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(54) **METHOD OF MANUFACTURING A PROPELLANT CONTAINER**

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(57) **ABSTRACT**

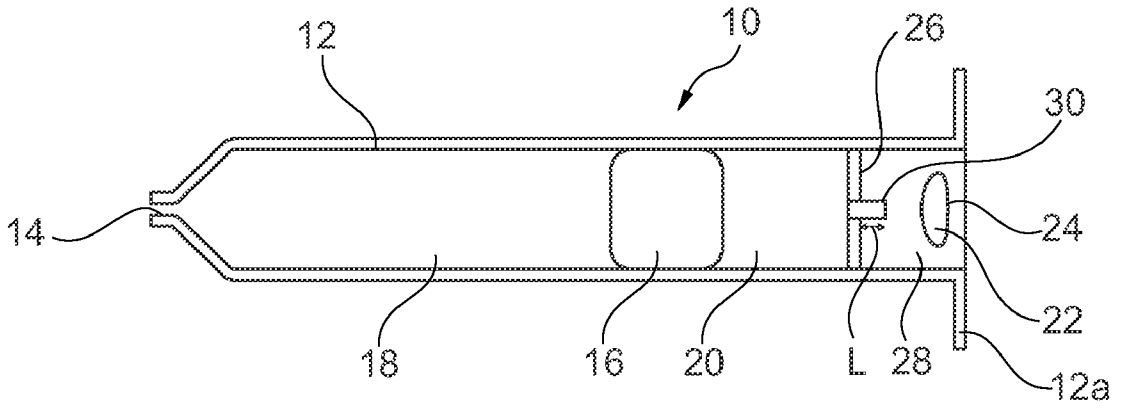
A method of manufacturing a container containing propellant includes

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, the 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 the 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 the upper seal, the lower seal, and the two side seals.



