that is present reduces in temperature as it gives up heat of vaporization by the mechanism described above in relation to the pressure profile of Figure 9. However, the decrease and the rate of decrease between points B and C in Figure 10 are less than the respective decrease and the rate of decrease in the pressure profile of Figure 9. In Figure 10, point C represents the end of delivery when the stopper 16 has reached the front of the barrel 12 and is no longer moving axially forwardly. Subsequent to point C being reached, the propellant in the second chamber 20 absorbs heat from the environment which increases the vapour pressure within the second chamber 20. This increase tends towards the vapour pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature) which is indicated at point D, where the time period between points C and D is a third time period. At point D there will still be some liquid propellant remaining in fluid communication with the second chamber.

[0059] Figure 11 shows an example of a pressure profile of a syringe 10 in accordance with the present invention where substantially only gas propellant is introduced into the second chamber 20. The pressure profile of Figure 11 is largely similar to that of Figure 10, however, in the pressure profile of Figure 11, there is substantially no change in the vapour pressure between points B and C. That is, during delivery, there is a substantially constant vapour pressure in the second chamber 20. As with the pressure profile of Figure 10, subsequent to the end of delivery (i.e. after point C), the vapour pressure increases as the propellant in the second chamber absorbs heat from the environment. At point D there will still be some liquid propellant remaining in fluid communication with the second chamber.

[0060] Comparing the pressure profiles of Figures 9, 10 and 11, it can be seen that the drop in vapour pressure between points B and C is reduced as the proportion of gas propellant relative to liquid propellant introduced into the second chamber 20 is increased. It is understood that this is predominantly due to the initial maximum of vapour pressure (i.e. the vapour pressure at point B) being reduced for more proportionally gaseous propellant introduced into the second chamber 20. That is, the vapour pressure in the second chamber 20 does not reach its vapour pressure at the temperature of its immediate environment (e.g. ambient temperature) during delivery when only gaseous or partially gaseous propellant is introduced into the second chamber 20.

[0061] Indeed, it is anticipated that for some syringes in accordance with the present invention, where only gaseous propellant is introduced into the second chamber 20 that there

will be no initial maximum prior to the end of delivery. That is, the initial increase in vapour pressure subsequent to point A will result in the movement of the stopper 16 and the expulsion of medicament, but at the end of delivery the vapour pressure will be at a level not previously exceeded in the delivery process. To put that another way, point C will represent the highest vapour pressure of the first and second time periods. In this scenario, following point C, the vapour pressure will increase as the propellant absorbs heat energy from its environment and tends towards the vapour pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature).

[0062] As described above, the form of the pressure profile produced by a propellant powered syringe 10 is determined by one of three parameters, namely i) the thermal properties of the syringe 10, ii) the rate of delivery of propellant into the second chamber 20, and iii) the phase of the propellant entering the second chamber 20. The embodiments described above demonstrate the effects of parameters ii) and iii) on the form of the pressure profile.

[0063] Figure 12, however, demonstrates the effects of parameter i) on the form of the pressure profile. In particular, Figure 12 represents the pressure profile of a syringe 10 in accordance with the present invention, similar to the syringe that produced the pressure profile of Figure 9. However the syringe 10 associated with the pressure profile of Figure 12 additionally includes apparatus to further cool the propellant in the second chamber 20 during use. By “further cool” is meant reducing the temperature of the propellant in the second chamber 20 by an amount that is more than if the apparatus to further cool were not present, i.e. where the only reduction in temperature in liquid propellant is due to loss of latent heat of vaporization. The skilled person will appreciate that the propellant in the second chamber 20 can be further cooled by several methods within the scope of the present invention. For example, a coolant or refrigerant (which may be an additional supply of the propellant) may be applied to the outside of the barrel 12 proximate the second chamber 20 so that the portion of the barrel 12 proximate the second chamber 12 is cooled thereby removing some of its thermal energy such that it has less thermal energy to supply to the propellant in the second chamber 20. If the part of the barrel 12 proximate the second chamber 20 has less thermal energy to provide to the propellant in the second chamber 20, when the temperature of the liquid propellant falls as it loses heat of vaporization as it boils, the liquid propellant has less thermal energy available to it from the barrel 12 proximate the second chamber 20 as it otherwise would. Therefore, there is less thermal energy available to the liquid propellant in its immediate environment that may be absorbed by the liquid propellant to offset the reduction in temperature due to boiling. For this reason, during operation of the syringe 10, the drop in vapour pressure in the second chamber 20 is greater than it would otherwise be if no means to cool the propellant therein were in place. Indeed, any means or method that reduces the thermal energy

available to the liquid propellant in the second chamber 20 as it is boiling and causing the stopper 16 to move axially forwardly in the barrel 12 will result in a greater drop in vapour pressure in the second chamber 20 than would otherwise occur if no such means or method were in place.

[0064] In the case where a coolant or refrigerant is applied to the outside of the barrel 12 proximate the second chamber 20, the coolant or refrigerant may be channeled or otherwise caused to travel towards the injection site after cooling the barrel 12 (and the liquid propellant in the second chamber 20) to additionally provide cooling to the injection site. The cooling provided to the injection site may provide the effect of reducing the level of pain caused by the injection as perceived by the patient.

[0065] In other embodiments, thermally insulating material may be present on or around the barrel 12 proximate the second chamber 12 so that the thermal transfer of heat from the environment to the barrel 12 is reduced. In this embodiment, heat lost from the barrel 12 and absorbed by the liquid propellant in the second chamber 20 may not be replaced (or such replacement will at least be restricted) by absorption of heat by the barrel 12 from the external environment. Again, such measures will limit the heat transfer to the second chamber 20 which contains the propellant so that a greater vapour pressure drop will be exhibited.

[0066] Conversely, if more thermal energy is supplied to the second chamber 20 such that the liquid propellant contained therein is able to absorb more thermal energy during delivery than it otherwise would be able to, the drop in vapour pressure exhibited in the second chamber 20 during delivery may be reduced and even reduced to substantially zero. Thermal energy may be supplied to the second chamber 20 by active heating means, which for example may be achieved by providing a heat source that has a temperature above the ambient temperature so that thermal energy may be transferred from the heat source to the second chamber 20, and in particular to the propellant contained therein. Alternatively, the thermal properties of the syringe 10, e.g. the barrel 12, may be configured so as to increase the rate of heat transfer from the environment to the second chamber 20. For example, the materials of the syringe 10 may be chosen such that they have a high thermal conductivity to maximize heat transfer into the second chamber 20 so that the liquid propellant is able to absorb sufficient heat to offset (i.e. reduce or eliminate) the reduction in temperature due to vaporization. Of course, if using materials having high thermal conductivity to construct the syringe 10, the materials must also provide other desired physical properties (e.g. strength and durability) to a sufficient degree.

[0067] Thus, in accordance with the present invention a syringe 10 may be provided that has suitable properties such that upon actuation of the syringe 10, a desired pressure profile of vapour pressure in the second chamber is exhibited. The desired pressure profile may be dictated by the desire to produce a delivery having a particular pressure profile, to suit a

particular medicament or injection type, for example. Alternatively, the desired pressure profile may be dictated by the requirement to have a pressure feature of a particular type (e.g. magnitude, duration, gradient or rate etc.). The pressure feature may be used to trigger a subsequent action so that more complex modes of operation of the syringe can be utilized (as is described in more detail below).

[0068] As described above, the “first time period” is the time period between the initial release of propellant into the second chamber 20 and the initial maximum vapour pressure. Typically (although not always, as described above) the initial movement of the stopper 16 will be coincident with an initial maximum vapour pressure from which the vapour pressure decreases from over the second time period. The “second time period” is the time period between the initial forwardly axial movement of the stopper 16 and the point where forward axial movement of the stopper 16 is arrested (i.e. the end of the delivery phase when the stopper 16 reaches the front end of the barrel 12). The “third time period” is defined as the time period between the end of the second time period and the point where vapour pressure in the second chamber 20 reaches a predetermined level. In a preferable embodiment, the predetermined level determining the third time period is the vapour pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature).

[0069] In preferable embodiments, the syringe 10 in accordance with the present invention exhibits a pressure profile of vapour pressure in the second chamber 20 wherein the first time period is less than 1.0 seconds. In further preferable embodiments, it is preferable for the first time period to be shorter, such as less than 0.5 seconds, less than 0.2 seconds, or less than 0.1 seconds. In preferable embodiments, it is preferable for the second time period to be less than 15 seconds. However a second time period of around 15 seconds represents a relatively long delivery period, so in practice it may be more preferable if the second time period is less than 10 seconds and further preferably less than 5 seconds. In particularly preferable embodiments, the second time period is less than 3 seconds, less than 2 seconds, or less than 1 second. Where an initial maximum vapour pressure (a “first pressure”) is reached that is substantially coincident with the initial movement of the stopper 16 (i.e. coincident with the end of the first time period and the beginning of the second time period) it is preferable that this be less than 15 bar, or further preferably less than 10 bar, less than 8 bar or less than 6 bar. In a preferable embodiment, the first pressure is substantially equal to the vapour pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature). Defining the vapour pressure in the second chamber 20 at the end of the second time period (i.e. the start of the third time period) as a “second pressure”, in preferable embodiments the second pressure is preferably less than 99% of the first pressure, or further preferably less than 95% or less than 90% of the first pressure. Similarly, in preferable embodiments the second pressure is

preferably greater than 50% of the first pressure, or further preferably greater than 75% or greater than 85% of the first pressure. In preferable embodiments, the difference between the first pressure and the second pressure is more than 0.1 bar, and further preferably more than 0.5 bar or more than 1.0 bar.

