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(54) SYSTEM AND METHOD FOR FILLING CONTAINERS WITH LIQUID UNDER VARYING PRESSURE CONDITIONS

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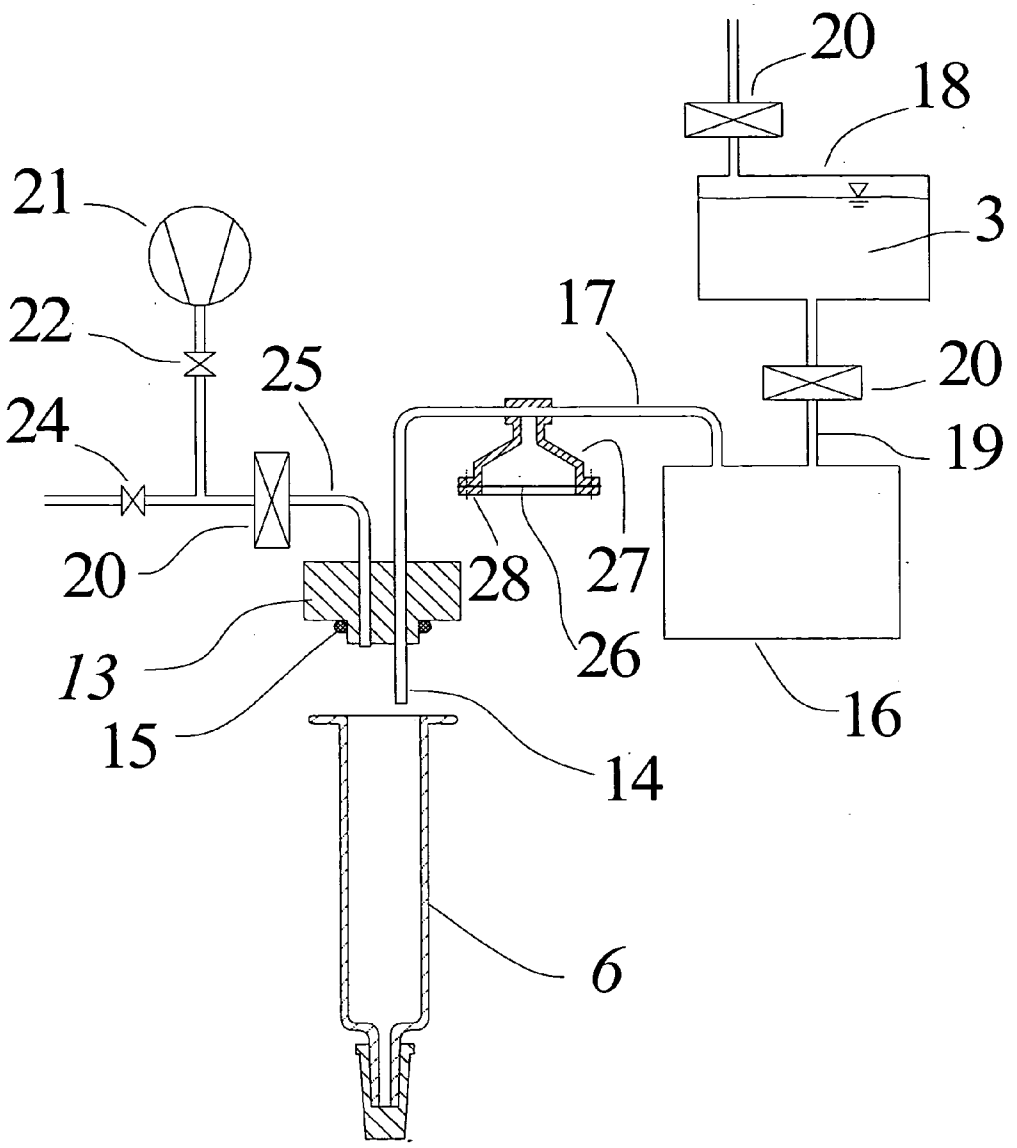
(57) **ABSTRACT**

A system and method for filling a container such as a syringe or vial with liquid is provided. Also provided is a system and method for closing a filled container with a stopper or piston gas-pocket free. The systems and methods are carried out at a minimum of two different pressure levels to provide filled and/or closed containers substantially without formation of gas pockets or foaming in the container. Also provided is a system and method for degassing liquid useful in the filling and closing processes.



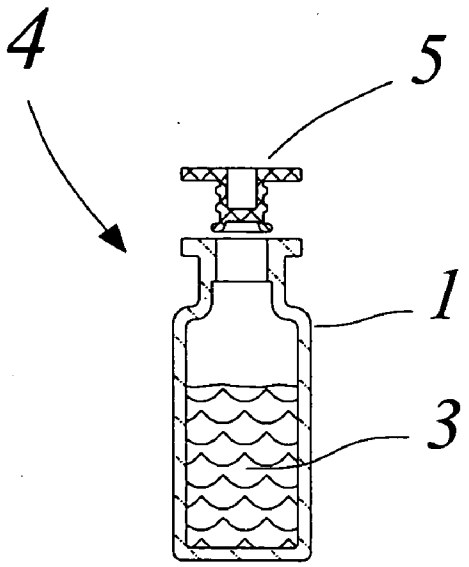


Fig. 1a

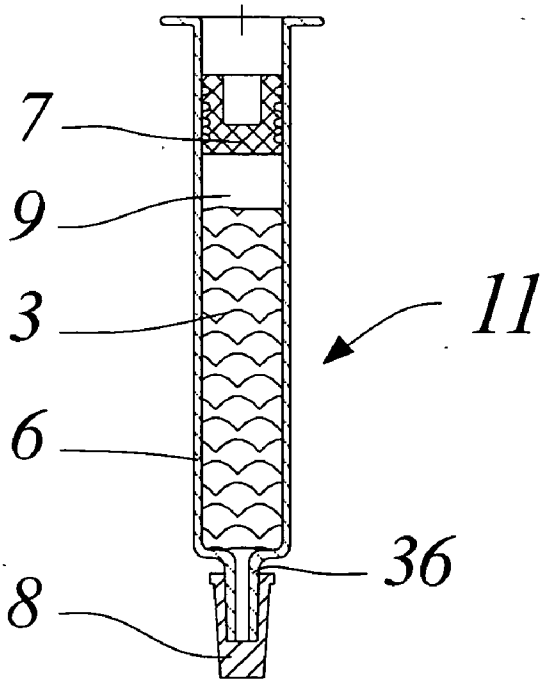


Fig. 1b
(Prior Art)