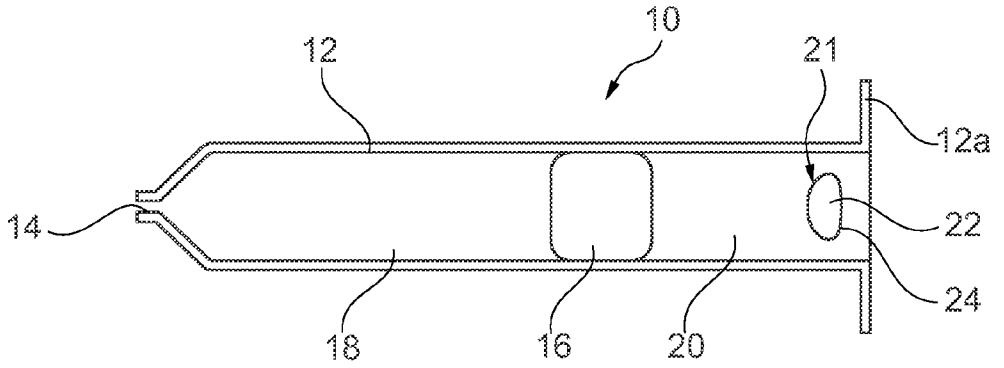


Fig. 1A

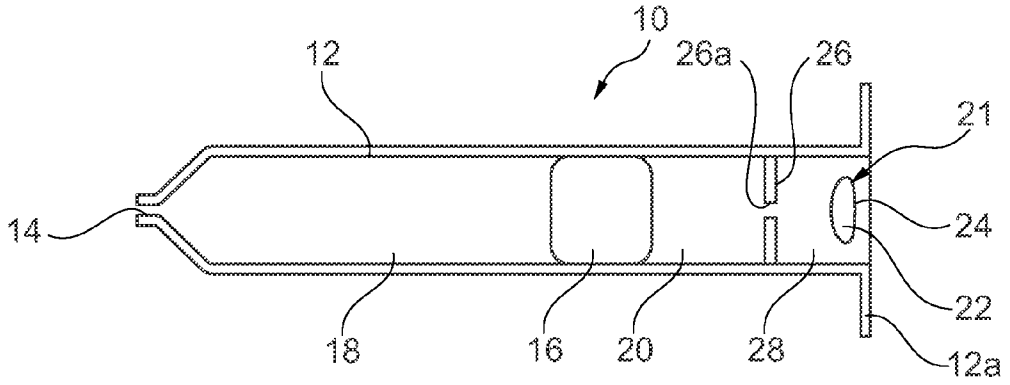


Fig. 1B

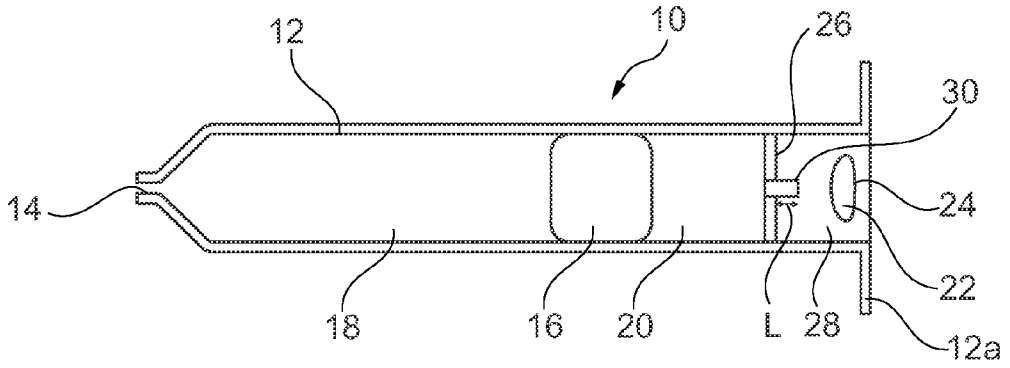


Fig. 1C

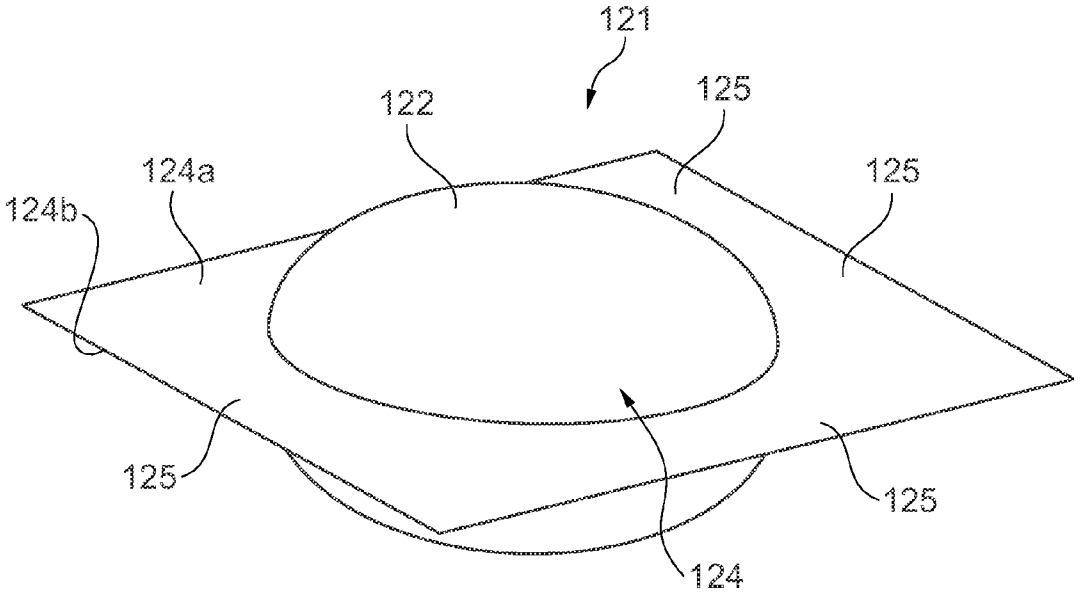


Fig. 2

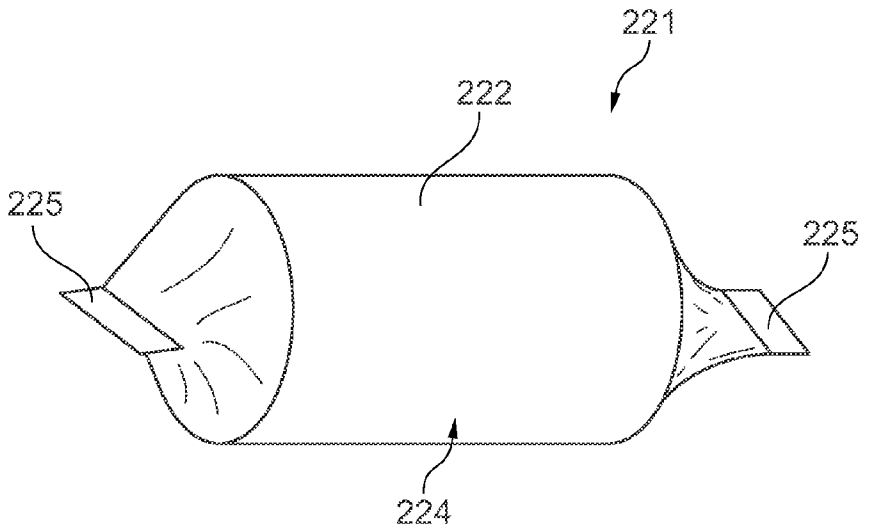


Fig. 3

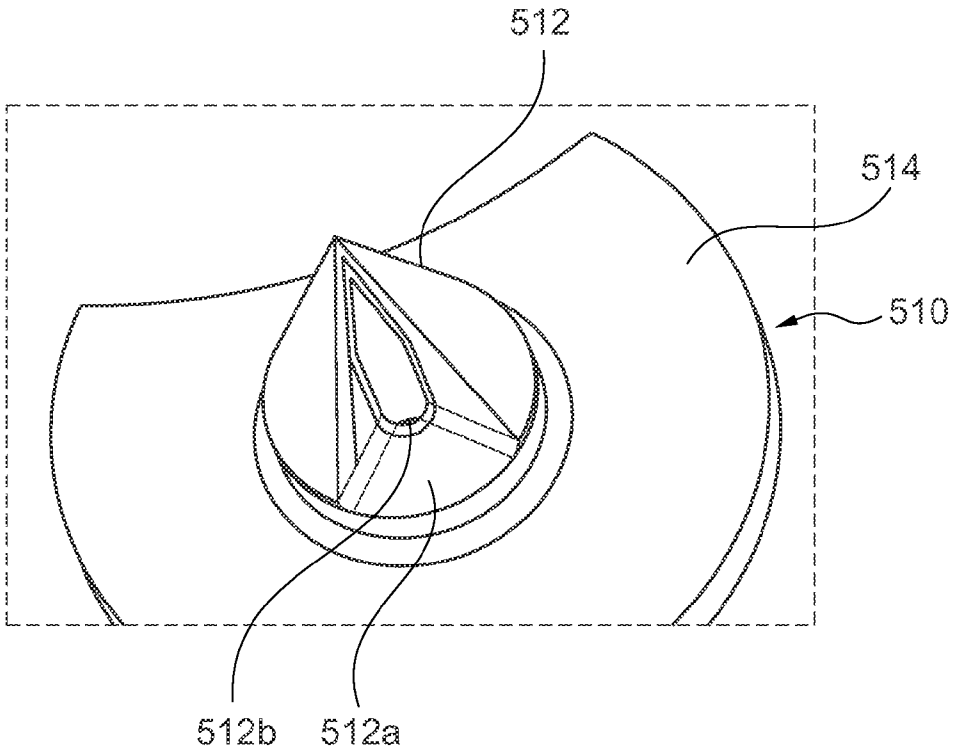


Fig. 4

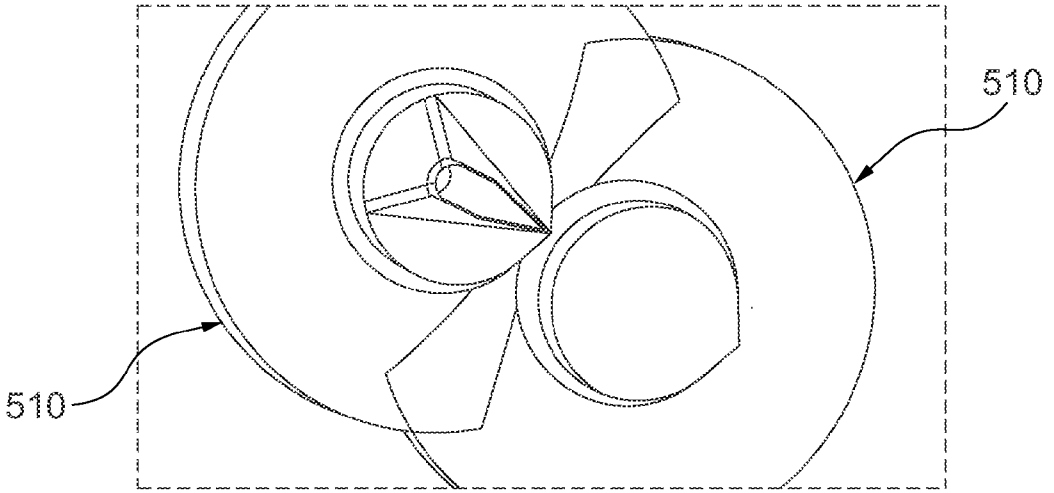


Fig. 5

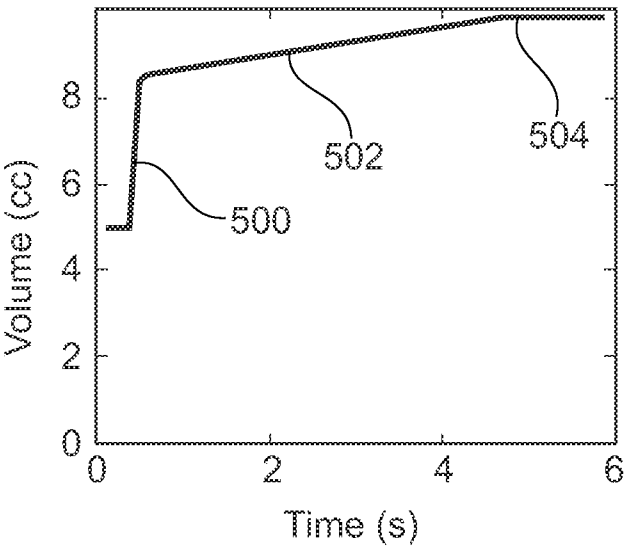


Fig. 6A
(PRIOR ART)

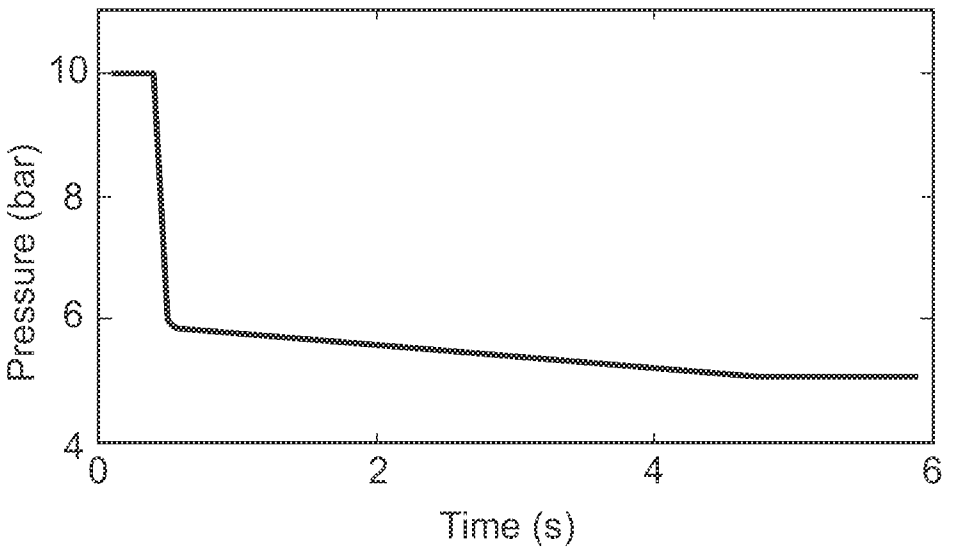


Fig. 6B
(PRIOR ART)