[0070] In any of the described embodiments of syringes in accordance with the present invention, the propellant containers shown in Figures 2 and 3 may be used. The skilled person will appreciate that other propellant containers may be used and that syringes made in accordance with the present invention are not necessarily limited to using the containers of Figures 2 or 3. In Figure 2, a container 121 is shown to be made of an upper sheet 124a and a lower sheet 124b which together form a rupturable wall 124 of the container 121. The sheets 124a, 124b are generally square or rectangular in shape in the embodiment shown in Figure 2 and are sealed to one another about their periphery forming seals 125. The seals 125 circumvent a central volume 122 formed between the sheets 124a, 124b. This volume 122 is equivalent to the third chamber described above in relation to container 22 and contains a volume of propellant which is predominantly in its liquid phase at the operating temperature of the syringe (e.g. ambient temperature) due to being in the sealed volume 122. However, given that some of the propellant will be in gaseous form due to vaporization, the propellant will exert an outward pressure from within the volume 122. Therefore, the seals 125 must be sufficient to prevent substantial loss of propellant from the volume 122. Indeed, an ideal seal 125 will entirely prevent propellant escaping therethrough from the volume 122, however in practice, the seals 125 may be such that a finite, albeit acceptable and not substantial, amount of propellant may escape from the volume 122. The magnitude of "acceptable" amount will depend upon the perceived shelf life of the container (i.e. the length of time that the container 121 may remain in storage following manufacture prior to use), and the volume of propellant required to perform the desired action.

[0071] The material that forms the sheets 124a, 124b is flexible and rupturable such that once ruptured (i.e. broken, torn or otherwise penetrated) a fluid pathway is provided therethrough into the volume 122 that is not resealable. The rupturable wall 124 is preferably substantially impermeable to the propellant contained in the volume 122. The actual gas permeability of the rupturable wall 124 may depend upon the chosen propellant contained in the volume 122. For example, for HFA 134a, it is preferable for the rupturable wall to have a gas permeability such that the volume of propellant remaining in the container 121 is sufficient to reliably deliver a dose of medicament. Therefore, the limitations on the gas permeability of the rupturable wall 124 are determined by the intended volume of medicament to be delivered and the initial volume of propellant contained in the container 121. To deliver a 1 ml dose of medicament, it is particularly preferable to ensure that there is at least 20 μ l of propellant in the container 121.

Therefore, over a two year storage period, a container 121 initially containing 100 µl of HFA propellant may lose up to 80 µl as gas through the rupturable wall 124 for there to be at least 20 µl remaining to deliver the 1 ml dose of medicament. In this example, the maximum gas permeability of the container 121 would be 0.365 g/(m².day). Whilst it would be preferable to have at least 20 µl of HFA propellant remaining after two years for delivering a 1 ml dose of medicament, a container 121 having a gas permeability that ensures that there is 5 µl or more of HFA propellant may be sufficient to ensure that enough propellant will remain after two years to deliver a 1 ml dose of medicament.

[0072] The rupturable wall 124 may include polyethylene and/or may include a polyamide and/or may include nylon and/or may include a cyclic olefin copolymer (COC) and/or may include a cyclic olefin polymer (COP). In some preferable embodiments, the rupturable wall may be composed substantially of nylon. In alternative embodiments, one or each sheet 124a, 124b may be formed of a laminate of two or more different materials selected from polyethylene, polyamide, and metals (e.g. a metallic foil). The selection of the two or more materials may be based upon one of the layers providing a substantially impermeable gas barrier to prevent the propellant from escaping from the volume 122, and another of the layers providing mechanical strength to resist the outward pressure exerted by gaseous propellant in the volume 122. The rupturable wall 124 may be formed by co-extruding two or more materials.

[0073] Regardless of the type of material selected to form the rupturable wall 124, the seals 125 are formed between two like materials. So, in the case where one or both of the sheets 124a, 124b comprise laminates of two or more materials, the sheets 124a, 124b are arranged such that the interface between them comprises two adjacent like materials which may form the seals 125. The seals 125 may be formed by any of heat sealing, sonic welding or by use of an adhesive.

[0074] The shape of the container 121 may differ from that shown in Figure 2. Indeed, any suitable shape that is able to contain the propellant in the volume 122 sealed by the seals 125 may be used in accordance with the present invention. However, the shape of the container should be such that the outward pressure exerted by the propellant is resisted to ensure that such pressure does not inadvertently rupture the container 121.

[0075] Figure 3 shows a container 221 in accordance with an alternative embodiment of the present invention. The container 221 has a generally cylindrical rupturable wall 224 that is pinched at either end to form seals 225 that are sealed by one of the above described sealing methods. The rupturable wall 224 defines a central volume 222 for containing fluid propellant that, again, is equivalent to the third chamber 22 of embodiments described above. The rupturable wall may be formed from the materials described above in connection with rupturable wall 124 of the embodiment of Figure 2. The container 221 has the advantage that fewer seals

125 are required since a single cylindrical piece of material is used to form the rupturable wall 224. Therefore, there are fewer potential leak paths that the propellant may escape the volume 222 through.

[0076] Either of the containers 121 and 221 may be used in any of the syringes described above in accordance with the present invention. Alternatively, the containers 121,221 may be used in other applications, including other medical devices. In particular, the containers 121,221 may be used as a power source in inhaler-type devices (e.g. nasal inhalers).

[0077] The containers 121,221 provide a small, convenient, portable, cost effective power source that may be used in a plethora of devices. For a re-usable syringe, for example, the containers 121,221 offer a simple and effective means to power the syringe over multiple uses, where the user removes a ruptured container 121,221 following an injection and replaces it with a new unruptured container 121,221 prior to the next use.

[0078] The propellant used in the containers 121,221 and indeed in any of the syringes described above may be any propellant that boils at a predetermined temperature. In preferable embodiments, the propellant is or contains HFA and further preferable is or contains HFA 134a. Indeed, mixtures of several propellant substances or propellant substances and additives may provide a propellant for use in accordance with the present invention. As described above, the propellant may be chosen to be one that boils at ambient temperature or one that boils at a temperature higher than ambient temperature, in which case a further heat source is required to cause the propellant to boil and move the stopper 16.

[0079] A schematic representation of a method of manufacturing a container, such as the container 221 shown in Figure 3, is shown in Figures 13A to 13D. Figure 13A shows an extruded tube 224 formed of a rupturable material that has been sealed at a lower end by a lower seal 225a. There are first sealing elements 306 and second sealing elements 308 positioned around the tube 224. The tube 224 defines a central volume 222 therein. A piercing element 302 is provided that is adapted to form an opening 304 through the material of the tube 224 so as to provide a fluidic channel between the central volume 222 and the outside of the tube 224.

[0080] The method includes the steps of using the piercing element 302 to form the opening 304. The tube 224 may be pressurized (i.e. a gaseous pressure may be applied in the central volume 222) to increase its rigidity so as to permit effective use of the piercing element 302. The opening 304 may be formed so that a complete hole is not created. This is not essential, but forming an opening 304 that does not result in the formation of loose material (a so-called "chad") minimizes the risk of loose material entering the central volume 222 and/or interfering with the manufacturing process. A horse-shoe shaped (i.e. U-shaped) opening 304 is one suitable opening that does result in chad formation. In one example, the piercing element 302

is a hypodermic needle.

[0081] The first sealing elements 304 may then be used to form a first upper seal 225b above (i.e. upstream) of the opening 304 as shown in Figure 13B. Substantially simultaneously, a propellant dispensing head 310 (which is connected to a source of propellant – not shown) is inserted into the opening 304 and seals the opening 304. The propellant dispensing head 310 may comprise seal rings to aid the sealing of the opening 304. In alternative embodiments, the propellant dispensing head 310 may additionally have the feature of being the piercing element 302 and may form the opening 304 at this stage (i.e. subsequent to the formation of the first upper seal 225b).

[0082] As shown in Figure 13C, a predetermined dose of propellant 300 is then introduced into the central volume 222 to fill the tube 224 to the desired level. A second upper seal 225c is then formed by second sealing element 308 below (i.e. downstream) each of the first upper seal 225b and the opening 304. After formation of the second upper seal 225c, the central volume 222 containing the propellant 300 is sealed at an upper end by second upper seal 225c and at a lower end by the lower seal 225a thus forming a propellant container 221. The container 221 may be cut along lower seal 225a and second upper seal 225c to separate the container 221.

[0083] The tube 224 is oriented with its longitudinal axis substantially parallel to the (gravitational) vertical so that the propellant 300 condenses at a lower end of the tube 224. With this arrangement, the second upper seal 225c can be formed above the level of liquid propellant and therefore reduces the risk of liquid propellant leaking from the tube 224 during formation of the container 221.