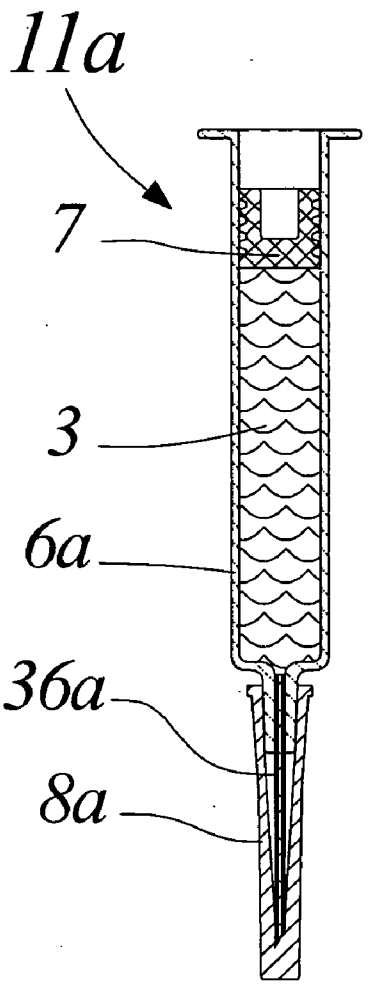


Fig. 1c

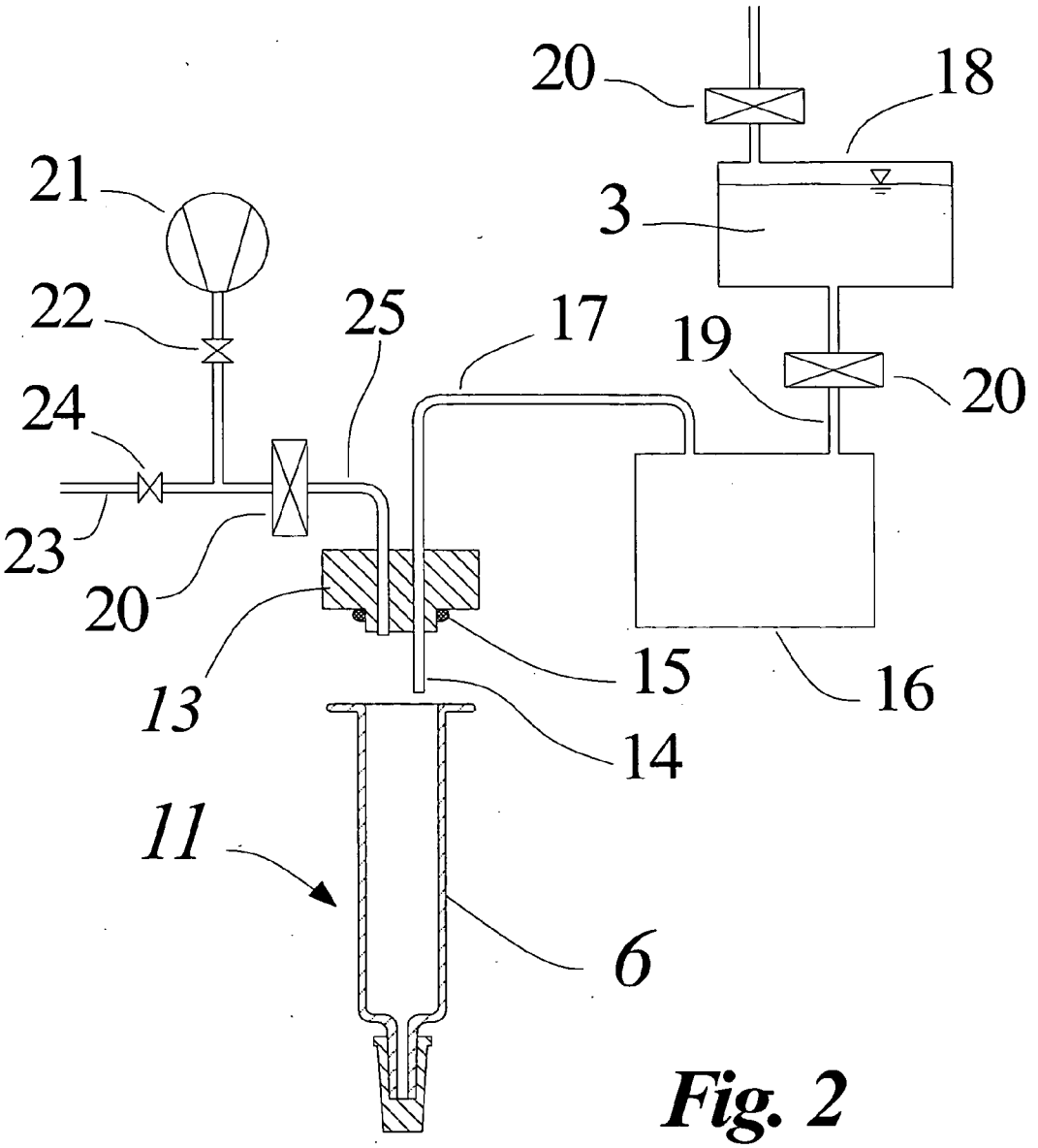


Fig. 2

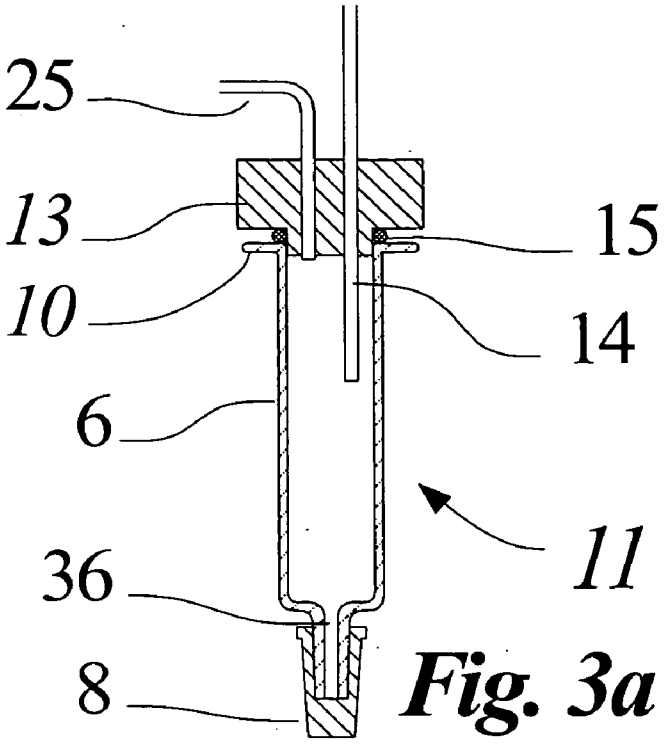


Fig. 3a

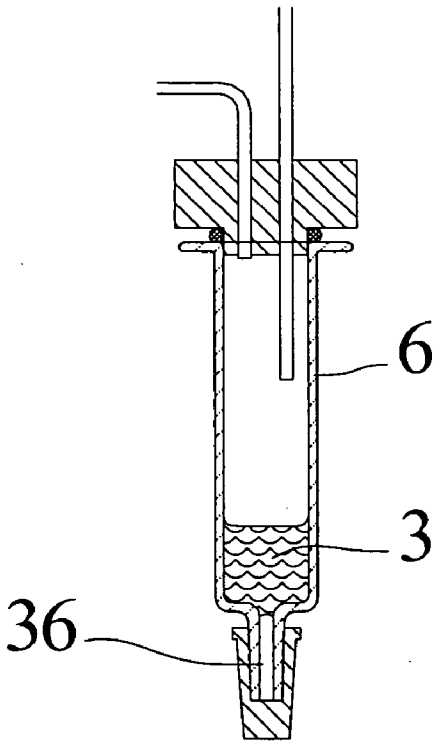


Fig. 3b

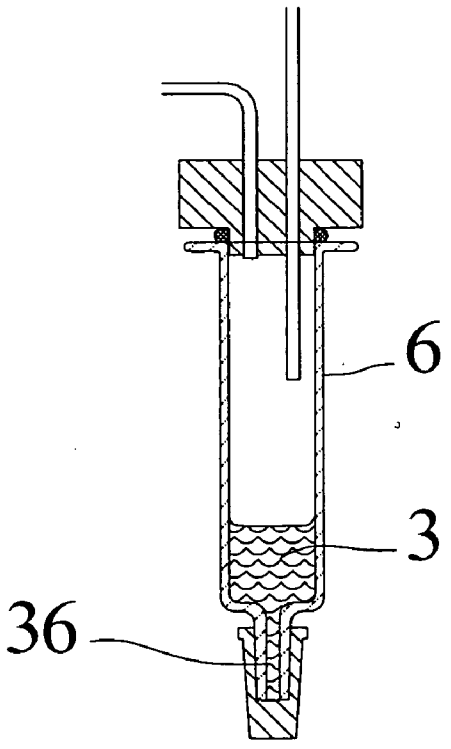


Fig. 3c

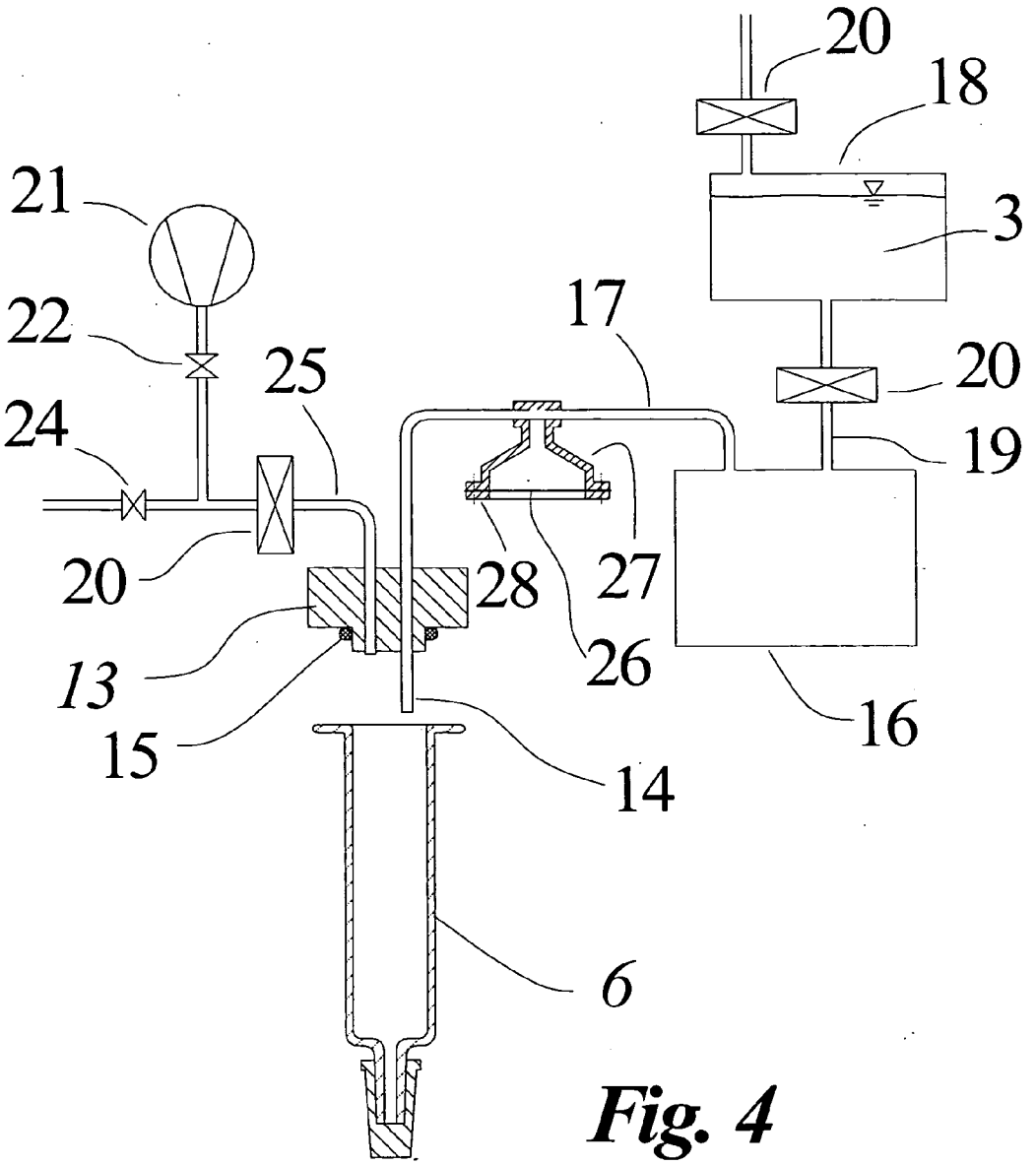


Fig. 4

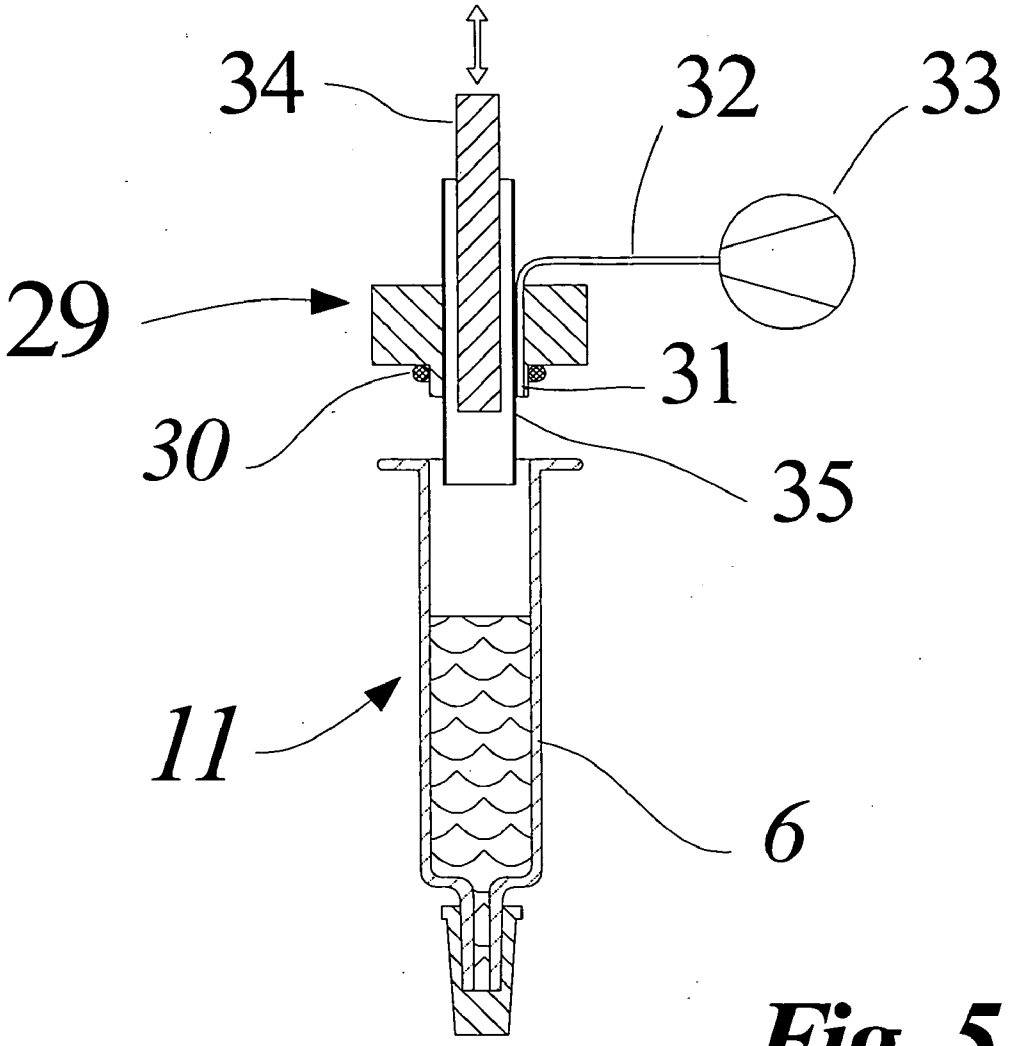


Fig. 5

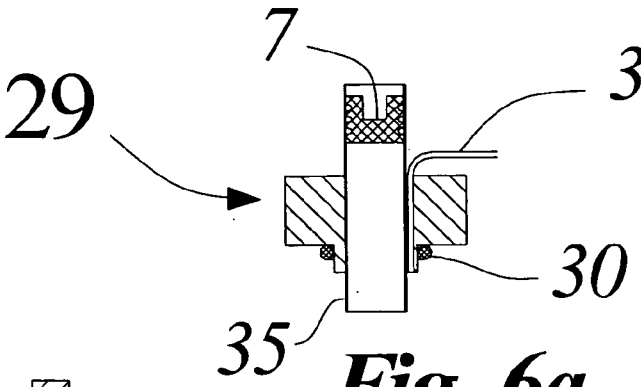


Fig. 6a

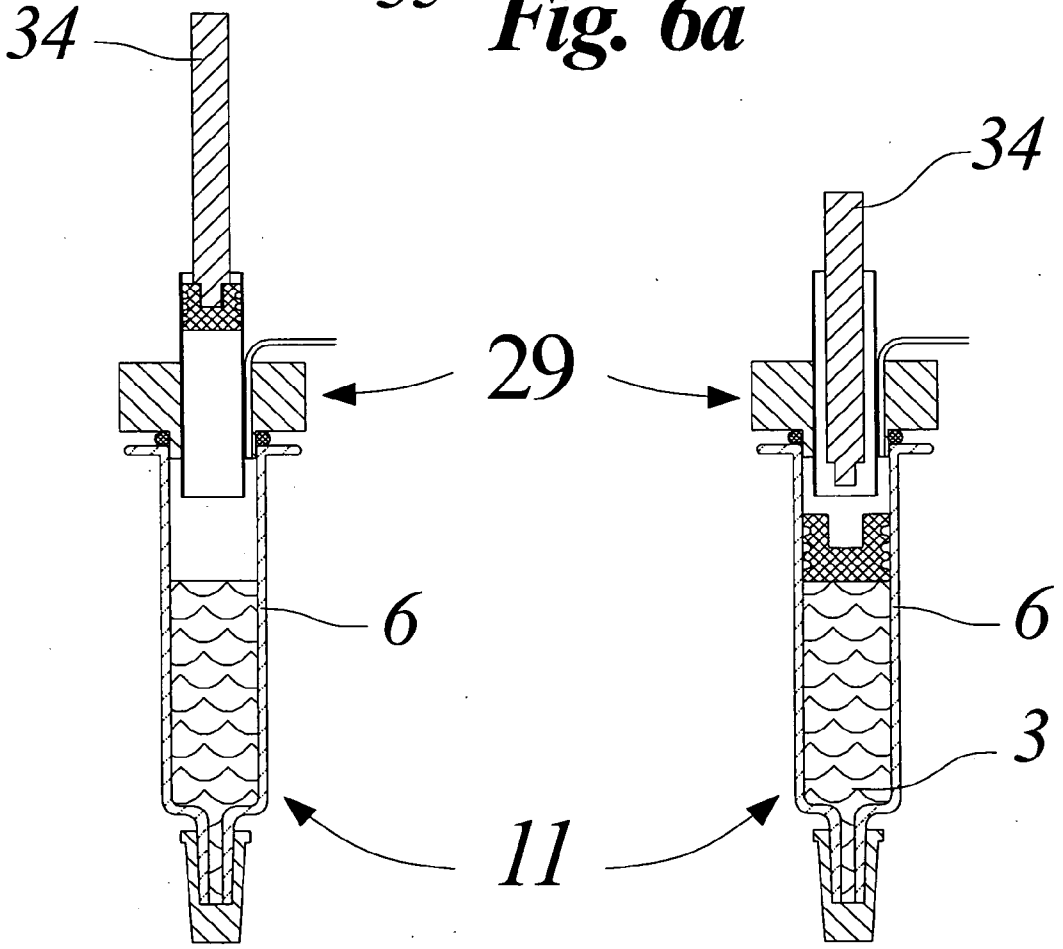


Fig. 6b

Fig. 6c

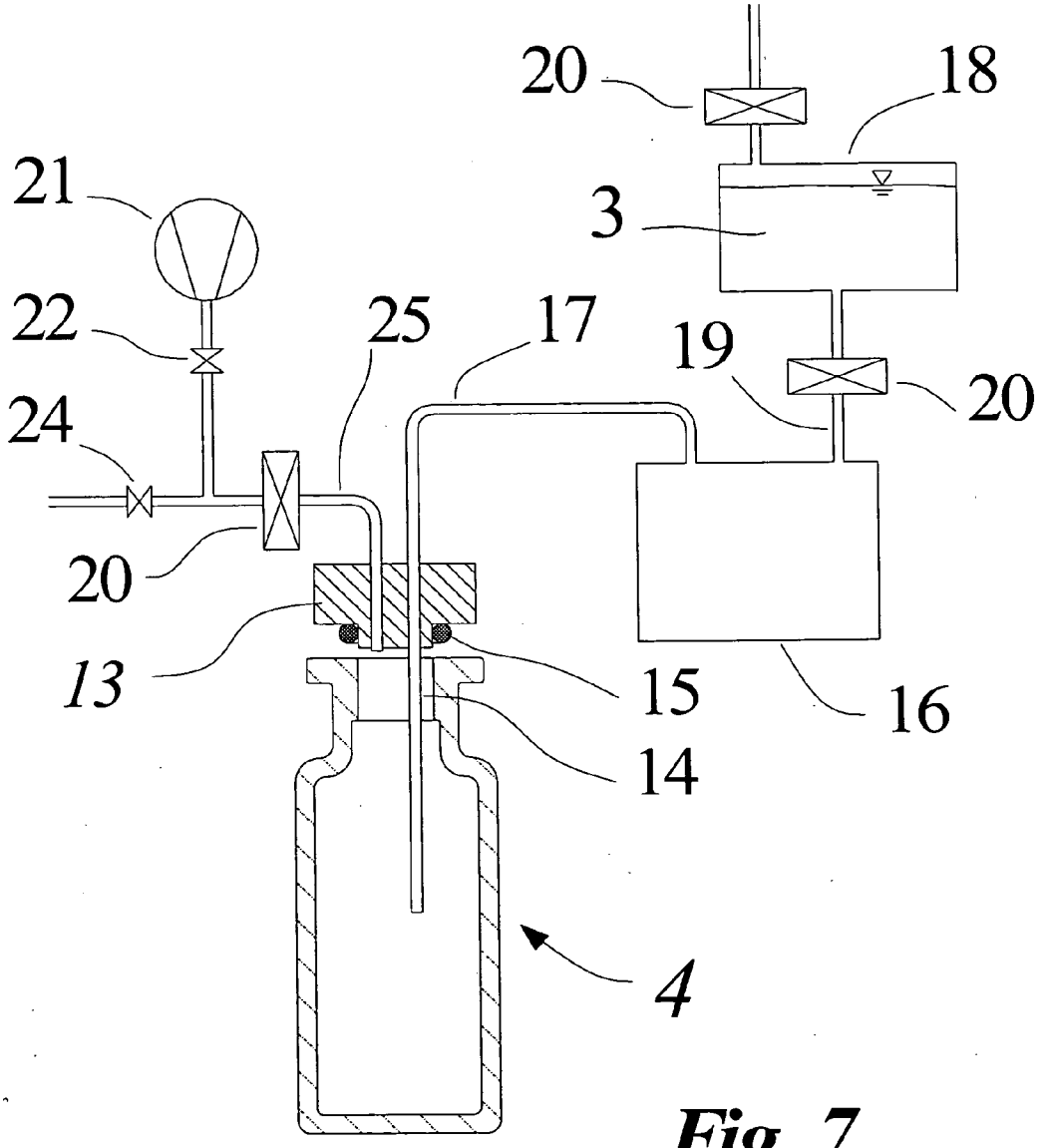


Fig. 7

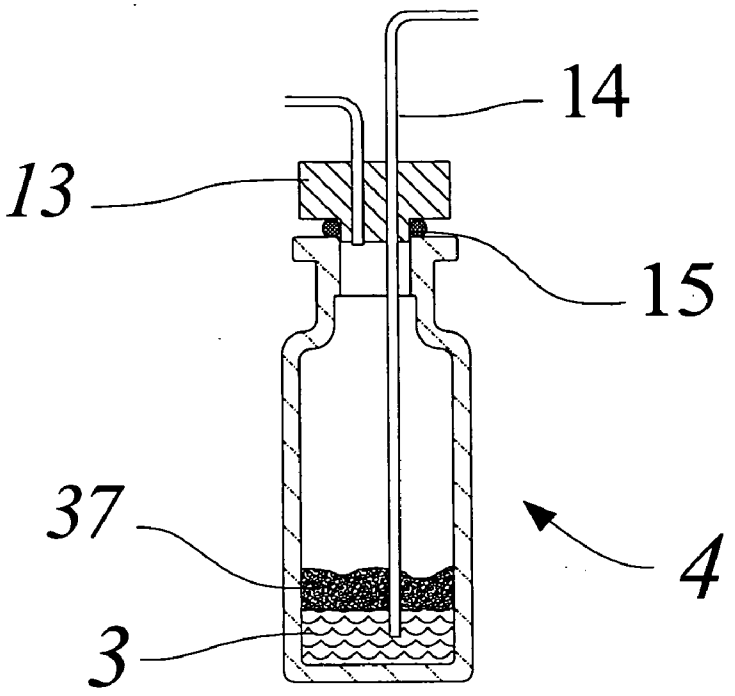


Fig. 8a

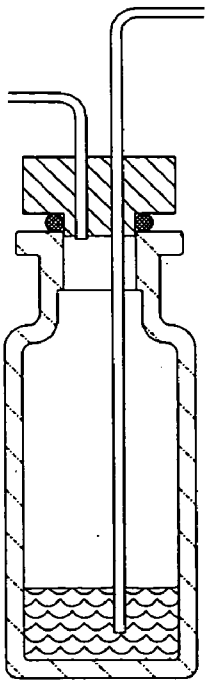


Fig. 8b

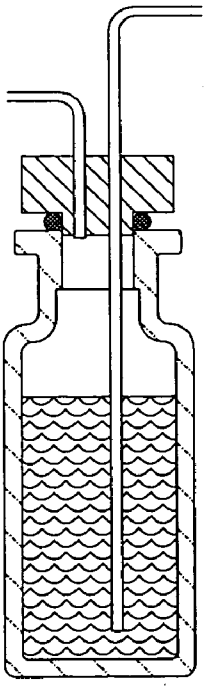


Fig. 8c

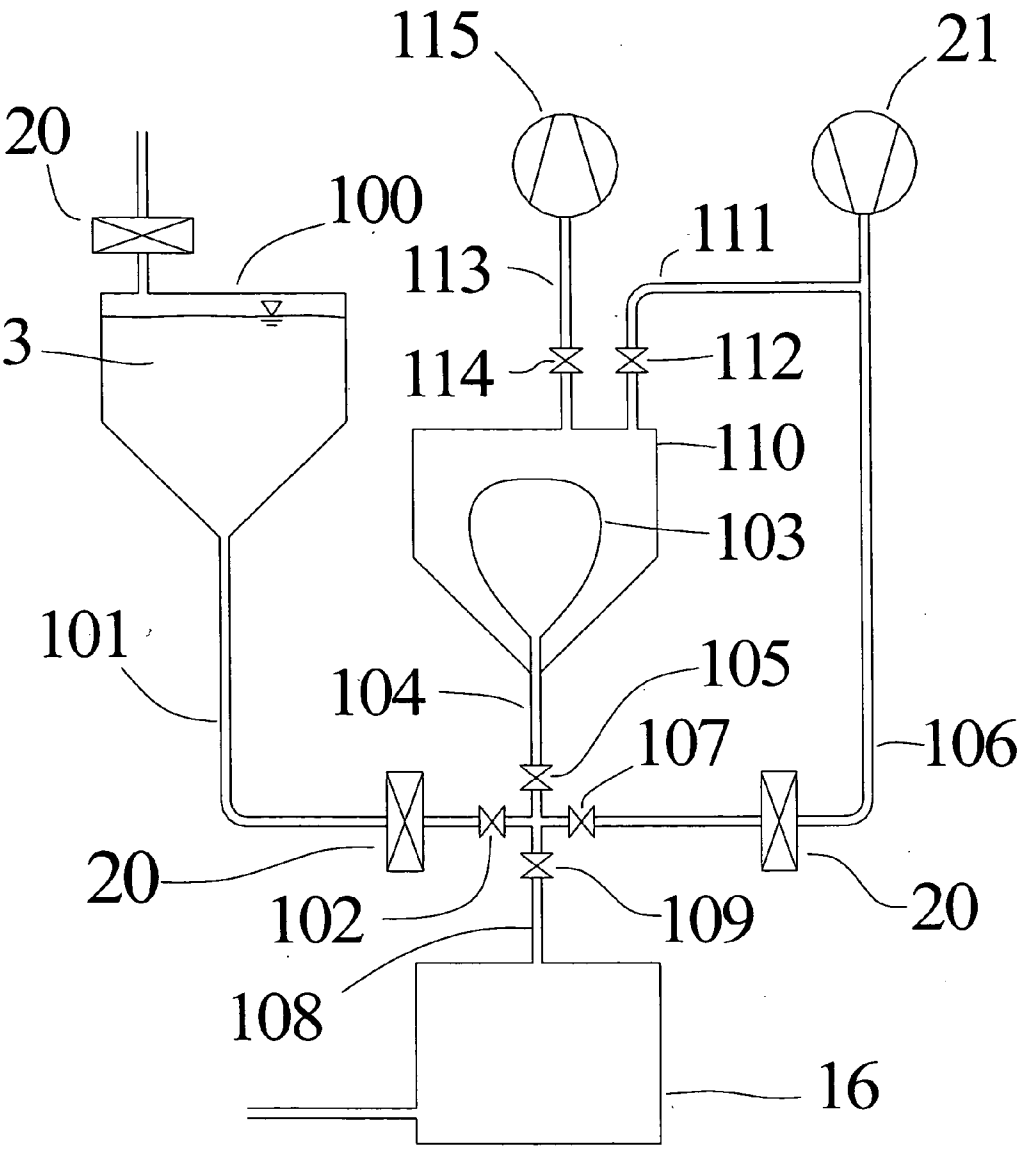

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Fig. 9

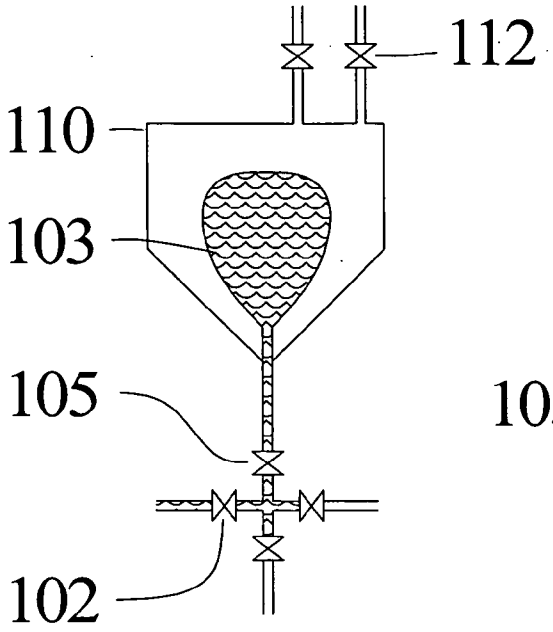

Fig. 10a

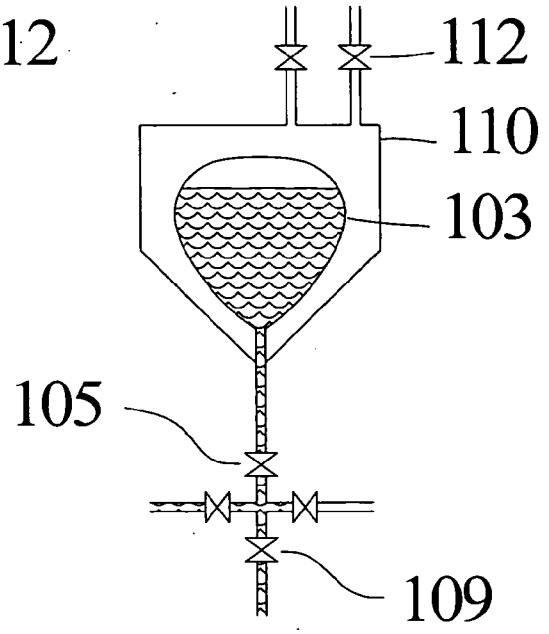

Fig. 10b

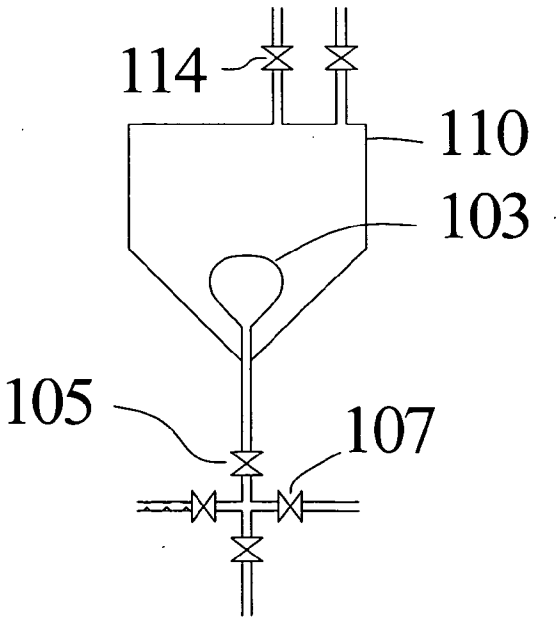

Fig. 10c

SYSTEM AND METHOD FOR FILLING CONTAINERS WITH LIQUID UNDER VARYING PRESSURE CONDITIONS

FIELD OF INVENTION

[0001] The present invention relates to systems and methods for filling containers with liquids, and more particularly to processes for filling containers at different pressure levels, such that the containers are filled substantially without formation of gas pockets or foaming.

BACKGROUND OF THE INVENTION