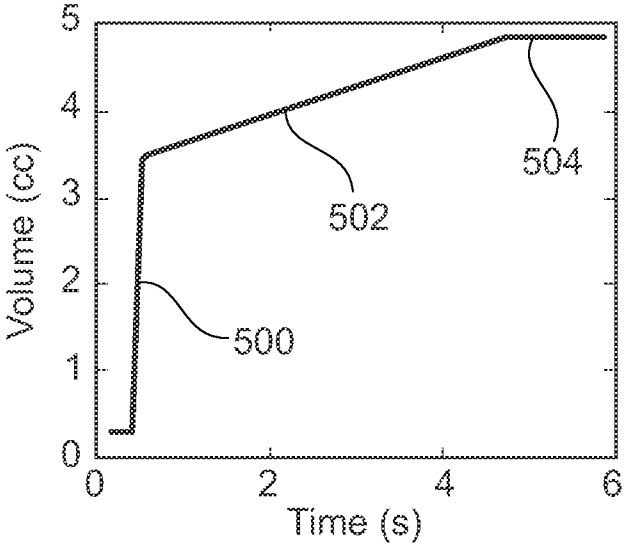


Fig. 7A
(PRIOR ART)

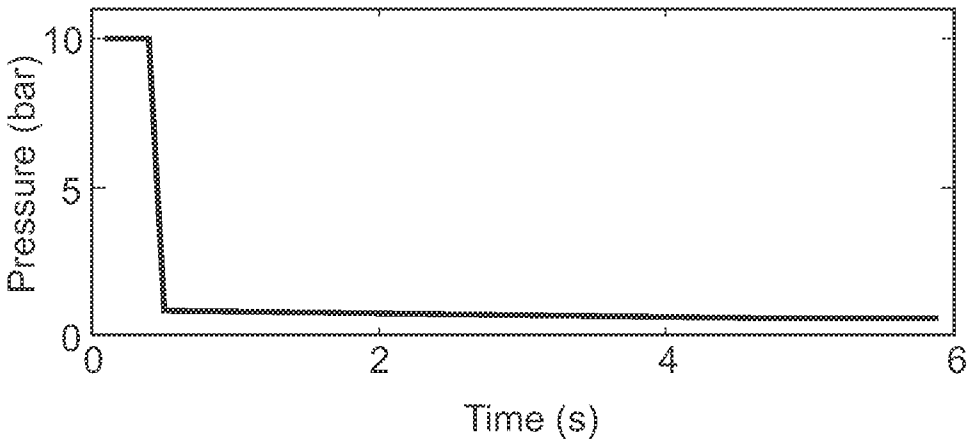


Fig. 7B
(PRIOR ART)