[0084] The extruded tube may be moved relative to the first sealing elements 306, second sealing elements 308, piercing element 302 and/or propellant dispensing head 310 so that the first upper seal 225b of the tube 224 becomes the lower seal 225a' of a subsequent tube 224' and the process can begin again to fill the subsequent tube 224'. The container 221 (and subsequent containers) can be cut/removed from the production line following their filling and sealing and prior to the filling and sealing of a subsequent container. Alternatively, several containers may be filled and sealed before being separated by cutting or otherwise separating along the seals. Thus, a continuous string of containers can be formed that are each easily handled and cut as required. The pitch of the containers (e.g. the distance between lower seal 225a and second upper seal 225c for container 221) may be altered to change the magnitude of the central volume 222 in accordance with the desired dose of propellant 300.

[0085] The first and second sealing elements 306, 308 may be any suitable sealing apparatus that are capable of forming heat seals, sonic welds or other seals, such as adhesive seals. The first and second sealing elements 306, 308 need not necessarily be capable of forming the same type of seal as one another.

[0086] A schematic representation of an alternative method of manufacturing a container, such as the container 121 shown in Figure 2, is shown in Figures 14A to 14C. Figure 14A shows two sheets 124a, 124b of like material being brought together by a set of rollers 412 rotating in direction R. Although the cross-sectional views shown in Figures 14A and 14B show only two rollers 412, the set actually comprises four rollers 412 as shown in the perspective view of Figure 14C. The rollers 412 are arranged in pairs such that the two sheets 124a, 124b of material come together between the pairs, where the two rollers of each pair are spaced and arranged along edges of the sheets 124a, 124b. The rotation of the rollers 412 along direction R causes the sheets 124a, 124b to come together with one another along their edges (which are coincident with the position of the rollers 412) and move downwards along direction D. The edges of the sheets 124a, 124b seal to one another to form side seals 125b, 125c. The rollers 412 may comprise means to form the side seals 125b, 125c or additional sealing apparatus may be employed to form the side seals 125b, 125c.

[0087] Sealing elements 408 seal the sheets 124a, 124b together across their entire width to form a lower seal 125a. A propellant dispensing head 410 is arranged between the sheets 124a, 124b and between the four rollers 412 and is arranged relative to the sheets 124a, 124b and the rollers 412 so that the sheets 124a, 124b form a seal with one another or the propellant dispensing head 410. The result is that a sealed central volume 122 is formed that is initially defined by the seals 125a, 125b, 125c and the seals between the sheets 124a, 124b and the propellant dispensing head 410.

In this position, the propellant dispensing head 410 is able to deposit a desired dose of propellant 300 into the central volume 122. Once the desired dose of propellant 300 has been deposited, the propellant dispensing head 410 may be switched off preventing further deposition of propellant 300 and the sealing elements 408 may then seal the sheets 124a, 124b above the deposited propellant 300 to form an upper seal 125d. This forms a container 121 that has a central volume 122 containing propellant 300 where the central volume 122 is defined by seals 125a, 125b, 125c, 125d. Any or all of the seals 125a, 125b, 125c, 125d may be heat seals, sonic welds or other seals, such as adhesive seals. In the non-limiting preferable embodiment shown in Figures 14A to 14C, the sealing element 408 includes a clamping part 408a and a sealing part 408b. The clamping part 408a may act independently of the sealing part 408b to mechanically clamp the sheets 124a, 124b together to isolate the propellant 300 contained in the central volume from the sealing part 408b. In this preferable embodiment, a more effective seal may be made by the sealing part 408b due to the absence of propellant. Indeed, in any method of manufacturing a container in accordance with the present invention (including that described above in relation to Figures 13A to 13D), it is preferable to use a clamp to isolate the propellant contained in the container prior to forming the (final) upper seal. Once the upper seal 125d has

been made, the clamping part 408a may be removed. The clamping part 408a and the sealing part 408b may be part of a single apparatus such as the sealing element 408 of Figures 14A to 14C, or, in other embodiments, they may be entirely separate and independent components.

[0088] The upper seal 125d may then form the lower seal 125a' of a subsequent container 121' (see Figure 14C) so that the process may be repeated to produce a series of connected containers 121, 121', ..., etc. Lower and upper seals 125a, 125d may be cut or otherwise severed to separate each container 121. This separation may be done when a series of containers has been produced or after the formation of each container 121.

[0089] The pitch of the containers (e.g. the distance between lower seal 125a and upper seal 125c) may be altered to change the magnitude of the central volume 122 in accordance with the desired dose of propellant 300.

[0090] Figures 15A to 15E show the various stages of manufacture of a container 121 in accordance with an alternative related embodiment. In Figure 15A, a laminate 128 is shown which comprises two sheets of rupturable material that are sealed together along seals 125 defining a volume 122 therebetween. In Figures 15A to 15E, only an upper sheet 124a of the laminate 128 is visible. The seals 125 include a lower seal 125a, two side seals 125b, 125c and a temporary upper seal 125d'. In some embodiments, the temporary upper seal 125d' may not be present. The seals 125 define a blister portion 126a, a neck portion 126b and a filling portion 126c. In the preferable embodiment shown in Figures 15A to 15E, the neck portion 126b is narrower compared with the blister portion 126a and the filling portion 126c. However, in alternative embodiments within the scope of the present invention, the neck portion 126b may not be narrower. The two sheets of rupturable material may be preformed (e.g. by vacuum forming) to define a larger volume 122 when sealed together. In alternative embodiments, however, the two sheets may be substantially flat and may be sealed together leaving an unsealed area on each which defines the volume 122.

[0091] In the case of flat sheets the filling process plastically deforms the sheets to form the container. If the walls are particularly thick, they may resist the internal pressure which may make filling difficult due to the stiffness of the walls. Preforming a volume permits the use of thicker materials which may resist higher temperatures and/or pressures when formed into a container.

[0092] Figure 15B shows the laminate 128 of Figure 15A that has been cut so as to remove the temporary upper seal 125d' and thus create an opening 130 of the volume 122 suitable for receiving propellant from a filling apparatus. For example, a nozzle of a filling apparatus could be inserted into the opening 130 to dispense propellant into the volume 122. In any event, the filling apparatus should seal to the opening 130 during filling. Once propellant has been dispensed into the volume 122, the laminate 128 is clamped by a clamping device across line

127 as shown in Figure 15C. In the embodiment shown in Figures 15A to 15E, the line 127 crosses the neck portion 126b, however, in alternative embodiments, it may be at any suitable point between the lower seal 125a and the filling apparatus. The clamping device seals the propellant in the volume 122 between line 127 and the lower seal 125a with sufficient force so as to substantially prevent any propellant from escaping from the volume 122. However, the clamping force should be chosen such that the laminate 128 is not structurally damaged since this may lead to failure of the container 121 before or during use as a power source for a syringe. A narrow neck portion 126b permits a lower clamping force to be used that will provide an adequate temporary seal whilst minimizing the risk of accidental damage.

[0093] Once clamped, an upper seal 125d is created between the line 127 of the clamp and the filling apparatus across the side seals 125b, 125c. The clamp may then be removed to leave the volume 122 defined by the lower seal 125a, the side seals 125b, 125c and the upper seal 125d and containing the propellant. The formed container 121 may then be used as a power source in a syringe where the container 121 is ruptured to release propellant.

[0094] Between clamping along line 127 and forming the upper seal 125d, it is preferable to allow or cause any propellant present between line 127 and the intended area of the upper seal 125d to disperse. This may be achieved by waiting a predetermined time for such propellant to disperse, and/or heat or a vacuum may be applied to actively encourage the dispersal.

[0095] The steps outlined above in relation to Figures 15A to 15E separate the processes of filling the container 121 and sealing the container with the upper seal 125d. By utilizing the step of clamping the laminate across line 127, the potential problem of propellant damaging the upper seal 125d is avoided.

[0096] The seals 125 may be any suitable seals as described above, however heat seals are particularly preferable and suitable.

[0097] Throughout the description, claims and figures of this specification, 0 bar is considered to be defined as atmospheric pressure, so that all values of pressure given in bar are relative to atmospheric pressure (0 bar).

[0098] Throughout the present specification, the term “syringe” relates to and includes any medicament delivery device having a medicament container with an outlet and a moveable stopper for expelling medicament therefrom. As examples, the syringe may include a needle, a nozzle or a conduit attached to the outlet. In other embodiments, the syringe may not include any further components downstream of the outlet. The syringe of the present invention may be or form part of a subcutaneous delivery device, a nasal delivery device, an otic delivery device, an oral delivery device, an ocular delivery device, an infusion device or any other suitable medicament delivery device.