[0002] Industrial applications frequently require containers to be filled using dedicated processes in order to fulfill special product or process requirements. Filling processes for liquids include standard processes carried out in many industries. Traditionally, it has been difficult to fill containers without including gas pockets.

[0003] Different dosing systems can be used for filling containers, including time pressure filling, peristaltic pumps, rotational piston pump systems, and other conventional filling arrangements. Some filling processes use vacuum to improve the process. Closing systems sometimes use vacuum to reduce the volume of enclosed gas in the container.

[0004] The need for accurate filling and closing of containers is particularly important to the pharmaceutical industry, which must follow strict requirements regarding sterility, accuracy, and package integrity. For example, German Patent DE 4320098 discloses a process for decanting a pharmaceutical product for use with high viscosity liquids. As described in this German patent, a filling process is performed under vacuum, and piston setting is also done under vacuum. However, this process would not be effective with low viscosity liquids because applying vacuum during piston setting would lead to eruption of the liquid. Moreover, during filling, the application of high vacuum would result in inaccurate dose volumes.

[0005] At least two major problems occur during filling and closing of containers containing liquids. First, the filling process often lacks accuracy. Sometimes liquid in the connection between the dosing system and a filling head releases gas when a vacuum is applied in the syringe body, and therefore more liquid is expelled than necessary. When this occurs, less liquid is expelled into the syringe in the next filling cycle. The requirement of high vacuum during stopper setting is another negative impact.

[0006] Second, gas may be trapped in the cone or the needle of the syringe by capillary force. This trapped gas will expand rapidly during evacuation for stopper setting, which can lead to eruptions in the syringe that wet the glass and the piston area, with a negative impact on quality.

[0007] Another problem with conventional filling technology is the tendency of some liquids to create a large amount of foam during the filling process. Foaming can disturb the closing process and result in product loss when the foam passes over the top of a vial or syringe. Additional problems with foaming include sterility, difficulty of inspection, and lack of cleanliness.

[0008] The use of degassed liquids can provide advantages in a filling process. U.S. Pat. No. 6,500,239 to Castellano et al. describes a system and method for removing dissolved gas from a solution, i.e., a degassing process. In Castellano et al., an opening in a degassing tank is connected to at least two other systems: a liquid source for filling the tank, and a gas removal source. Exposing the tank to more than one connection is undesirable, because it may lead to loss of sterility or product loss.

[0009] It would be desirable to provide an improved system and method for filling containers with liquid and closing the containers substantially without formation of gas pockets or foaming. The filling system, closing system, and related methods should overcome the deficiencies of the presently available methods and systems.

SUMMARY OF THE INVENTION

[0010] Systems and methods for filling and closing containers, such as syringes and rigid bodies, substantially without formation of gas pockets or foaming are disclosed. Such filling and closing processes are carried out at a minimum of at least two different pressure levels, or under varying pressure conditions. As a result, a syringe or rigid body can be filled with liquid and closed within normal cycle times commonly used in the industry, substantially without formation of gas pockets or foaming in the syringe or rigid body. Using the present invention, foaming can be substantially collapsed or prevented in rigid bodies such as vials or the like. Useful containers for gas-pocket free filling and closing include syringes with slideable pistons, although any other suitable type of container, for example, those used in the pharmaceutical industry, can be used with the present invention. The liquid filled into the container can be any suitable liquid to be packaged, including but not limited to pharmaceutical and diagnostic liquids.