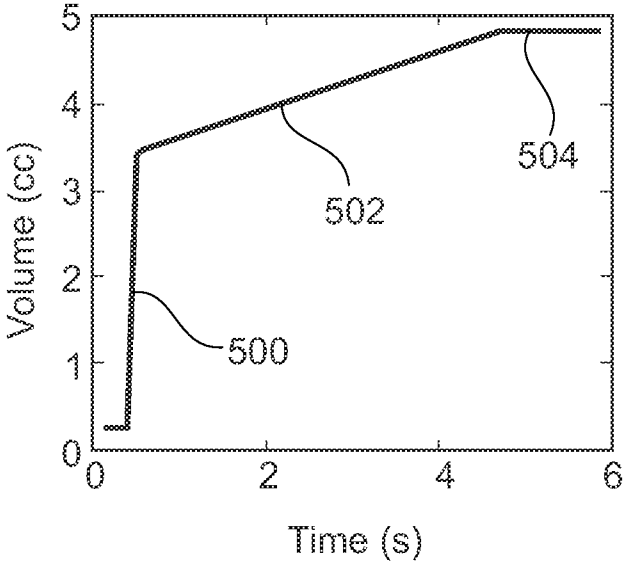

Volume (cc)
Time (s)
500
502
504
0
1
2
3
4
5
0
2
4
6

Fig. 8A

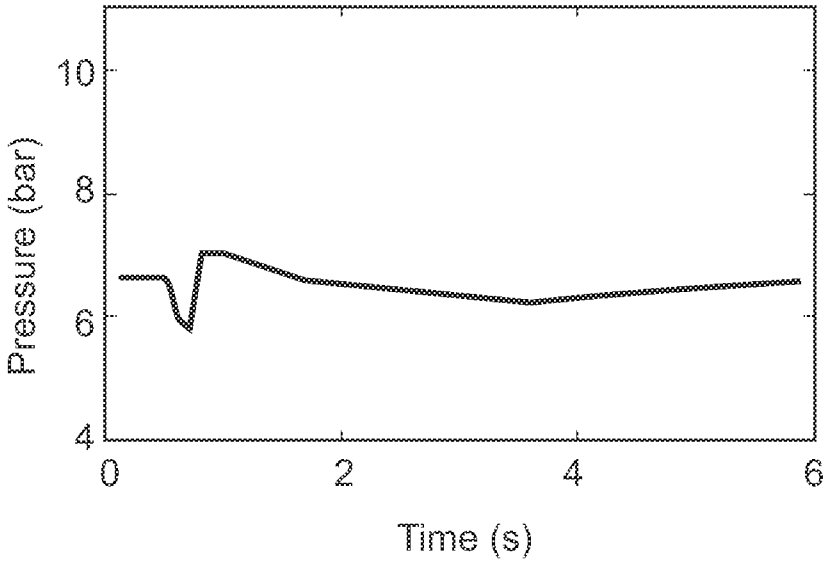

Pressure (bar)
Time (s)
4
6
8
10
0
2
4
6

Fig. 8B

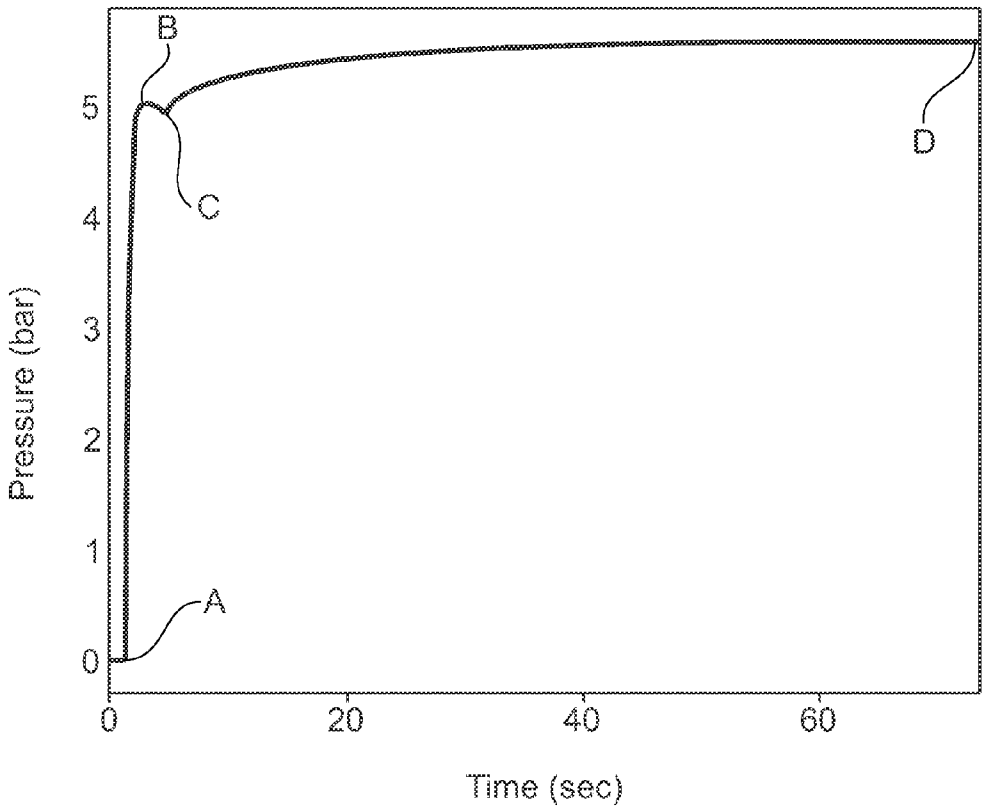


Fig. 9

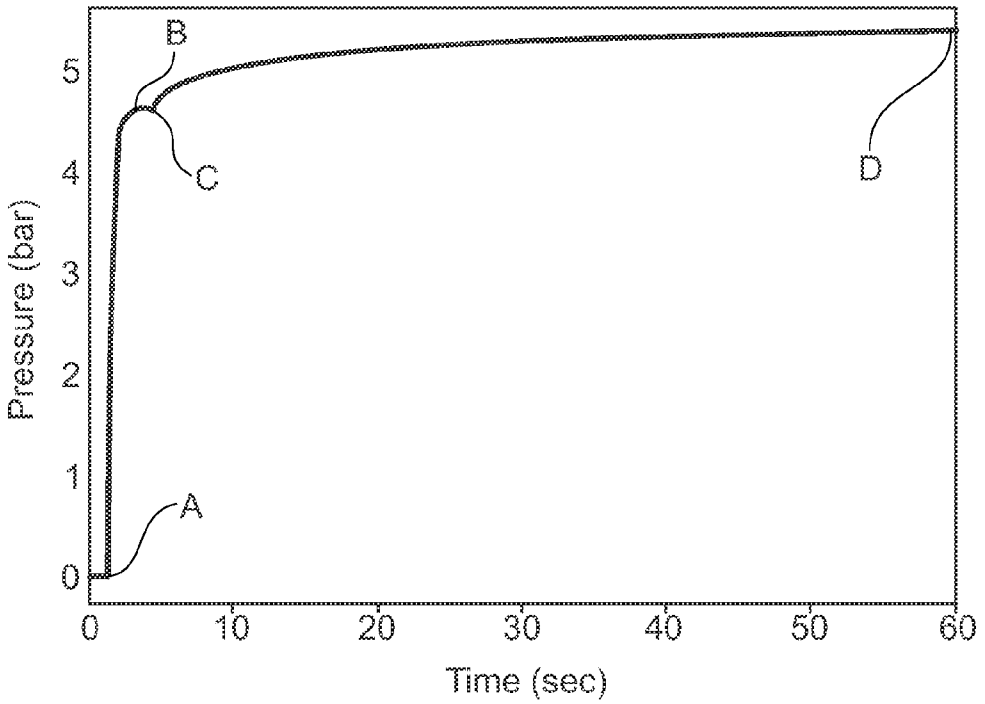

B
C
D
A
Pressure (bar)
0
1
2
3
4
5
0
10
20
30
40
50
60
Time (sec)

Fig. 10

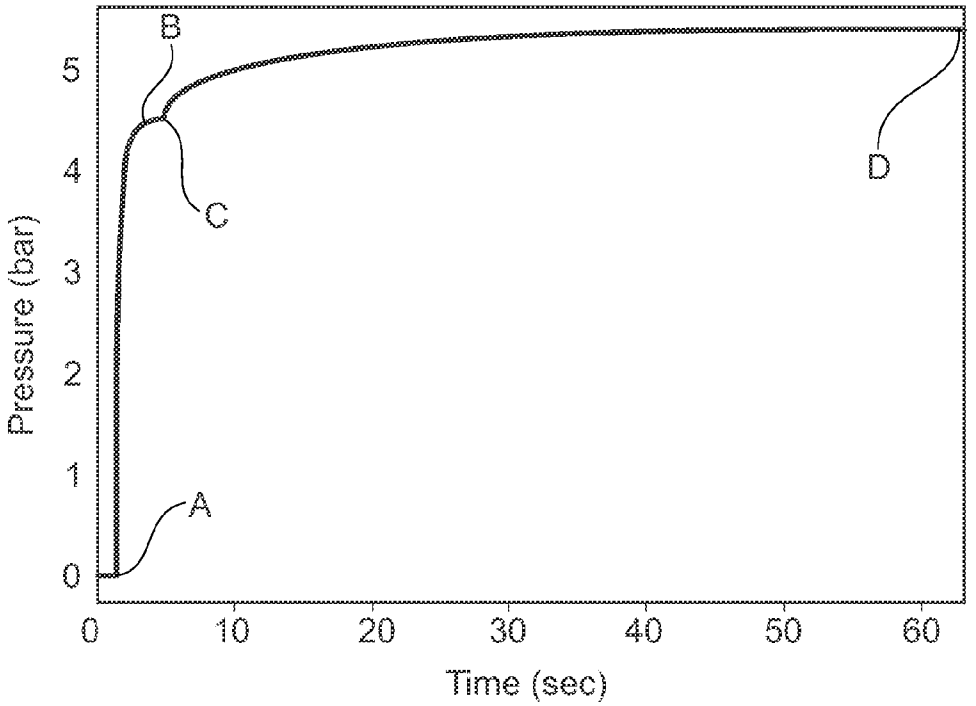

B
C
D
A
Pressure (bar)
0
1
2
3
4
5
0
10
20
30
40
50
60
Time (sec)