[0099] Throughout the description and claims of this specification, the words “comprise” and “contain” and variations of them mean “including but not limited to”, and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[00100] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[00101] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

CLAIMS

1. A method of manufacturing a container containing propellant comprising the steps of:
 - i) providing a container having an opening;
 - ii) placing a propellant dispensing apparatus in fluid communication with the opening;
 - iii) depositing liquid propellant in the container using said propellant dispensing apparatus;
 - iv) temporarily clamping the container to itself so as to substantially fluidly isolate a volume of dispensed liquid propellant in a central volume defined by the temporary clamp;
 - v) sealing the container to itself at a location that is not across the central volume; and
 - vi) removing the temporary clamp so as to leave propellant sealed in the container.
2. A method according to claim 1, wherein prior to step v), propellant present in the container that is not in the central volume is allowed to disperse.
3. A method according to claim 2, wherein heating is applied to encourage dispersal of propellant present in the container that is not in the central volume.
4. A method according to claim 2, wherein a vacuum is applied to remove propellant present in the container that is not in the central volume.
5. A method according to any one of claims 2 to 4, wherein a predetermined period of time is allowed to elapse between performing steps iv) and v) so as to allow dispersal of propellant present in the container that is not in the central volume.
6. A method according to any one of the preceding claims, wherein said propellant includes a hydrofluoroalkane (HFA).
7. A method according to claim 6, wherein said HFA is HFA 134a, HFA 422d, HFA 507c, or HFA 245fa.

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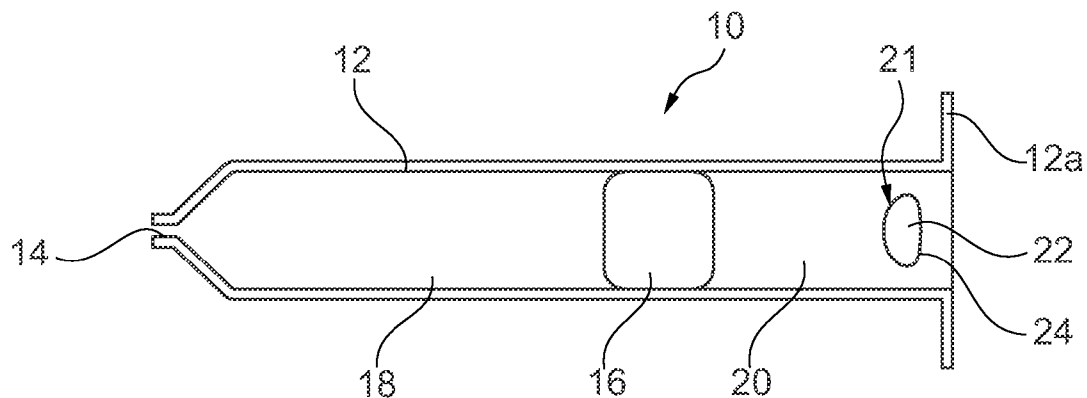


Fig. 1A

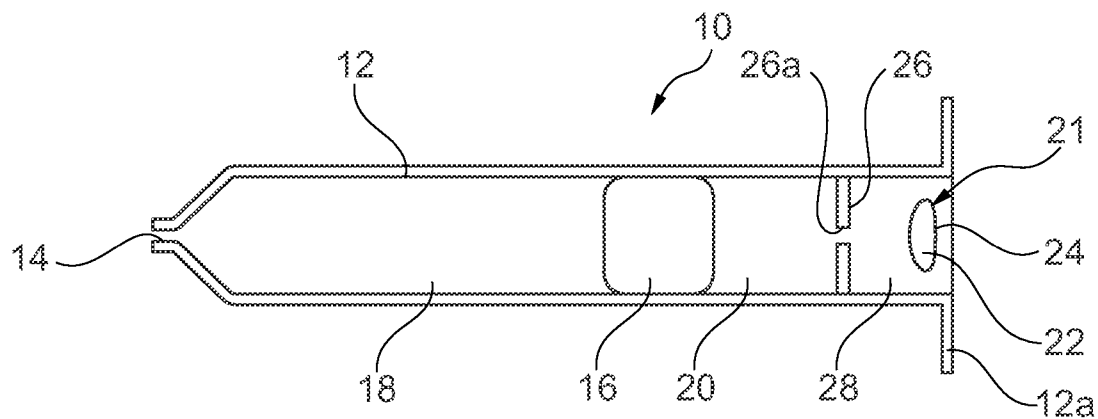


Fig. 1B

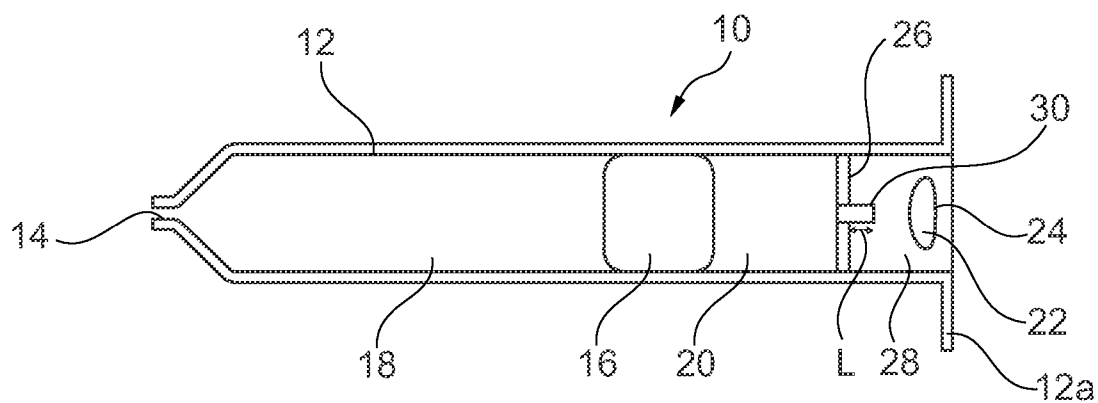


Fig. 1C

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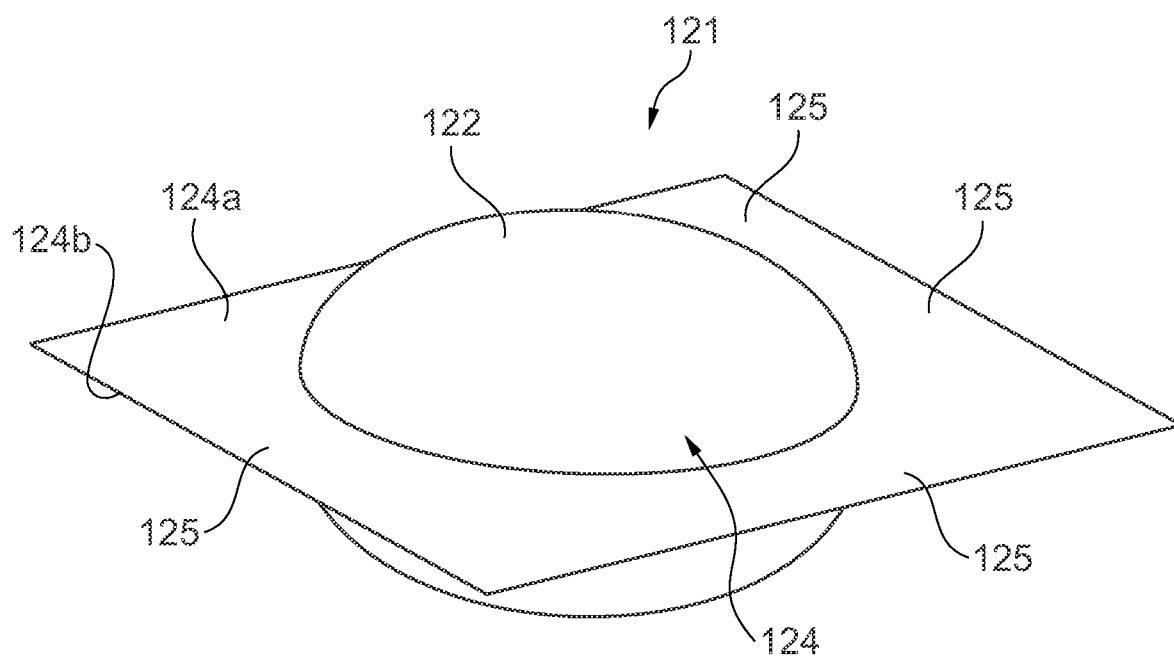