[0011] In addition, gas substantially does not become trapped by capillary forces in the container, and any foam produced during filling tends to collapse upon increasing the pressure in accordance with the present invention. Closing processes of the invention include setting of a stopper or piston within the container. Further, the invention encompasses degassing of the liquid used to fill a container prior to undergoing the filling process.

[0012] A system for filling a container with liquid can include a dosing unit for supplying the liquid to the container, a filling head for receiving the liquid from the dosing unit and transferring the liquid to inside of the container when the filling head engages the container, and a vacuum pump connected to the filling head for providing vacuum to inside of the container, where a pressure inside the container is regulated to at least two different pressure levels during filling. As a result, the container is filled substantially without formation of gas pockets in the container.

[0013] A method for filling a container with liquid can include steps of: providing the container with an open end for receiving the liquid, engaging a filling head with the container such that the filling head and the container form a seal, opening a vacuum source to inside of the container, thereby reducing the pressure to a first pressure level, supplying a portion of a predetermined dose of the liquid from a dosing unit to inside of the container through the filling head, closing the vacuum source, thereby raising the pressure inside the container from the first pressure level to a second pressure level, and supplying a remainder of the

predetermined dose of the liquid from the dosing unit to inside of the container such that the container is filled substantially without formation of gas pockets in the container.

[0014] A method for closing a container containing liquid, can include steps of: providing the container with an open end for receiving a piston; engaging an insertion tool having a first seal with the container, the insertion tool having a duct for receiving the piston, and the piston in the duct forming a second seal; applying vacuum to inside of the container, thereby reducing the pressure to a lower pressure level; operating a pressing tool to force the piston through the duct; and releasing the piston out of the duct and into the container, wherein a pressure difference across the piston drives the piston into the container until the piston reaches a surface of the liquid.

[0015] A system for closing a container containing liquid can include an insertion tool having a first seal for engaging with the container; a duct extending through the insertion tool for receiving a piston; and a vacuum pump for applying vacuum in the container to reduce a pressure level and cause the piston to be transferred through the duct until the piston reaches a surface of the liquid.

[0016] According to the above-described systems and methods for filling and closing containers substantially without formation of gas pockets or foaming, standard dosing systems can be used to provide accurate dosing volumes in standard cycle times. One advantage of the filling process is that in a subsequent closing process, during evacuation for piston setting, there is no eruption in the liquid, even when this evacuation is accomplished very quickly and the pressure level is low. Another advantage of the invention is that liquids that tend to create foam can also be filled under a plurality of different pressure levels.

[0017] A system for degassing a liquid can include a pressure vessel enclosing a soft bag, the pressure vessel being regulated to at least two different pressure levels, a liquid source for supplying a predetermined dose of liquid to the soft bag, and a vacuum pump connected to the pressure vessel for providing vacuum to inside of the pressure vessel, wherein the vacuum reduces the pressure in the soft bag and causes gas to separate from degassed liquid in the soft bag, the separated gas being removable upon raising the pressure in the soft bag.

[0018] A method for degassing a liquid can include steps of: providing a pressure vessel enclosing a soft bag, the pressure vessel being regulated to at least two different pressure levels, supplying a portion of a predetermined dose of liquid to the soft bag, applying vacuum to the pressure vessel to reduce the pressure in the soft bag and causing gas to separate from degassed liquid in the soft bag, supplying a remainder of the predetermined dose of liquid to the soft bag; and removing the separated gas from the soft bag.

[0019] Other aspects and embodiments of the invention are discussed below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] For a fuller understanding of the nature and desired objects of the present invention, reference is made to the following detailed description taken in conjunction with the accompanying drawing figures wherein like reference character denote corresponding parts throughout the several views and wherein:

[0021] FIG. **1**A is a cross-sectional side view of a rigid body which can be filled with liquid and closed according to the present invention;

[0022] FIG. **1**B (PRIOR ART) is a cross-sectional side view of a syringe, but where the syringe contains a gas pocket undesirably formed during a prior art filling process;

[0023] FIG. **1**C is a cross-sectional side view of another syringe which has been filled and closed substantially without formation of a gas pocket according to the present invention;

[0024] FIG. **2** is a schematic view in cross-section of a system for filling syringes according to the present invention;

[0025] FIGS. **3**A to **3**C are cross-sectional side views of a syringe body during various steps of a filling process using the system of FIG. **2**;

[0026] FIG. **4** is a schematic view in cross-section of an alternate system for filling syringes;

[0027] FIG. **5** is a schematic view in cross-section of a system for closing syringes according to the present invention;

[0028] FIGS. **6**A to **6**C are cross-sectional side views of a syringe body during various steps of a closing process using the system of FIG. **5**;

[0029] FIG. **7** is a schematic view in cross-section of a system for filling rigid bodies with foam-free liquid according to the present invention;

[0030] FIGS. **8**A to **8**C are cross-sectional side views of a rigid body during various steps of a filling process using the system of FIG. **7**;

[0031] FIG. **9** is a schematic view in cross-section of a system for degassing liquid; and

[0032] FIGS. **10**A to **10**C are cross-sectional side views of various steps of a degassing process using the system of FIG. **9**.

DEFINITIONS

[0033] The instant invention is most clearly understood with reference to the following definitions:

[0034] As used in the specification and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

[0035] As used herein, the term "substantially," for example, in "substantially without formation of gas pockets," refers to almost no gas pockets, although filling and closing processes having very few gas pockets are encompassed by the present invention.

[0036] As used herein, the terms "syringe" and "rigid body" or "vial" generally refer to any container for receiving liquid, including but not limited to syringes and rigid bodies or vials, or any other container which is capable of being filled with a liquid product and/or closed.

DETAILED DESCRIPTION OF THE INVENTION

[0037] Systems and methods for filling and closing containers substantially without formation of gas pockets or foaming are disclosed. FIGS. **1**A to **1**C depict examples of containers that can be filled and/or closed according to the present invention. As shown in FIG. **1**A, a rigid body or vial **4** can be partially filled with liquid **3**. The rigid body **4** includes a hollow element **1** for holding the liquid **3**, and a stopper **5** which serves as a closing element. As depicted in FIG. **1**A, the rigid body **4** has been partially filled with liquid, but has not yet been closed.

[0038] Referring to FIG. **1**B (PRIOR ART), a syringe **11** is another type of container which can be filled with liquid and closed according to the present invention. The syringe **11** includes a syringe body **6** for holding liquid **3** inside the syringe, which is closed at a top end by a piston **7**, where a cone **36** formed at a bottom end of the syringe body **6** preferably is closed by a tip cap **8**. The piston **7** can be any suitable component for closing the syringe **11**, for example, a slideable stopper.

[0039] Although the syringe **11** shown in FIG. **1**B is the type of container useful with the present invention, in the state shown in FIG. **1**B, the syringe **11** has been partially filled with liquid according to a prior art filling process, and undesirably contains a gas pocket **9**. FIG. **1**B is an example of a prior art filling process which has resulted in formation of gas pockets inside of the syringe body **6**. It is preferred to fill liquid **3** in the syringe **11** and close the piston **7** over the syringe **11** substantially without any gas pockets forming inside the syringe body **6**. FIG. **1**C depicts another syringe **11***a* containing liquid, where the syringe has been filled and closed according to the present invention substantially without formation of any gas pockets.

[0040] The syringes **11** and **11***a* shown in FIGS. **1**B and **1**C, respectively, are suitable for use with the present invention. The syringe **11***a* shown in FIG. **1**C differs from the syringe **11** shown in FIG. **1**B in that the syringe **11***a* includes a syringe body **6***a* terminating with a pre-assembled injection needle **36***a*, which can be covered with a tip cap **8***a*. In FIG. **1**C, the syringe **11***a* has been filled with liquid **3** substantially without formation of any gas pockets, in accordance with the present invention.

[0041] A system for filling containers according to the present invention is depicted in FIG. **2**. The system of FIG. **2** can be used to fill one or more rigid bodies or syringes, for example, of the type depicted in FIGS. **1**A to **1**C. Alternatively, the system of FIG. **2** can be used to fill any suitable container. Referring to FIG. **2**, it is desirable to fill a syringe **11** with liquid, substantially without formation of any gas pockets in the syringe body **6**. The system includes a filling head **13** configured to receive a filling needle **14**, where the filling head **13** further includes a seal **15**. The seal **15** can be an O-ring or any suitable seal for allowing the filling head **13** to engage the syringe body **6** substantially without leaking of fluid, such as liquid or gas, outside of the syringe body **6**. A pipe **17** (also referred to as a "first pipe" or "connection pipe") is connected to the filling needle **14** and preferably runs through the filling head **13**, where the pipe **17** is fluidly connected to a dosing unit **16**, and the dosing unit **16** is connected to a reservoir **18** through a second pipe **19**. This arrangement forms a liquid connection for transferring liquid to a container such as the syringe body **6**. Preferably the reservoir **18** contains a liquid product to be filled into the syringe body **6**, and the dosing unit **16** is any conventional device used for preparing predetermined doses of product to be filled into containers.