Fig. 11

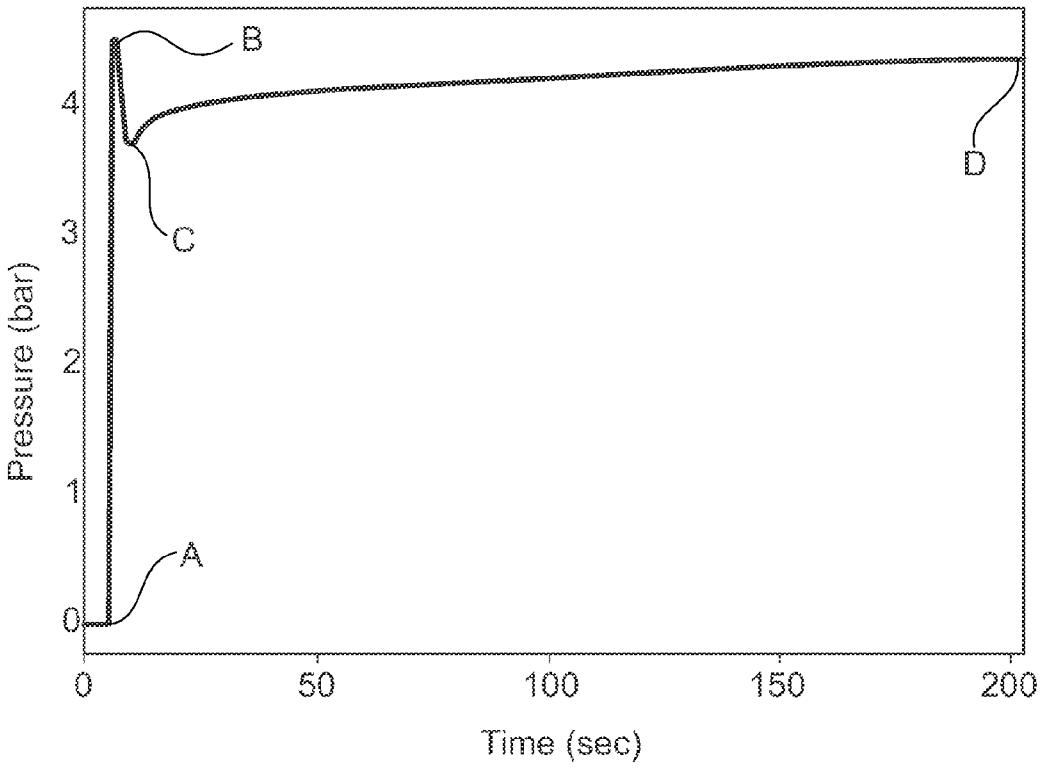


Fig. 12

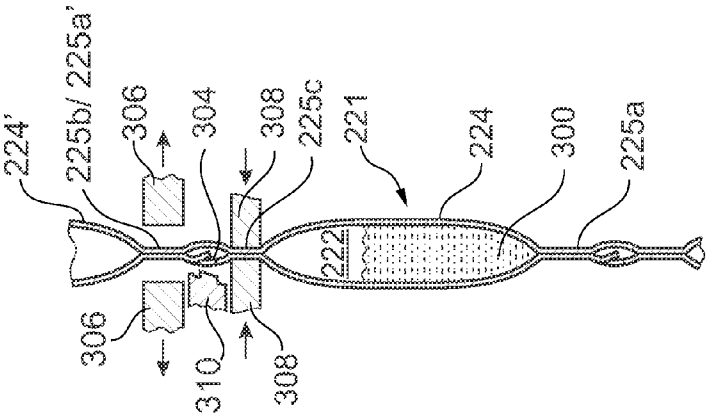


Fig. 13D

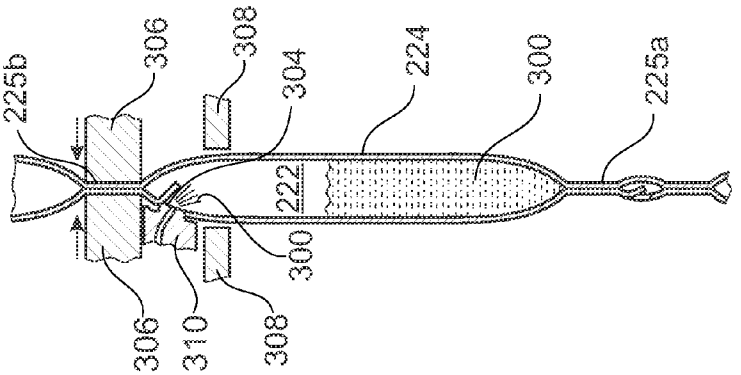


Fig. 13C

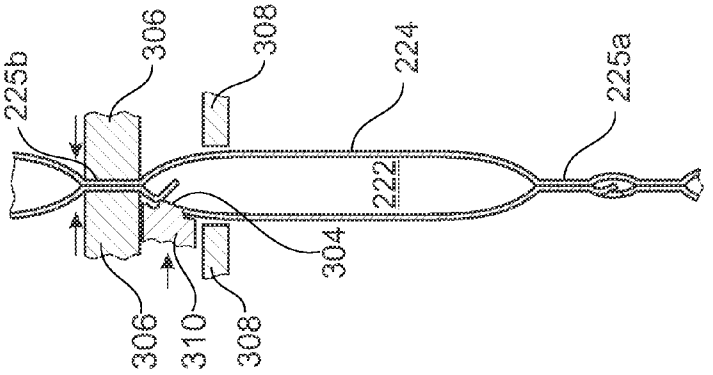


Fig. 13B

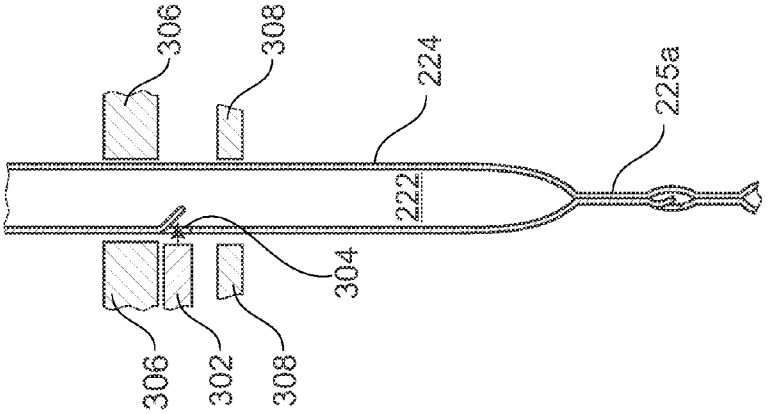


Fig. 13A

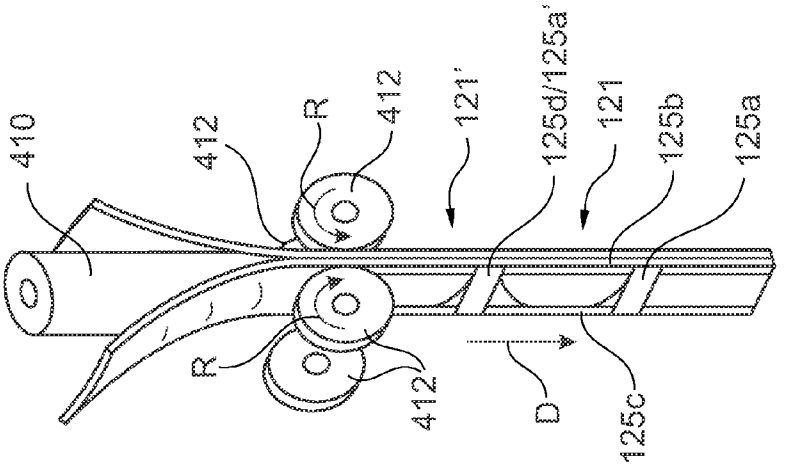


Fig. 14C

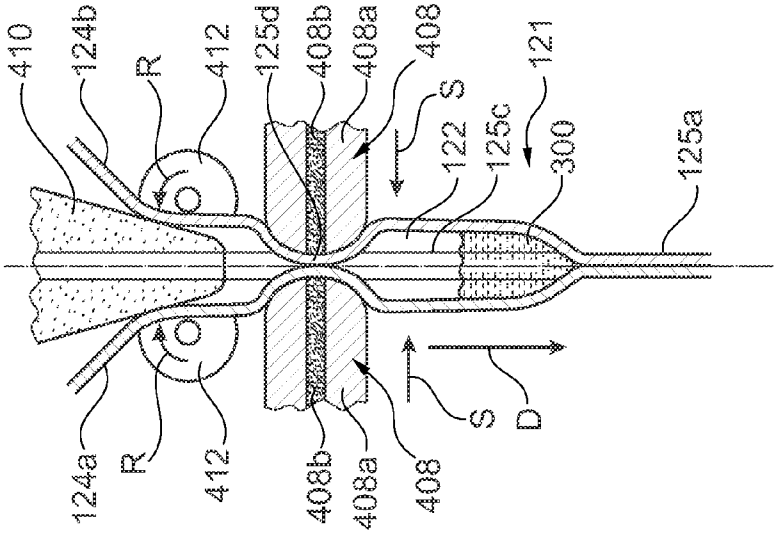


Fig. 14B

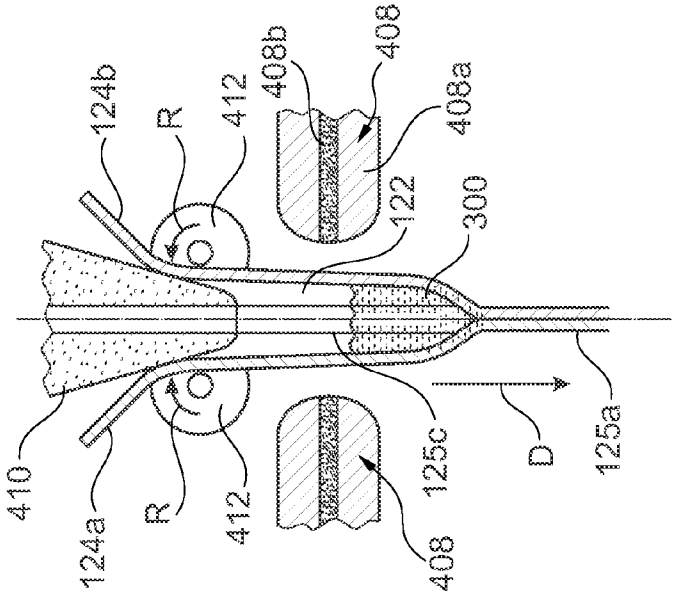


Fig. 14A

METHOD OF MANUFACTURING A PROPELLANT CONTAINER

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a US national phase under 35 USC §371 of International Application No. PCT/GB2013/051510, filed Jun. 7, 2013, which claims priority to United Kingdom patent application GB 1210082.2, filed Jun. 7, 2012. Priority application GB 1210082.2 is hereby incorporated by reference.