Fig. 2

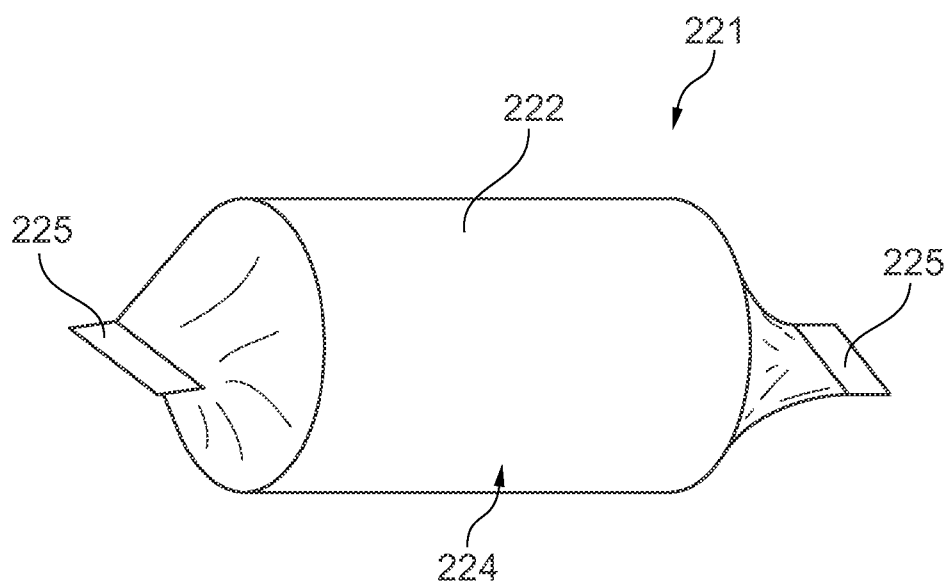


Fig. 3

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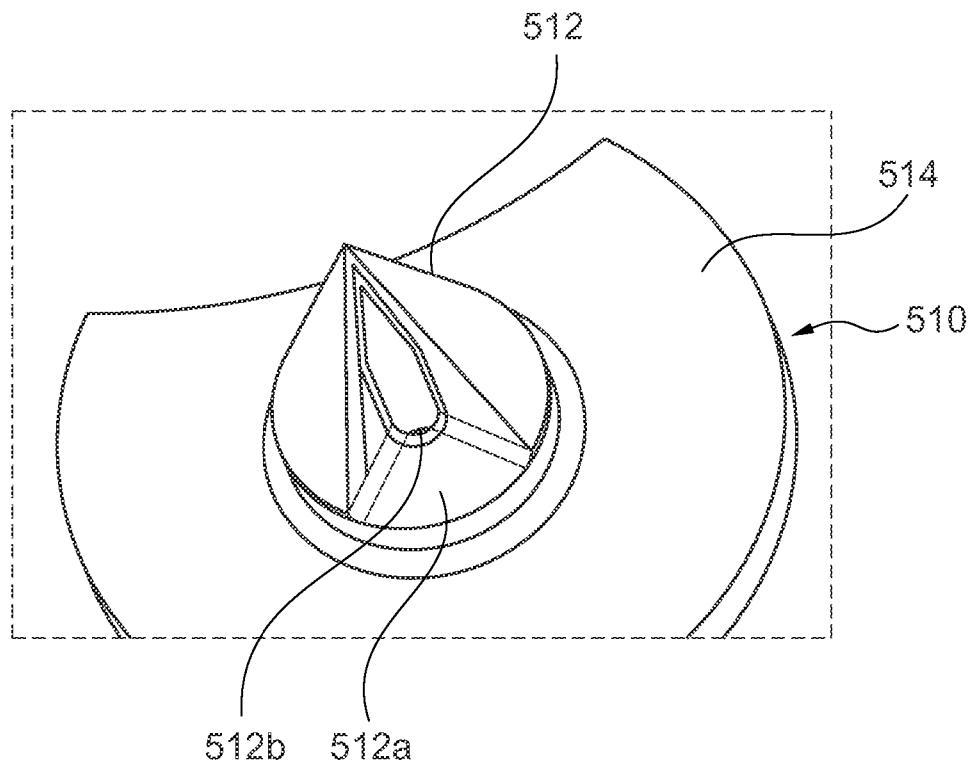


Fig. 4

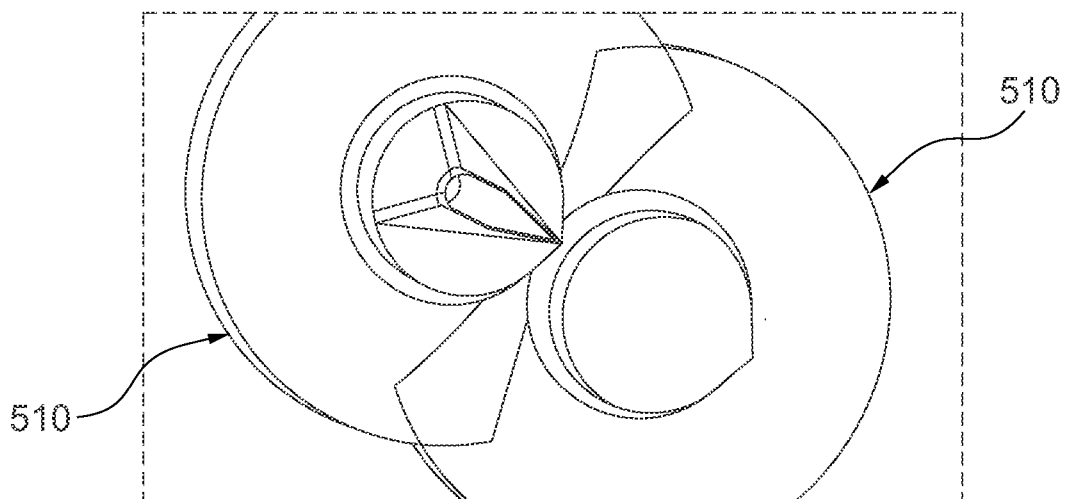


Fig. 5

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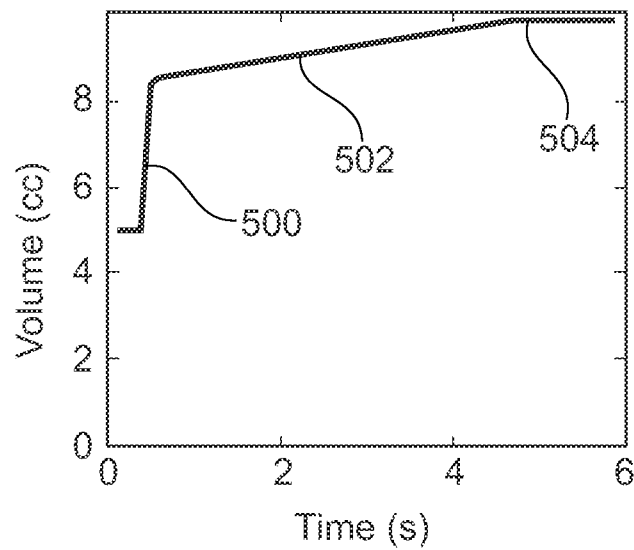


Fig. 6A
(PRIOR ART)

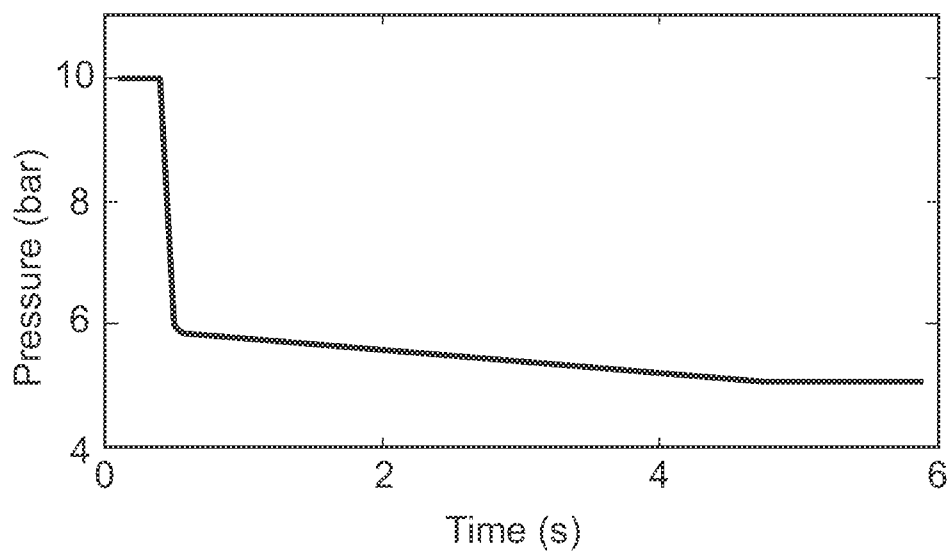


Fig. 6B
(PRIOR ART)

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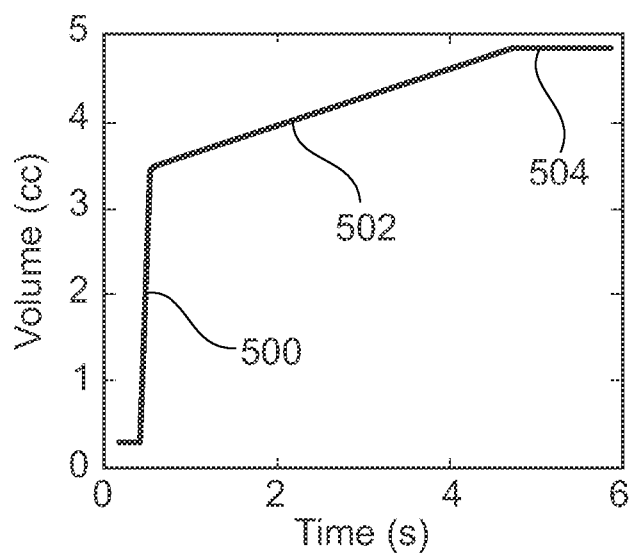


Fig. 7A
(PRIOR ART)