[0042] Referring to FIG. **2**, in addition to the above-referenced liquid connection, the filling head **13** also has a gas connection **25** including one or more pipes connected to a vacuum pump **21** by a vacuum valve **22**. The piping used to form the gas connection **25** further includes a pressure release connection **23** having a valve **24**. The piping used as part of the liquid connection and/or the gas connection optionally can include one or more filters **20** for removing particulates and/or contaminants to keep the process clean and sterile.

[0043] A method for filling a container such as the syringe body **6** can be described with reference to FIGS. **3**A to **3**C, using the system provided in FIG. **2**. Referring to FIG. **3**A, according to a first step of the method, the filling head **13** is brought into engagement with the syringe body **6** such that the seal **15** contacts a top portion of the syringe body, preferably on a rim **10** of the syringe body **6**. The seal **15** preferably is configured to provide a fluid-tight engagement between the filling head **13** and the syringe body **6**. At the same time, the filling needle **14** is lowered into the syringe body **6**.

[0044] In a second step of the method, the valve **24** for the pressure release connection **23** is closed, and the valve **22** for the vacuum pump **21** is opened (see FIG. **2**). According to this step, gas is removed from the syringe body **6**, thereby reducing the pressure preferably to less than about 100 mbar.

[0045] In a third step of the method, the dosing system begins to operate, and a portion of the predetermined dose stored in the dosing unit **16** is dispensed through the filling needle **14** into the syringe body **6**. This step is shown schematically in FIG. **3**B, where liquid **3** is shown filling into the syringe body **6**. Capillary forces prevent the liquid **3** from filling the cone **36** of the syringe body **6**. To guarantee that no more than the predetermined dose is transferred to the syringe body, the total interior volume of the filling needle **14** and the connection pipe **17** preferably should be less than the predetermined dose volume.

[0046] In a fourth step of the method, the valve **22** for the vacuum pump **21** is closed, and the pressure release valve **24** is opened. As a result, the pressure in the syringe body **6** rises to ambient pressure, and because of this pressure increase, the liquid **3** is forced into the cone **36**. Referring to FIG. **3**C, the bottom end of the syringe **11** is completely filled with the liquid **3**.

[0047] In a fifth step of the method, the dosing system operates again, and the remainder of the predetermined dose is transferred from the dosing unit **16** to the syringe body **6** via the filling needle **14**. Subsequently, in a final step, the syringe body **6** and the filling head **13** are separated, and the next cycle can be started. The above-described method for filling a container with liquid is illustrative, and the steps may be varied or certain steps omitted, such that the method would still be considered to fall within the scope of the present invention.

[0048] According to the above-described filling process illustrated in FIGS. **2** and **3**A-**3**C, liquid is filled into a

syringe substantially without formation of gas pockets. Filling is accomplished without trapping any significant quantity of gas in the syringe at least because filling occurs at a minimum of two different pressure levels. In the third step of the above filling process, the dosing unit dispenses only a portion of a predetermined dose into the syringe body at a lower pressure. Subsequently, the pressure in the syringe body is increased, and the dosing system is then operated to transfer the remainder of the liquid into the syringe. Although the exemplary method has been described with two stages of liquid transfer at two different pressure levels, additional stages may be provided, and the liquid may be transferred at three of more distinct pressure levels.

[0049] Referring to FIG. **4**, an alternate system for filling syringes is depicted schematically. FIG. **4** is similar to the system shown in FIG. **2**, but further includes a pressure sensitive membrane **26** provided along the connection pipe **17**. The membrane **26** can be positioned in a membrane housing **27** and is preferably fixed thereto using a membrane clamp ring **28**. The system of FIG. **4** can be used in conjunction with a method for filling syringes as described with reference to FIGS. **2** and **3**A-**3**C, with the exception that in the third step of the method, liquid is not directly transferred to the filling needle **14** by using the dosing system (dosing unit **16**). Instead, the liquid product is transferred to the filling needle **14** by deflecting the membrane **26** under the influence of a pressure difference between ambient pressure on the upper side of the membrane **26**, and the vacuum in the syringe body **6**. Subsequently, the pressure level in the syringe body **6** rises to ambient pressure, and the liquid and/or gas moves backwards through the filling needle **14**. The dosing unit **16** then delivers the predetermined dose under ambient pressure. According to this alternate filling system and method, the pressure in the syringe rises from a first pressure level (vacuum pressure) to a second pressure level (ambient pressure). An advantage to this system is that the dosing unit is operated only under ambient pressure, which is preferred to meet high dose accuracy requirements of some applications, and allows the system to operate independently of the particular type of dosing unit or dosing system.

[0050] In the system of FIG. **4**, the pressure sensitive membrane **26** optionally can be provided in the connection pipe **17** itself. For example, if the material of the pipe **17** is sufficiently elastic to be compressed by the pressure difference between ambient air on the outside and the inside vacuum, it will have the same effect as the membrane **26** depicted in FIG. **4**.

[0051] As described above, the systems of FIGS. **2** and **4**, and corresponding methods of FIGS. **3**A to **3**C are used to fill a predetermined dose of liquid into a syringe, and thus constitute a filling process. A subsequent closing process must be provided for closing the syringe or like container.

[0052] Referring to FIG. **5**, a system for closing the syringe **11** involves inserting a piston to cap or close the syringe body **6**. As shown in FIG. **5**, an insertion tool **29** is provided with a seal **30** such as an O-ring or other known sealing mechanism. The seal **30** surrounds a shaft of the insertion tool **29**, and a bypass **31** is positioned inside the shaft and seal **30**. The bypass **31** preferably is in fluid communication with a connection pipe **32**, the pipe **32** being connected to a vacuum pump **33**, which is preferably operated continuously. The insertion tool **29** includes a duct **35** which is configured and arranged to allow passage of a piston therethrough during a process for setting the piston and closing the syringe **11**. The system of FIG. **5** further includes a pressing tool **34** for moving the piston through the duct **35** at least from a first position to a second position closing the syringe **11**.

[0053] A method for closing a container such as a syringe **11** is described with reference to FIGS. **5** and **6**A-**6**C. Referring to FIG. **6**A, in a first step, a piston **7** is placed in the insertion tool **29** from the top.

[0054] According to a second step, the pressing tool **34** engages a back end of the piston **7**. Also, the syringe body **6** is pressed against the seal **30** of the insertion tool **29**, forming a first seal (see FIG. **6**B). The piston **7** within the insertion tool **29** and the seal **30** of the insertion tool **29** held against the syringe body **6** maintain a pressure-tight environment inside of the syringe body **6**. In the state depicted in FIG. **6**B, the vacuum pump **33** is operated to evacuate any gas or liquid from the syringe body **6** (see also FIG. **5**). As a result, the piston **7** is compressed in the insertion tool **29** and is held within the duct **35** at a pressure level of about one bar, where the piston **7** arranged within the duct **35** forms a second seal.

[0055] Subsequently, in a third step depicted in FIG. **6**C, the pressing tool **34** is moved downwardly to force the piston **7** out of the duct **35** of the insertion tool **29**. As the piston **7** exits the duct **35**, it expands and forms a seal against the inside wall of the syringe body **6**.

[0056] Then, in a fourth step, after the piston **7** has left the insertion tool **29**, ambient air is permitted to flow through the duct **35**, and the pressure rises above the piston **7**. This forms a pressure difference across the piston **7**, and the resulting force is sufficient to push the piston **7** down in the syringe body **6** until the piston **7** contacts a top surface of the liquid **3**.

[0057] In a fifth step, the syringe body **6** and the piston insertion tool **29** are separated, where the syringe **11** has been filled and closed substantially without the formation of gas pockets.

[0058] Referring to FIG. **7**, a system for filling rigid bodies or vials with liquid substantially without foaming is depicted. The system of FIG. **7** is similar to the filling system depicted in FIG. **2**, but where a rigid body **4** is the type of container being filled in FIG. **7**. Using the system of FIG. **7**, the rigid body **4** can be filled substantially without foaming, resulting in a substantial foam-free liquid in the rigid body **4**. The system includes a filling head **13** configured to receive a filling needle **14**, the filling head **13** being formed with a seal **15**, as previously described with reference to FIG. **2**. The filling head **13** is fluidly connected with a dosing unit **16** via a connecting pipe (or "first pipe") **17**. The dosing unit **16** is fluidly connected with a reservoir **18** via a second pipe **19**.

[0059] As shown in FIG. **7**, in addition to a liquid connection, the filling head **13** also has a gas connection **25** including one or more pipes connected to a vacuum pump **21** via a vacuum valve **22**. The piping used to form the gas connection **25** further includes a pressure release conduit **23** having a valve **24**. The piping used for the liquid connection and/or gas connection optionally can include one or more

filters **20** to maintain sterility. The above-described system depicted in FIG. **7** is particularly useful for filling rigid bodies or vials with a foam-creating liquid.