FIELD OF THE DISCLOSURE

[0002] This invention relates to a method of manufacturing a container, and in particular to a method of manufacturing a container containing propellant.

BACKGROUND

[0003] Automatically actuatable 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.

[0004] 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.

[0005] It is an object of the present invention to provide a method of manufacturing a container for containing propellant. Preferably, the container is one that is suitable for use as a power source in a syringe.

BRIEF SUMMARY OF THE DISCLOSURE

[0006] The present invention is defined in the appended claims.

[0007] In accordance with a first aspect of the present invention there is provided a method of manufacturing a container containing propellant comprising the steps of:

[0008] i) sealing a first sheet of rupturable material to a second sheet of rupturable material to form a lower seal and two side seals;

[0009] ii) placing a propellant dispensing apparatus in fluid communication with a central volume defined by the lower seal, the two side seals and a seal between the propellant dispensing apparatus and the first and second sheets;

[0010] iii) depositing propellant in the central volume using the propellant dispensing apparatus; and

[0011] iv) sealing the first sheet to the second sheet to form an upper seal to form a container where the propellant is contained between the upper seal, the lower seal, and the two side seals.

[0012] 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 the subsequent container. Rollers may be provided to move the first and second sheets relative to the propellant dispensing apparatus, the rollers bringing the first sheet and the second sheet together along their respective edges for formation of the two side seals. The rollers may be configured to also form the two side seals. two pairs of separate rollers may be provided.

[0013] The lower seal and the upper seal may be severed to form a discrete container.

[0014] 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;

[0015] wherein step iv) comprises forming the upper seal at a position that is not between the temporary clamp and the lower seal; and

[0016] the temporary clamp is removed following formation of the upper seal.

[0017] 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.

[0018] Any or each of the lower seal, the upper seal and the two side seals may be a heat seal, a sonic weld, or an adhesive seal.

[0019] In accordance with a second aspect of the present invention, there is provided a method of manufacturing a container containing propellant comprising the steps of:

[0020] i) providing a tube of rupturable material;

[0021] ii) sealing a lower end of the tube to form a lower seal;

[0022] iii) sealing an upper end of the tube to form a first upper seal and defining an internal volume between the first upper seal and the lower seal;

[0023] iv) forming an opening in the tube;

[0024] v) depositing propellant in the internal volume through the opening; and

[0025] 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.

[0026] 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.

[0027] Step iv) may be performed prior to performing step iii).

[0028] 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.

[0029] The tube of rupturable material may be an extruded tube.

[0030] At least steps i) to vi) may be performed when the extruded tube has not been cut from the extrusion line.

[0031] The first upper seal may become the lower seal of a tube extending above thereof such that the method may be repeated for the tube extending above thereof.

[0032] Any or each of the lower seal, the first upper seal and the second upper seal may be a heat seal, a sonic weld, or an adhesive seal.

[0033] The step of forming an opening in the tube preferably produces substantially no loose material.

[0034] In accordance with a third aspect of the present invention there is provided a method of manufacturing a container containing propellant comprising the steps of:

[0035] i) providing a container having an opening;

[0036] ii) placing a propellant dispensing apparatus in fluid communication with the opening;

[0037] iii) depositing liquid propellant in the container using the propellant dispensing apparatus;

[0038] 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;

[0039] v) sealing the container to itself at a location that is not across the central volume; and

[0040] vi) removing the temporary clamp.

[0041] 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.

[0042] The propellant may include a hydrofluoroalkane (HFA) which may be HFA 134a

[0043] In accordance with a fourth aspect of the present invention, there is provided 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 the propellant and the one or more seals are formed between two like materials, wherein the container is a power source for actuating the syringe and causing the stopper to move axially in the barrel.

[0044] The one or more seals may be formed by heat sealing, sonic welding, or adhesives. The material may have a gas permeability of 0.365 g/(m2·day). The material may include polyethylene, or a polyamide. The material may include nylon and may consist substantially of nylon. The material may comprise a laminate of polyethylene and a polyamide. The material may comprise a laminate of polyethylene and a metal. The metal may be a metallic foil. The container may be formed from two sheets of the material, wherein the chamber is defined by an area where the two sheets are not bonded to one another and the 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 the material initially having two open ends, wherein the two open ends are pinched closed to form two sealed ends. The propellant may include a hydrofluoroalkane (HFA) and may be HFA 134a.

[0045] 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

[0046] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which:

[0047] FIG. **1**A 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;

[0048] FIG. **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;

[0049] FIG. **1**C is a schematic cross sectional view of the syringe of FIG. **1**B additionally comprising a fluid conduit extending into the propellant chamber;

[0050] FIG. **2** shows an embodiment of a container for containing propellant in accordance with the present invention;

[0051] FIG. **3** shows an alternative embodiment of a container for containing propellant in accordance with the present invention;

[0052] FIG. **4** shows a rupturing portion in accordance with an embodiment of the present invention;

[0053] FIG. **5** shows an alternative rupturing portion in accordance with an embodiment of the present invention;

[0054] FIG. **6**A 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 FIG. **6**B shows the corresponding time-dependent pressure profile;

[0055] FIG. **7**A 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 FIG. **7**B shows the corresponding time-dependent pressure profile;

[0056] FIG. **8**A shows a time-dependent gas volume profile of a propellant powered syringe in accordance with an embodiment of the present invention, and FIG. **8**B shows the corresponding time-dependent pressure profile;

[0057] FIG. **9** shows a pressure profile of vapor 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;

[0058] FIG. **10** shows a pressure profile of vapor 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;

[0059] FIG. **11** shows a pressure profile of vapor 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;

[0060] FIG. **12** shows a pressure profile of vapor 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;

[0061] FIGS. **13**A to **13**D are schematic cross sectional views representing a method of filling a propellant container in accordance with an embodiment of the present invention;

[0062] FIGS. **14**A and **14**B are schematic cross sectional views representing a method of filling a propellant container in accordance with an alternative embodiment of the present invention, and FIG. **14**C is a schematic perspective view of a further step of the method represented by FIGS. **14**A and **14**B;

[0063] and

[0064] FIGS. **15**A to **15**E show various stages of a method of manufacturing a propellant filled container in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION

[0065] A syringe **10** according to an embodiment of the present invention is shown in FIG. **1**A. 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 **12***a* 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 FIG. **1**A, the propellant source is a container **21** which comprises a rupturable wall **24** defining a third chamber **22** containing propellant.

[0066] 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.

[0067] 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**. FIG. **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 **512***a* and a bore **512***b* running therethrough. The conical element **512** projects from a base **514** through which the bore **512***b* 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 **512***b*. 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 **512***a* 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 **512***b* facilitates direct and efficient passage of both liquid and gaseous propellant between the third chamber **22** and second chamber **20**.

[0068] 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, FIG. **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**.

[0069] 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**.

[0070] 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.

[0071] 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.

[0072] 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 vapor 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.

[0073] 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**.

[0074] 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 vapor pressure in the second chamber **20**.

[0075] 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 vapor 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 vapor 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**.

[0076] 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 vapor pressure in the second chamber **20**. This increase in vapor pressure tends towards the vapor 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 vapor pressure in the second chamber **20** will reach the vapor pressure of the propellant at the temperature of its immediate environment given long enough as equilibrium is reached.

[0077] The magnitude of the drop in vapor pressure in the second chamber **20** during delivery from the initial vapor 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**.

[0078] As an example, a 0.5 bar drop in vapor 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 vapor 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**.

[0079] 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. FIG. **6**A 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 FIG. **6**A, when the reservoir is opened the compressed gas expands rapidly at **500** as the compressed gas fills the dead volume behind the stopper.