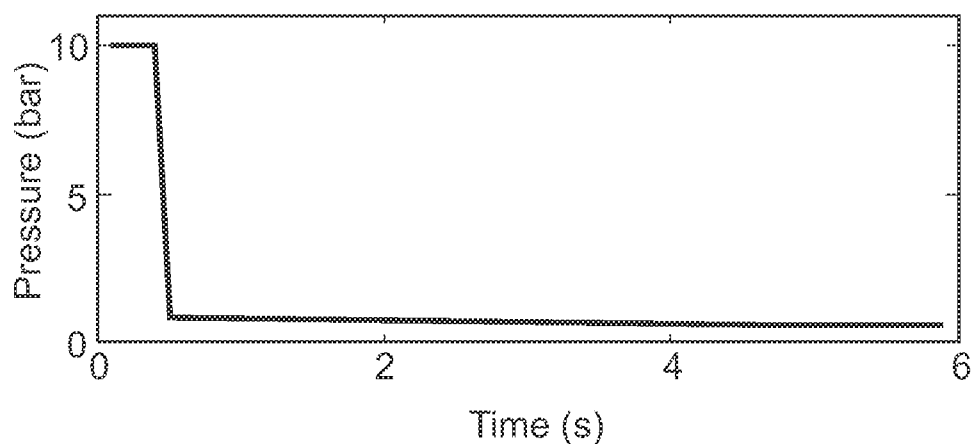


Fig. 7B
(PRIOR ART)

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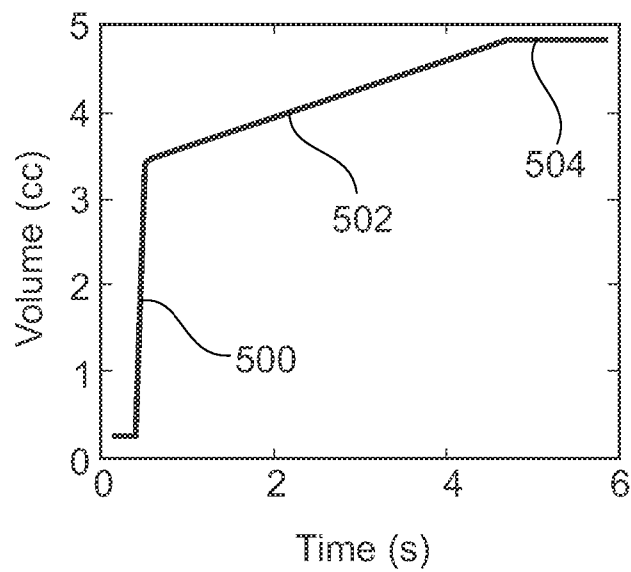


Fig. 8A

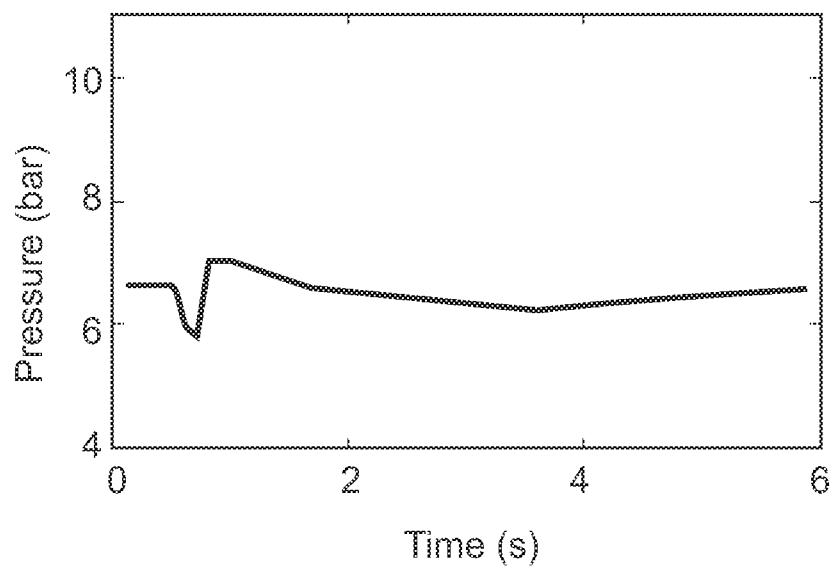


Fig. 8B

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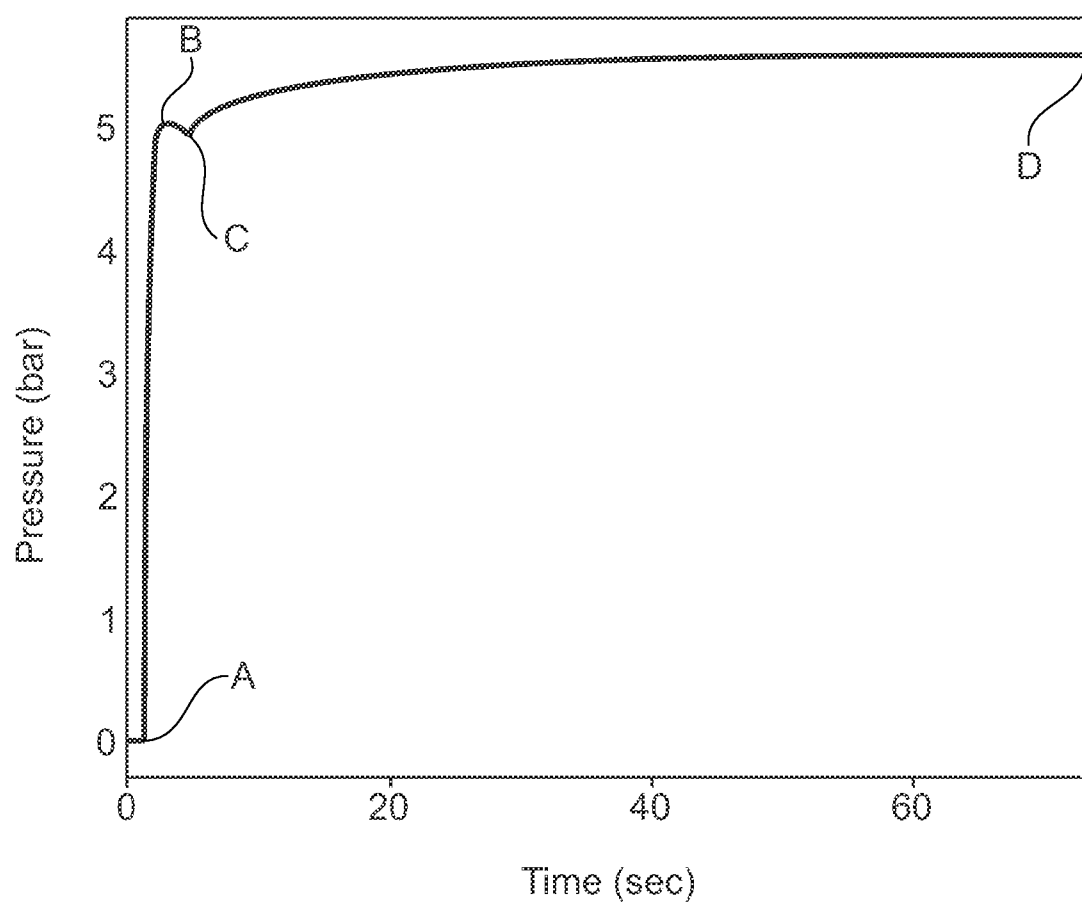


Fig. 9

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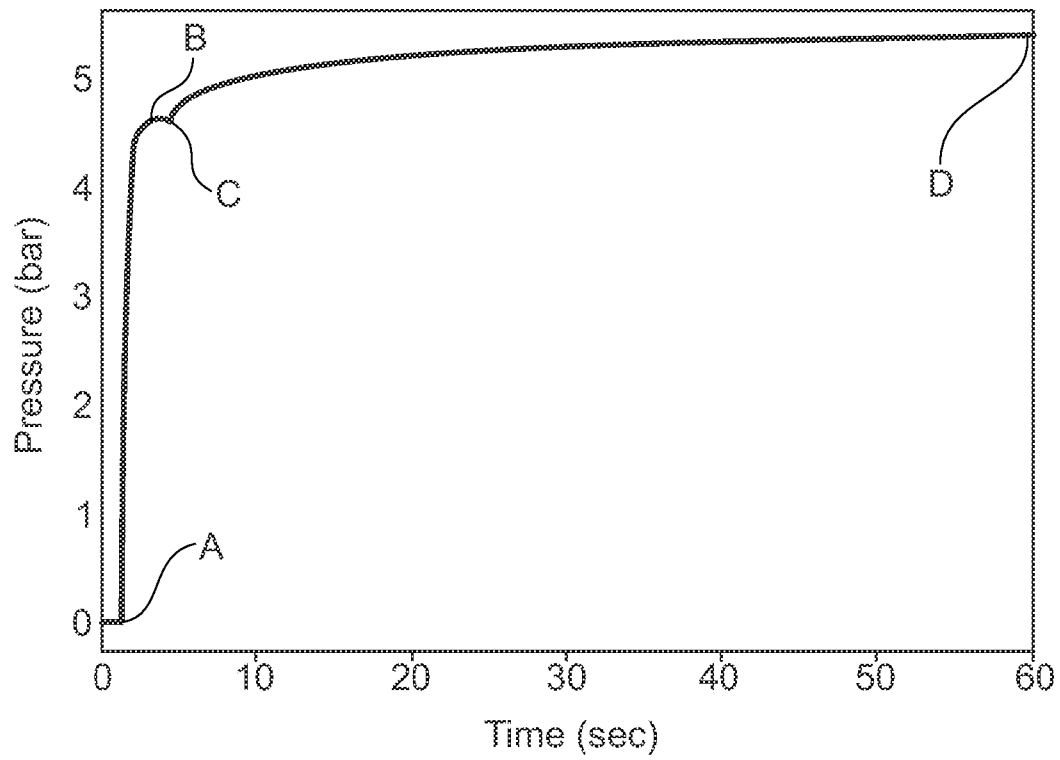


