



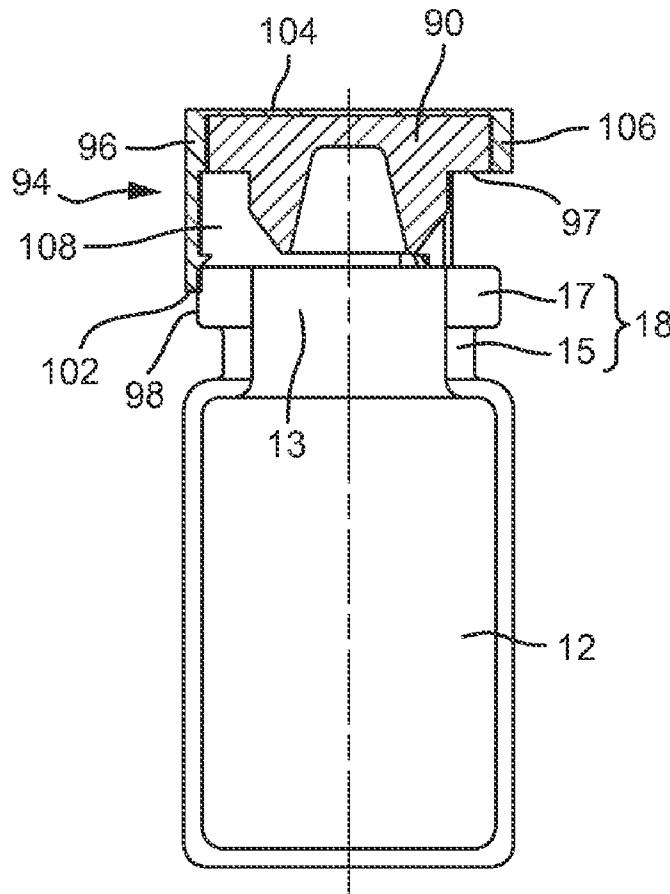
US 20090001042A1

(19) **United States**(12) **Patent Application Publication**
Sever et al.(10) **Pub. No.: US 2009/0001042 A1**(43) **Pub. Date: Jan. 1, 2009**(54) **CONTAINER-CLOSURE SYSTEM FOR USE
IN LYOPHILIZATION APPLICATIONS**(52) **U.S. Cl. 215/248; 215/277; 215/307; 215/363**(76) **Inventors:** **Robert Sever**, Arlington Heights,
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(21) **Appl. No.: 12/144,872**(22) **Filed: Jun. 24, 2008****Related U.S. Application Data**(60) **Provisional application No. 60/937,232, filed on Jun.
26, 2007.****Publication Classification**(51) **Int. Cl.**
B65D 51/16 (2006.01)
B65D 41/50 (2006.01)(57) **ABSTRACT**

A container closure system for use in lyophilization processes employing depressurization to initiate nucleation is provided. The present container closure system includes a container and a closure element disposed proximate to and adapted for sealing the opening of the container. The closure element includes a first sealing surface adapted for sealably contacting an interior surface of the container and a second sealing surface adapted for sealably contacting the top surface of the container when the container closure system is in a closed position. The closure element also includes a plurality of closure legs extending from the second sealing surface that define a plurality of side vents between each of the closure legs when the container closure system is in the open position. The length, thickness, number, and shape of the legs are chosen to produce an effective total side vent area that is at least 50% of the area of the container opening. Alternatively, the length, thickness, number, and shape of the legs are chosen to produce an effective total side vent area that is greater than the cumulative surface area of the outwardly facing surface of the closure legs.



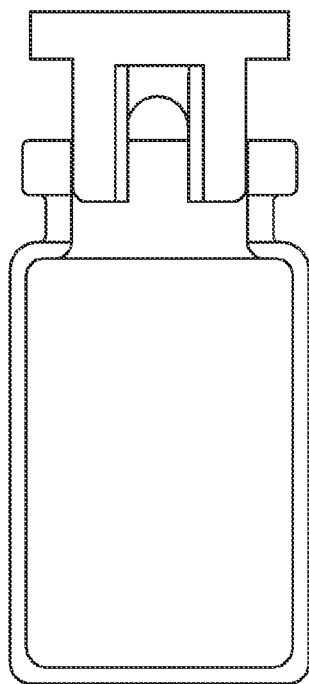


FIG. 1B
(Prior Art)

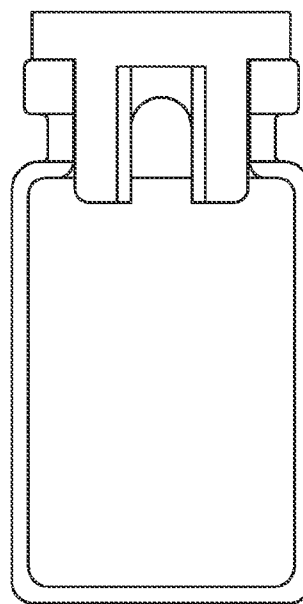


FIG. 1C
(Prior Art)

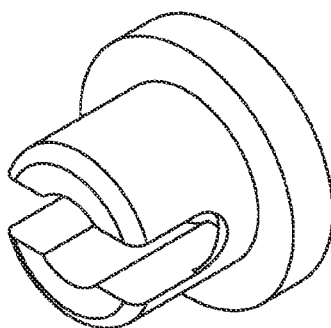


FIG. 1A
(Prior Art)