[0080] 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 FIG. **6**A, 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 FIG. **6**A.

[0081] Since the quantity nRT is constant for adiabatic expansion, the pressure of the gas drops as the volume increases. This is shown in FIG. **6**B which shows a time-dependent pressure profile corresponding to the volume profile of FIG. **6**A. 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 FIG. **6**B, 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. FIGS. **6**A and **6**B 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).

[0082] FIGS. **7**A and **7**B relate to a syringe where the reservoir of compressed gas is small (0.3 cc) relative to the internal volume of the system. FIG. **7**A shows the time-dependent volume profile of the compressed gas, and FIG. **7**B shows the corresponding time-dependent pressure profile of the compressed gas. Again, FIG. **7**A 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 FIG. **7**A. The corresponding pressure profile shown in FIG. **7**B 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.

[0083] 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. FIG. **8**A 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 FIG. **8**A. 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 vapor pressure and therefore maintains a more constant pressure as shown in FIG. **8**B. 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 FIGS. **6**B and **7**B. Consequently, the present invention offers a much more consistent pressure profile with a very small initial volume of propellant.

[0084] In the syringes associated with each of FIGS. **6**A to **8**B, the dead internal volume into which the compressed gas or vaporized propellant initially expands into is ~3 cc.

[0085] FIG. **9** shows an example of a pressure profile (i.e. vapor pressure vs. time within the second chamber **20**) exhibited by a syringe such as the one described above in relation to FIG. **1**A 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 vapor pressure over a first time period (typically of the order of 10-100 ms) up to point B. At point B, the vapor 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 vapor pressure drops during delivery. This is shown in the pressure profile of FIG. **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 vapor pressure at C is lower than the vapor pressure at B. A third time period between point C and point D represents the vapor increase in the second chamber **20** as the propellant therein absorbs heat from the environment. This increase tends towards the vapor pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature). Indeed, point D represents substantially this vapor pressure. For the pressure profile of FIG. **9**, the vapor pressure at D is greater than both the vapor 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 vapor 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.

[0086] The pressure profile of FIG. **9** reveals that there is not necessarily a simple constant pressure acting on the stopper **16** (i.e. the vapor 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.

[0087] Further embodiments of syringes **10** in accordance with the present invention are described below with reference to FIGS. **1**B and **1**C. Given the differences in configuration, the various embodiments of syringes **10** will each exhibit a different pressure profile of vapor pressure in the second chamber **20** during use.

[0088] A further embodiment of a syringe in accordance with the present invention is shown in FIG. **1**B. The syringe **10** of FIG. **1**B 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 **26***a* therethrough. The non-rupturable wall **26** defines a fourth chamber **28** which is fluidly connected to the second chamber **20** via aperture **26***a* which defines a propellant channel. The fourth chamber **28** contains a container **21** as described above in relation to FIG. **1**A. 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 **26***a*. The extent of the aperture **26***a* 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 **26***a* 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 **26***a* 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**.

[0089] Yet another embodiment of a syringe **10** in accordance with the present invention is shown in FIG. **1**C. The syringe **10** of FIG. **1**C is largely the same as the syringe of FIG. **1**B 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.

[0090] 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 μl 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 μl 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.

[0091] The pressure profile of vapor 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 vapor 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.

[0092] The passage of propellant through the propellant conduit **30** or aperture **26***a* does not constitute "regulated delivery". Indeed, passage through the propellant conduit **30** or aperture **26***a* constitutes bolus delivery of the propellant into the second chamber **20**.

[0093] Unless otherwise stated, all described features of the syringe of FIG. **1**A (excluding the form of the third chamber **22**) may be applicable to any one or more of the syringes of FIGS. **1**B and **1**C. Indeed, any non-mutually exclusive features of any one or more of the syringes of FIGS. **1**A to **1**C may be applicable to any other of the syringes of FIGS. **1**A to **1**C.

[0094] FIG. **10** shows an example pressure profile of vapor 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 FIG. **10** shows that propellant enters the second chamber **20** at point A and immediately results in an increase of vapor pressure in the second chamber **20** to an initial maximum vapor pressure and point B. The rate of increase of vapor pressure decreases slightly immediately prior to reaching point B. The change from point A to point B occurs over a first time period. The vapor 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 FIG. **9**. However, the decrease and the rate of decrease between points B and C in FIG. **10** are less than the respective decrease and the rate of decrease in the

pressure profile of FIG. **9**. In FIG. **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 vapor pressure within the second chamber **20**. This increase tends towards the vapor 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.

[0095] FIG. **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 FIG. **11** is largely similar to that of FIG. **10**, however, in the pressure profile of FIG. **11**, there is substantially no change in the vapor pressure between points B and C. That is, during delivery, there is a substantially constant vapor pressure in the second chamber **20**. As with the pressure profile of FIG. **10**, subsequent to the end of delivery (i.e. after point C), the vapor 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.

[0096] Comparing the pressure profiles of FIGS. **9**, **10** and **11**, it can be seen that the drop in vapor 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 vapor pressure (i.e. the vapor pressure at point B) being reduced for more proportionally gaseous propellant introduced into the second chamber **20**. That is, the vapor pressure in the second chamber **20** does not reach its vapor 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**.

[0097] 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 vapor 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 vapor pressure will be at a level not previously exceeded in the delivery process. To put that another way, point C will represent the highest vapor pressure of the first and second time periods. In this scenario, following point C, the vapor pressure will increase as the propellant absorbs heat energy from its environment and tends towards the vapor pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature).

[0098] 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.

[0099] FIG. **12**, however, demonstrates the effects of parameter i) on the form of the pressure profile. In particular, FIG. **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 FIG. **9**. However the syringe **10** associated with the pressure profile of FIG. **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 vapor 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 vapor pressure in the second chamber **20** than would otherwise occur if no such means or method were in place.

[0100] 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.

[0101] 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 vapor pressure drop will be exhibited.

[0102] 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 vapor 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.

[0103] 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 vapor 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).

[0104] 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 vapor pressure. Typically (although not always, as described above) the initial movement of the stopper **16** will be coincident with an initial maximum vapor pressure from which the vapor 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 vapor pressure in the second chamber **20** reaches a predetermined level. In a preferable embodiment, the predetermined level determining the third time period is the vapor pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature).

[0105] In preferable embodiments, the syringe **10** in accordance with the present invention exhibits a pressure profile of vapor 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 vapor 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 vapor pressure of the propellant at the temperature of its immediate environment (e.g. ambient temperature). Defining the vapor 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.

[0106] In any of the described embodiments of syringes in accordance with the present invention, the propellant containers shown in FIGS. **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 FIG. **2** or **3**. In FIG. **2**, a container **121** is shown to be made of an upper sheet **124***a* and a lower sheet **124***b* which together form a rupturable wall **124** of the container **121**. The sheets **124***a*, **124***b* are generally square or rectangular in shape in the embodiment shown in FIG. **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 **124***a*, **124***b*. 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 **125**. 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 **125** may remain in storage following manufacture prior to use), and the volume of propellant required to perform the desired action.

[0107] The material that forms the sheets **124***a*, **124***b* 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 μl 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/(m^2·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.

[0108] 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 **124***a*, **124***b* 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.

[0109] 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 **124***a*, **124***b* comprise laminates of two or more materials, the sheets **124***a*, **124***b* 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.

[0110] The shape of the container **121** may differ from that shown in FIG. **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**.

[0111] FIG. **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 FIG. **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.

[0112] 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).

[0113] 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.

[0114] 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**.

[0115] A schematic representation of a method of manufacturing a container, such as the container **221** shown in FIG. **3**, is shown in FIGS. **13**A to **13**D. FIG. **13**A shows an extruded tube **224** formed of a rupturable material that has been sealed at a lower end by a lower seal **225***a*. 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**.

[0116] 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.

[0117] The first sealing elements **304** may then be used to form a first upper seal **225***b* above (i.e. upstream) of the opening **304** as shown in FIG. **13**B. 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 **225***b*.