Fig. 10

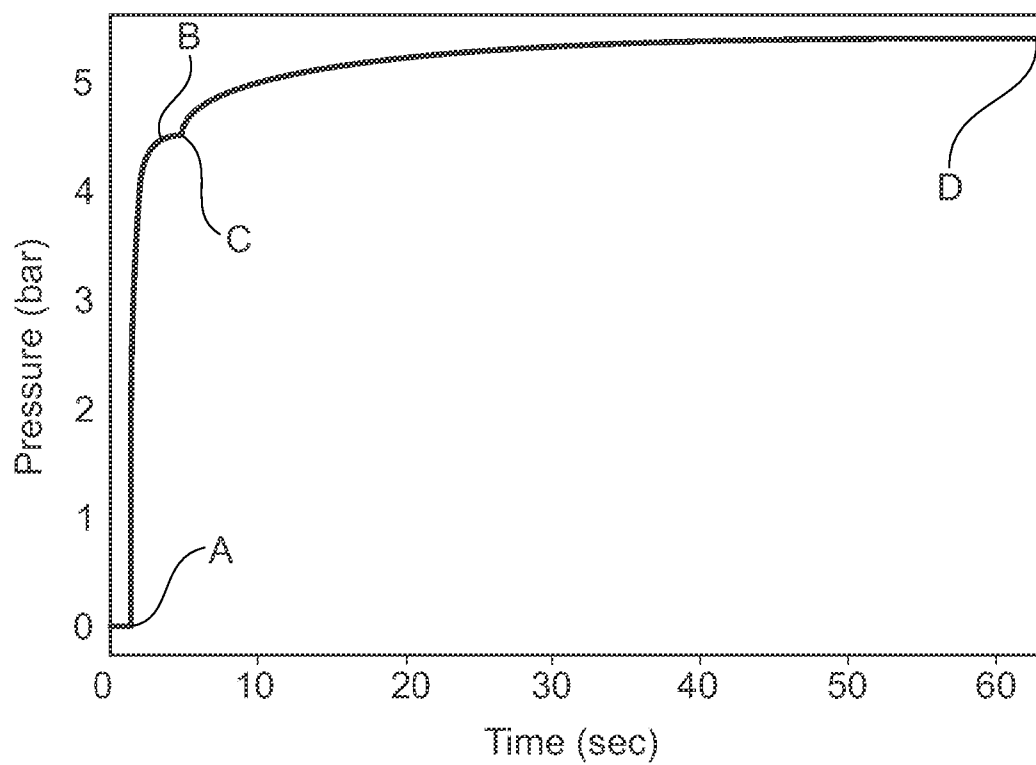


Fig. 11

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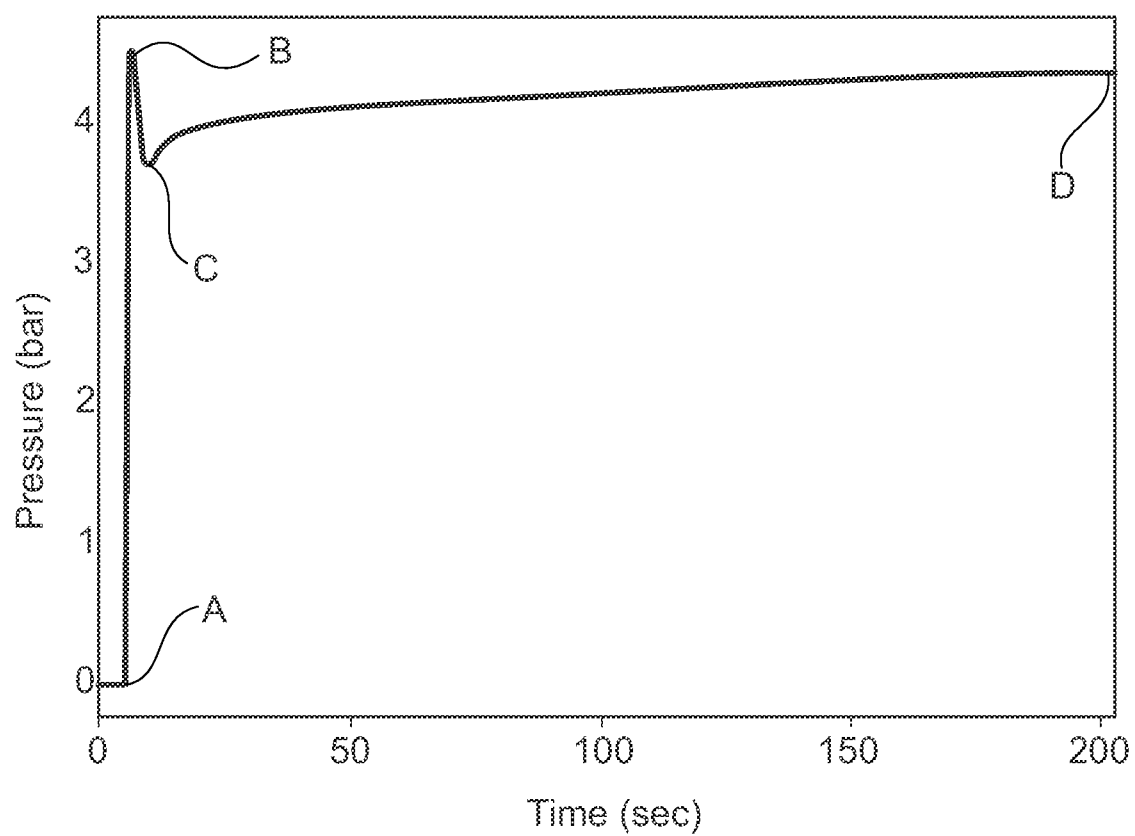