[**0060**] In the system of FIG. **7**, preferably the filling needle **14** for filling the rigid body **4** is longer than the filling needle **14** depicted in FIG. **2**. The longer filling needle is useful for preventing foaming of the liquid during delivery of a dose of liquid to the rigid body **4**.

[**0061**] A method for filling a container such as the rigid body **4** can be described with reference to FIGS. **7** and **8**A-**8**C. Referring to FIG. **7**, in a first step, an empty rigid body **4** and the filling head **13** are assembled together such that the seal **15** is brought into tight engagement with the top of the rigid body **4**. Second, the pressure release valve **24** is closed, and the valve **22** for the vacuum pump **21** is opened (see FIG. **7**). As a result, gas is removed from the rigid body **4** to form a reduced pressure.

[**0062**] In a third step, a first portion of a predetermined dose is transferred through the filling needle **14** into the rigid body **4**. The free flow of liquid against the bottom of the rigid body **4** results in the production of foam **37** (see FIG. **8**A). At this stage, liquid **3** and foam **37** are both present in the rigid body **4**.

[**0063**] In a fourth step, the valve **22** for the vacuum pump **21** is closed, and the pressure release valve **24** is opened. As a result, the pressure in the rigid body **4** rises to ambient pressure, and during this pressure increase, the foam **37** substantially collapses because it contains only a small amount of gas (see FIG. **8**B).

[**0064**] In a fifth step, the dosing unit **16** is re-activated, and the remainder of the predetermined dose is transferred into the rigid body **4** via the filling needle **14**, while a dispensing end of the needle **14** preferably is positioned below the liquid surface. This subsurface filling of liquid into the rigid body **4** can help avoid the creation of foam.

[**0065**] According to the above-described process for filling a rigid body, the rigid body can be filled substantially without foaming. Alternatively, the process described with reference to FIGS. **2** and **3**A-**3**C could simply be adapted for use with rigid bodies or vials. In any event, filling is accomplished substantially without formation of gas pockets and/or foaming.

[**0066**] Systems and methods for degassing liquids are encompassed by the present invention. In particular, the dissolved gas level of the liquid used for filling a container, such as the liquid used in the previously described systems and methods for filling syringes or rigid bodies/vials, can impact such systems and methods for producing gas-pocket free syringes and foam-free rigid bodies or vials. A suitable system for degassing liquid is described with reference to FIG. **9**.

[**0067**] As shown in FIG. **9**, liquid **3** is stored in a storage tank **100**. A connecting pipe **101** is fluidly connected to the storage tank **100**, where the connecting pipe **101** has a valve **102**, and terminates in a link to other pipes. The other pipes forming this link include a first pipe **104** which connects to a soft bag **103** preferably housed within a pressure vessel **110**. The first pipe **104** incorporates a valve **105**. A second pipe **106** includes a valve **107**, the second pipe **106** being connected with a vacuum pump **21**. A third pipe **108** making up the link includes a valve **109**, and is connected with a dosing unit **16**. Optionally, one or more filters **20** may be included to keep the system clean and sterile.

[**0068**] According to the system of FIG. **9**, the soft bag **103** preferably is enclosed within the pressure vessel **110**. The pressure vessel **110** has a connecting pipe **111** including a valve **112** that leads to a vacuum pump **21**. The pressure vessel **110** also has a second pipe **113** with a valve **114** connected to a supply of compressed air **115**.

[**0069**] A degassing process according to the present invention can be described with reference to FIGS. **9** and **10**A-**10**C. In a first step, the valves **102** and **105** are opened, allowing liquid **3** to be transferred from the storage tank **100** to the soft bag **103** (see FIG. **9**), preferably until the soft bag is filled to approximately one-half of its capacity, as depicted schematically in FIG. **10**A. To support this transfer step, the valve **112** may also be opened. All of these valves are closed after the soft bag is filled to a desired level.

[**0070**] In a second step, the valve **112** is opened, thereby reducing the pressure in the vessel **110** by applying vacuum inside the vessel **110**. As a result, the pressure in the soft bag **103** is reduced, causing any dissolved gas to separate from the liquid in the soft bag **103** (see FIG. **10**B). After some time elapses, a pressure-specific equilibrium is reached with a degassed liquid and the separated gas present in the soft bag **103**. All valves of the system are then closed.

[**0071**] In a third step, the valves **105** and **109** are opened, and the filling process through the dosing unit **16** is carried out until all degassed liquid is used. Then, the valves are closed. Finally, in a fourth step, the valves **105**, **107**, and **114** are opened, and the separated gas is removed through the pipe **104** until the soft bag **103** is empty (see FIG. **10**C). Then, all valves are closed, and the degassing process can be repeated.

[**0072**] The above-described process can be used to prepare degassed liquid for use in a filling system and process for filling a container, such as a syringe and rigid body/vial, which will further reduce the possibility of gas pocket formation or foaming of liquid in the container.

[**0073**] Although preferred embodiments of the invention have been described using specific terms, such description is for illustrative purposes only, and it is to be understood that changes and variations may be made without departing from the spirit or scope of the following claims.

INCORPORATION BY REFERENCE

[**0074**] The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

What is claimed is:

1. A system for filling a container with liquid, comprising:

a dosing unit for supplying the liquid to the container;

a filling head for receiving the liquid from the dosing unit and transferring the liquid to inside of the container when the filling head engages the container; and

a vacuum pump connected to the filling head for providing vacuum to inside of the container;

wherein a pressure inside the container is regulated to at least two different pressure levels during transfer of the liquid through the filling head.

2. The system of claim 1, where the two different pressure levels include ambient pressure and a pressure of the vacuum supplied by the vacuum pump.

3. The system of claim 1, further comprising a filling needle received in the filling head, the filling needle delivering the liquid to inside of the container.

4. The system of claim 3, wherein the filling needle is received inside the container.

5. The system of claim 4, wherein the dosing unit is connected to the filling needle for supplying the liquid in a predetermined dose to the filling needle.

6. The system of claim 5, further comprising a pressure sensitive membrane provided between the dosing unit and the filling needle to control transfer of the liquid.

7. The system of claim 1, wherein the filling head includes a seal for engaging the container.

8. The system of claim 1, further comprising a gas connection for delivering the vacuum from the vacuum pump to the filling head.

9. The system of claim 8, wherein the gas connection includes a pressure release connection.

10. The system of claim 1, wherein the container is defined by a rigid body.

11. The system of claim 10, wherein the rigid body is filled substantially without foaming of the liquid.

12. The system of claim 1, wherein the liquid is a pharmaceutical or diagnostic liquid.

13. A method for filling a container with liquid, comprising the steps of:

providing the container with an open end for receiving the liquid;

engaging a filling head with the container such that the filling head and the container form a seal;

opening a vacuum source to inside of the container, thereby reducing the pressure to a first pressure level;

supplying a portion of a predetermined dose of the liquid from a dosing unit to inside of the container through the filling head;

closing the vacuum source, thereby raising the pressure inside the container from the first pressure level to a second pressure level; and

supplying a remainder of the predetermined dose of the liquid from the dosing unit to inside of the container such that the container is filled substantially without formation of gas pockets in the container.

14. The method of claim 13, wherein the container is a syringe having a top portion with the open end and a bottom portion defining a cone.

15. The method of claim 14, wherein during the step of closing the vacuum source, the liquid is forced into the cone of the syringe.

16. The method of claim 13, wherein during the step of supplying the portion of the predetermined dose, foam is formed in the container, and during the step of closing the vacuum source and raising the pressure in the container, the foam is substantially collapsed in the container.

17. A method for closing a container containing liquid, comprising the steps of:

providing the container with an open end for receiving a piston;

engaging an insertion tool having a first seal with the container, the insertion tool having a duct for receiving the piston, and the piston in the duct forming a second seal;

applying vacuum to inside of the container, thereby reducing the pressure to a lower pressure level;

operating a pressing tool to force the piston through the duct; and

releasing the piston out of the duct and into the container, wherein a pressure difference across the piston drives the piston into the container until the piston reaches a surface of the liquid.

18. A system for closing a container containing liquid, comprising:

an insertion tool having a first seal for engaging with the container;

a duct extending through the insertion tool for receiving a piston; and

a vacuum pump for applying vacuum in the container to reduce a pressure level and cause the piston to be transferred through the duct until the piston reaches a surface of the liquid.

19. The system of claim 18, wherein the vacuum pump is operated continuously.

20. A system for degassing a liquid, comprising:

a pressure vessel enclosing a soft bag, the pressure vessel being regulated to at least two different pressure levels;

a liquid source for supplying a predetermined dose of liquid to the soft bag; and

a vacuum pump connected to the pressure vessel for providing vacuum to inside of the pressure vessel, wherein the vacuum reduces the pressure in the soft bag and causes gas to separate from degassed liquid in the soft bag, the separated gas being removable upon reaching equilibrium of the gas in the liquid.

21. The system of claim 20, wherein the degassed liquid is removed from the soft bag prior to removal of the separated gas.

22. The system of claim 20, wherein the soft bag has a single outlet, the outlet being connected to a pipe for liquid and gas transfer.

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