[0118] As shown in FIG. **13**C, 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 **225***c* is then formed by second sealing element **308** below (i.e. downstream) each of the first upper seal **225***b* and the opening **304**. After formation of the second upper seal **225***c*, the central volume **222** containing the propellant **300** is sealed at an upper end by second upper seal **225***c* and at a lower end by the lower seal **225***a* thus forming a propellant container **221**. The container **221** may be cut along lower seal **225***a* and second upper seal **225***c* to separate the container **221**.

[0119] 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 **225***c* 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**.

[0120] 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 **225***b* of the tube **224** becomes the lower seal **225***a*' 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 **225***a* and second upper seal **225***c* for container **221**) may be altered to change the magnitude of the central volume **222** in accordance with the desired dose of propellant **300**.

[0121] 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.

[0122] A schematic representation of an alternative method of manufacturing a container, such as the container **121** shown in FIG. **2**, is shown in FIGS. **14**A to **14**C. FIG. **14**A shows two sheets **124***a*, **124***b* of like material being brought together by a set of rollers **412** rotating in direction R. Although the cross-sectional views shown in FIGS. **14**A and **14**B show only two rollers **412**, the set actually comprises four rollers **412** as shown in the perspective view of FIG. **14**C. The rollers **412** are arranged in pairs such that the two sheets **124***a*, **124***b* of material come together between the pairs, where the two rollers of each pair are spaced and arranged along edges of the sheets **124***a*, **124***b*. The rotation of the rollers **412** along direction R causes the sheets **124***a*, **124***b* 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 **124***a*, **124***b* seal to one another to form side seals **125***b*, **125***c*. The rollers **412** may comprise means to form the side seals **125***b*, **125***c* or additional sealing apparatus may be employed to form the side seals **125***b*, **125***c*.

[0123] Sealing elements **408** seal the sheets **124***a*, **124***b* together across their entire width to form a lower seal **125***a*. A propellant dispensing head **410** is arranged between the sheets **124***a*, **124***b* and between the four rollers **412** and is arranged relative to the sheets **124***a*, **124***b* and the rollers **412** so that the sheets **124***a*, **124***b* 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 **125***a*, **125***b*, **125***c* and the seals between the sheets **124***a*, **124***b* and the propellant dispensing head **410**.

[0124] 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 **124***a*, **124***b* above the deposited propellant **300** to form an upper seal **125***d*. This forms a container **121** that has a central volume **122** containing propellant **300** where the central volume **122** is defined by seals **125***a*, **125***b*, **125***c*, **125***d*. Any or all of the seals **125***a*, **125***b*, **125***c*, **125***d* may be heat seals, sonic welds or other seals, such as adhesive seals. In the non-limiting preferable embodiment shown in FIGS. **14**A to **14**C, the sealing element **408** includes a clamping part **408***a* and a sealing part **408***b*. The clamping part **408***a* may act independently of the sealing part **408***b* to mechanically clamp the sheets **124***a*, **124***b* together to isolate the propellant **300** contained in the central volume from the sealing part **408***b*. In this preferable embodiment, a more effective seal may be made by the sealing part **408***b* 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 FIGS. **13**A to **13**D), 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 **125***d* has been made, the clamping part **408***a* may be removed. The clamping part **408***a* and the sealing part **408***b* may be part of a single apparatus such as the sealing element **408** of FIGS. **14**A to **14**C, or, in other embodiments, they may be entirely separate and independent components.

[0125] The upper seal **125***d* may then form the lower seal **125***a*' of a subsequent container **121**' (see FIG. **14**C) so that the process may be repeated to produce a series of connected containers **121**, **121**', . . . , etc. Lower and upper seals **125***a*, **125***d* 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**.

[0126] The pitch of the containers (e.g. the distance between lower seal **125***a* and upper seal **125***c*) may be altered to change the magnitude of the central volume **122** in accordance with the desired dose of propellant **300**.

[0127] FIGS. **15**A to **15**E show the various stages of manufacture of a container **121** in accordance with an alternative related embodiment. In FIG. **15**A, 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 FIGS. **15**A to **15**E, only an upper sheet **124***a* of the laminate **128** is visible. The seals **125** include a lower seal **125***a*, two side seals **125***b*, **125***c* and a temporary upper seal **125***d*'. In some embodiments, the temporary upper seal **125***d*' may not be present. The seals **125** define a blister portion **126***a*, a neck portion **126***b* and a filling portion **126***c*. In the preferable embodiment shown in FIGS. **15**A to **15**E, the neck portion **126***b* is narrower compared with the blister portion **126***a* and the filling portion **126***c*. However, in alternative embodiments within the scope of the present invention, the neck portion **126***b* may not be narrower. The two sheets of rupturable material may be preformed (e.g. by vacuum form-

ing) 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**.

[0128] 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.

[0129] FIG. **15**B shows the laminate **128** of FIG. **15**A that has been cut so as to remove the temporary upper seal **125***d*' 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 FIG. **15**C. In the embodiment shown in FIGS. **15**A to **15**E, the line **127** crosses the neck portion **126***b*, however, in alternative embodiments, it may be at any suitable point between the lower seal **125***a* and the filling apparatus. The clamping device seals the propellant in the volume **122** between line **127** and the lower seal **125***a* 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 **126***b* permits a lower clamping force to be used that will provide an adequate temporary seal whilst minimizing the risk of accidental damage.

[0130] Once clamped, an upper seal **125***d* is created between the line **127** of the clamp and the filling apparatus across the side seals **125***b*, **125***c*. The clamp may then be removed to leave the volume **122** defined by the lower seal **125***a*, the side seals **125***b*, **125***c* and the upper seal **125***d* 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.

[0131] Between clamping along line **127** and forming the upper seal **125***d*, it is preferable to allow or cause any propellant present between line **127** and the intended area of the upper seal **125***d* 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.

[0132] The steps outlined above in relation to FIGS. **15**A to **15**E separate the processes of filling the container **121** and sealing the container with the upper seal **125***d*. By utilizing the step of clamping the laminate across line **127**, the potential problem of propellant damaging the upper seal **125***d* is avoided.

[0133] The seals **125** may be any suitable seals as described above, however heat seals are particularly preferable and suitable.

[0134] 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).

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

1. 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.

2. The method according to claim **1**, wherein the first and second sheets 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.

3. The method according to claim 2, wherein rollers are 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.

4. The method according to claim 3, wherein said rollers are configured to also form said two side seals.

5. The method according to claim 3, wherein two pairs of separate rollers are provided.

6. The method according to claim 1, wherein said lower seal and said upper seal are severed to form a discrete container.

7. The method according to claim 1, wherein after step iii) and prior to step iv) the first sheet and second sheet are temporarily clamped together by a temporary clamp between the lower seal and the seal made between the propellant dispensing apparatus and the first and second sheets;

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.

8. The method according to claim 7, wherein the step of temporarily clamping the first sheet to the second sheet is 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.

9. The method according to claim 1, wherein any or each of said lower seal, said upper seal and said two side seals is a heat seal, a sonic weld, or an adhesive seal.

10-19. (canceled)

20. 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 with a temporary clamp 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.

21. The method according to claim 20, wherein prior to step v), allowing propellant present in the container that is not in the central volume to disperse.

22. The method according to claim 21, and applying heat to encourage dispersal of propellant present in the container that is not in the central volume.

23. The method according to claim 21, and applying a vacuum to remove propellant present in the container that is not in the central volume.

24. The method according to claim 21, and allowing a predetermined period of time 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.

25. The method according to claim 1, wherein said propellant includes a hydrofluoroalkane (HFA).

26. The method according to claim 25, wherein said HFA is HFA 134a.

27. 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.

28. The syringe according to claim 27, wherein said one or more seals are formed by heat sealing, sonic welding, or adhesives.

29-38. (canceled)

39. The syringe according to claim 27, wherein said propellant includes a hydrofluoroalkane (HFA).

40. The syringe according to claim 39, wherein said HFA is selected from the group consisting of: HFA 134a, HFA 422d, HFA 507c and HFA 123.

41-42. (canceled)

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