Fig. 12

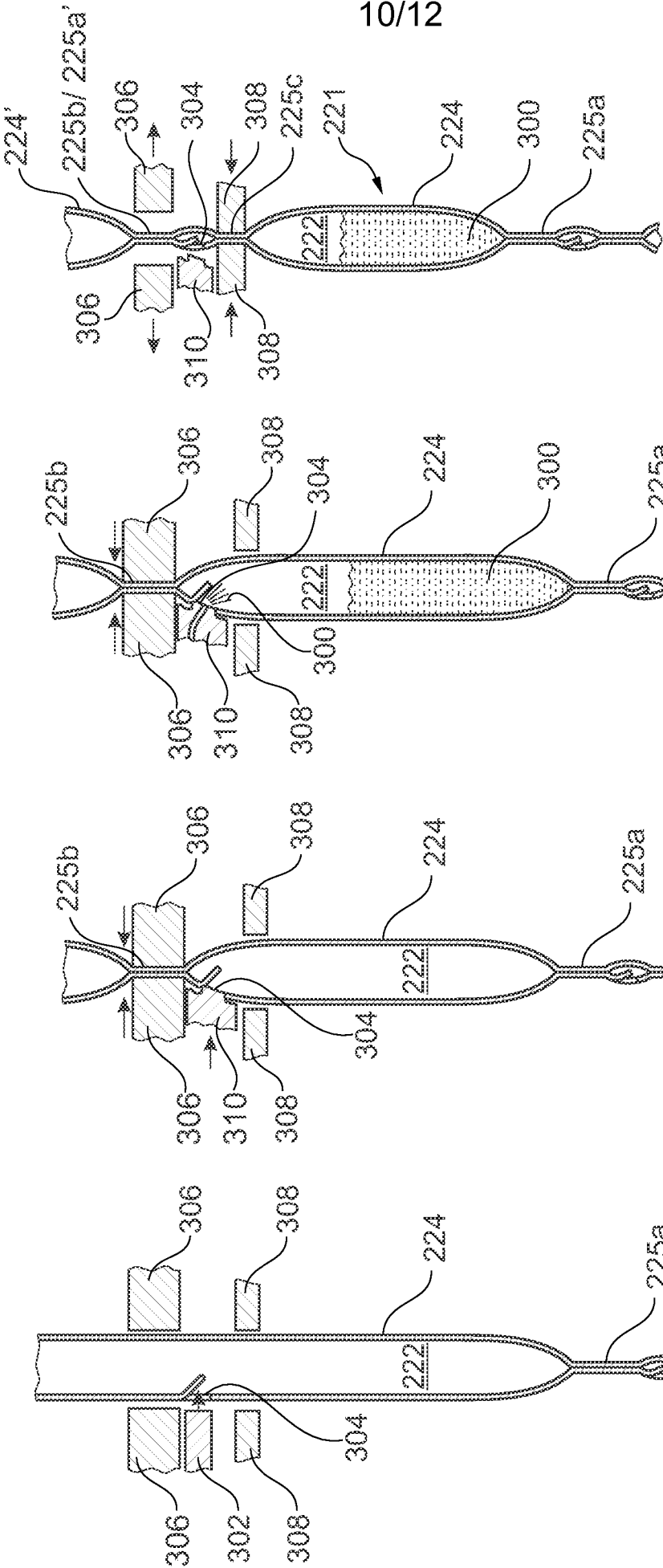


Fig. 13D

Fig. 13C

Fig. 13B

Fig. 13A

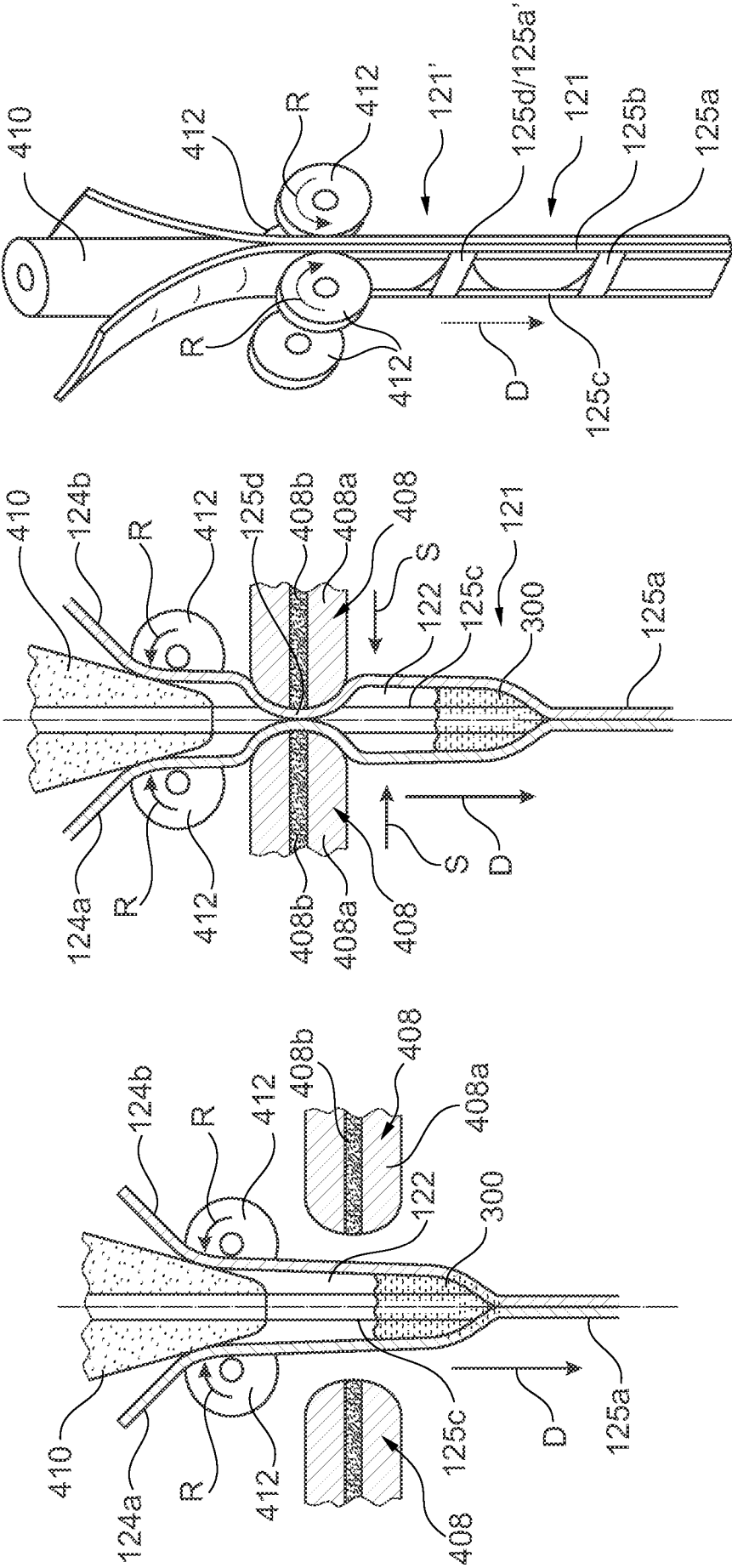


Fig. 14A

Fig. 14B

Fig. 14C

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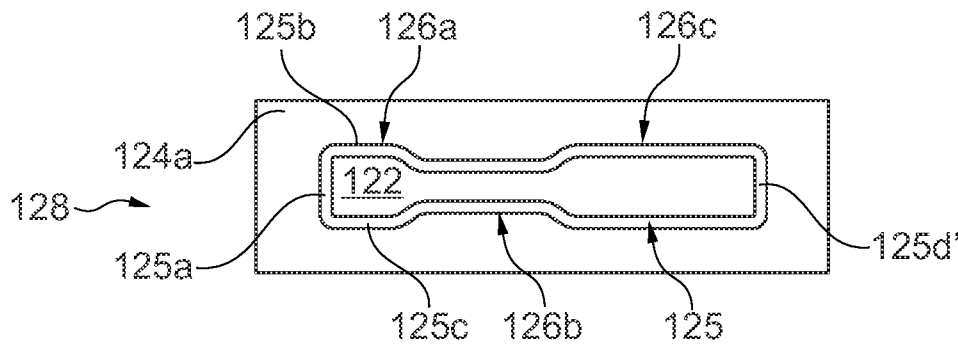


Fig. 15A

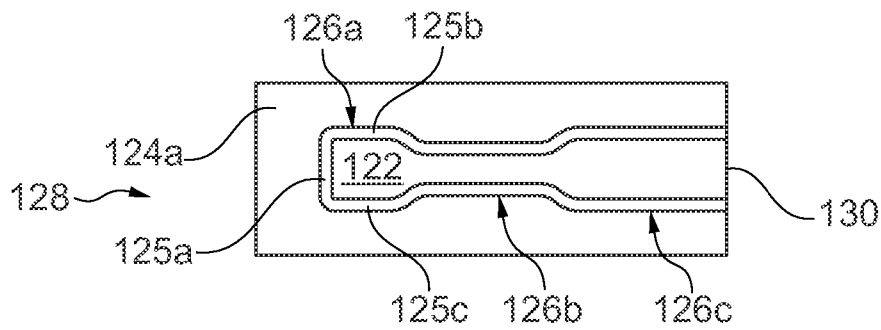


Fig. 15B

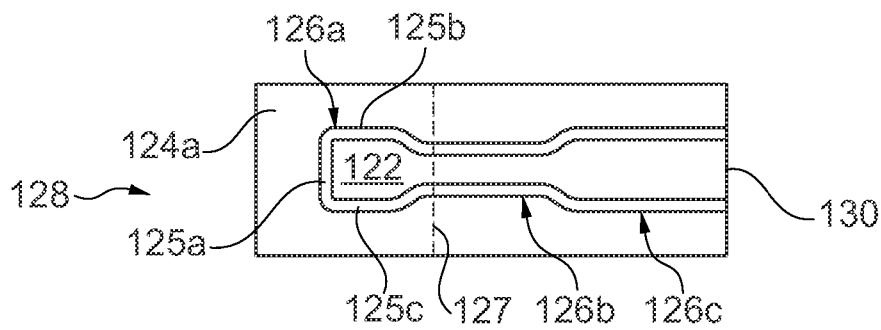


Fig. 15C

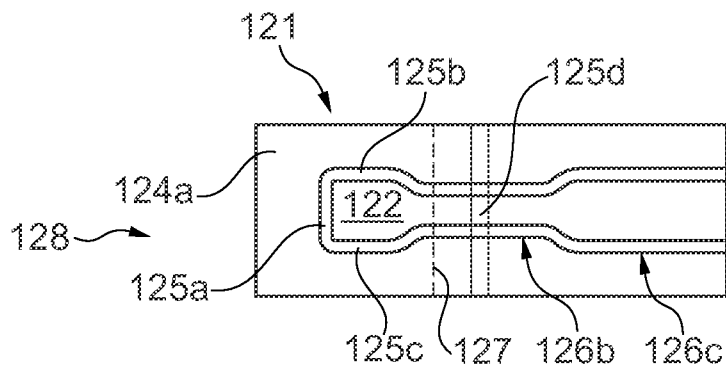


Fig. 15D

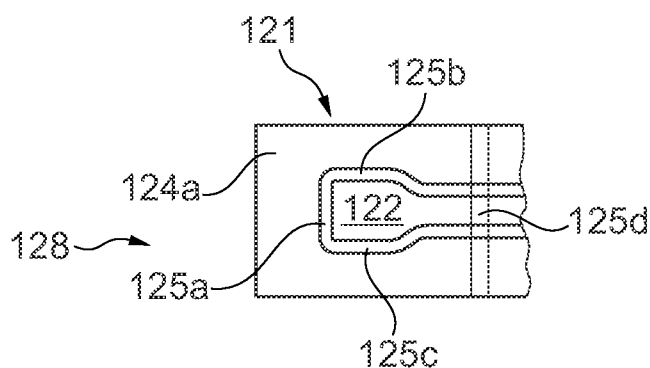


Fig. 15E