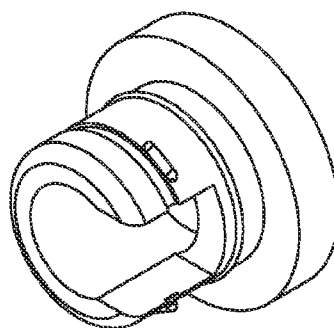


FIG. 2
(Prior Art)

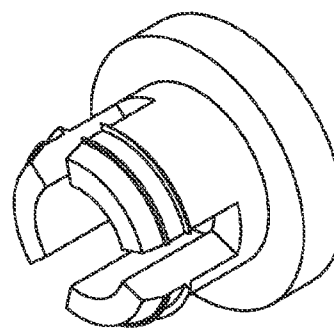


FIG. 3
(Prior Art)

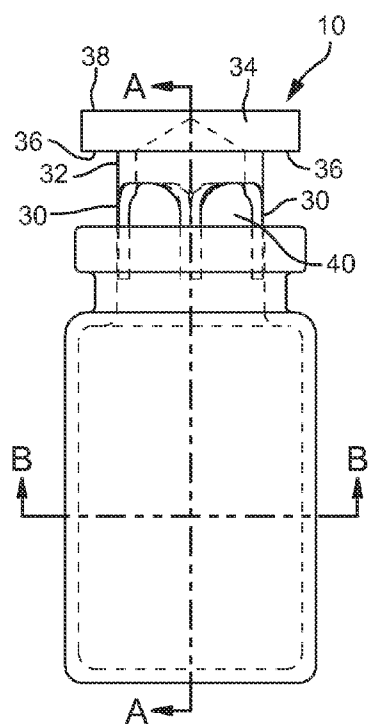


FIG. 4

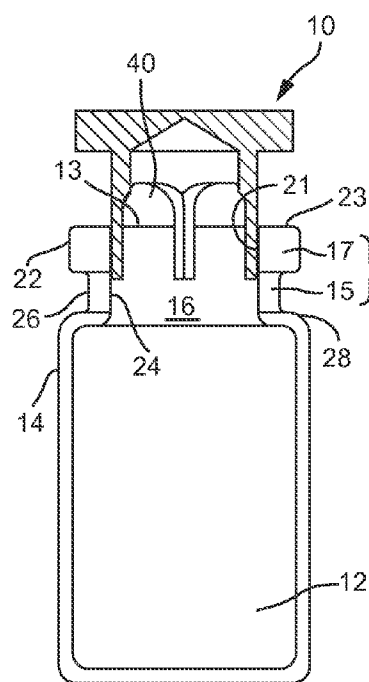


FIG. 4A

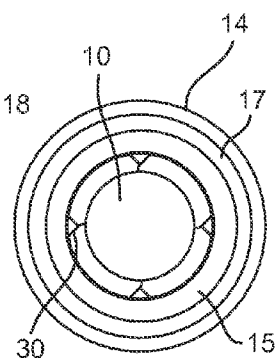


FIG. 4B

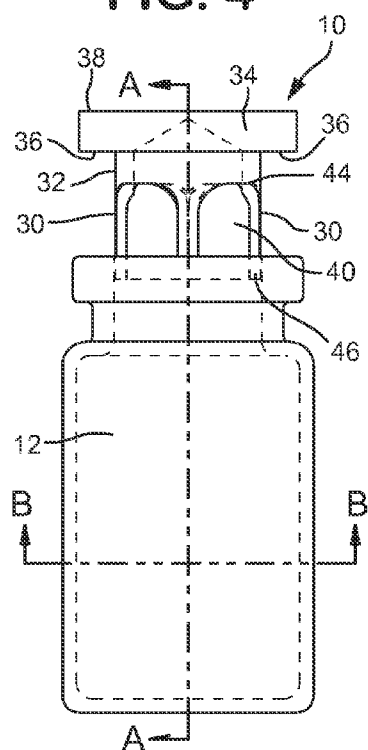


FIG. 5

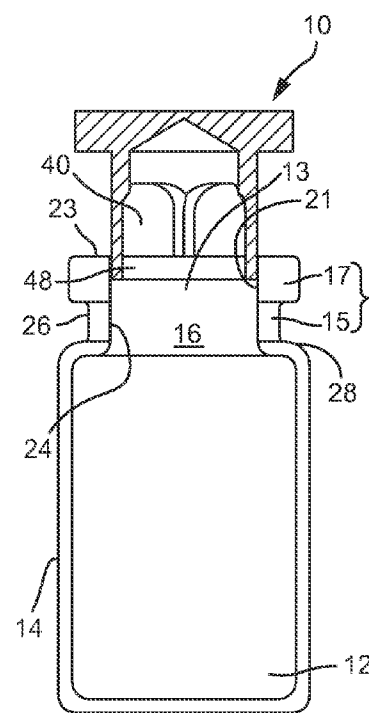


FIG. 5A

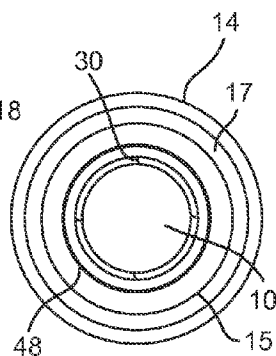
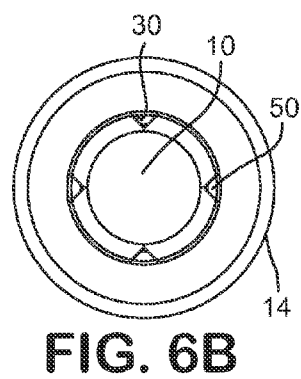
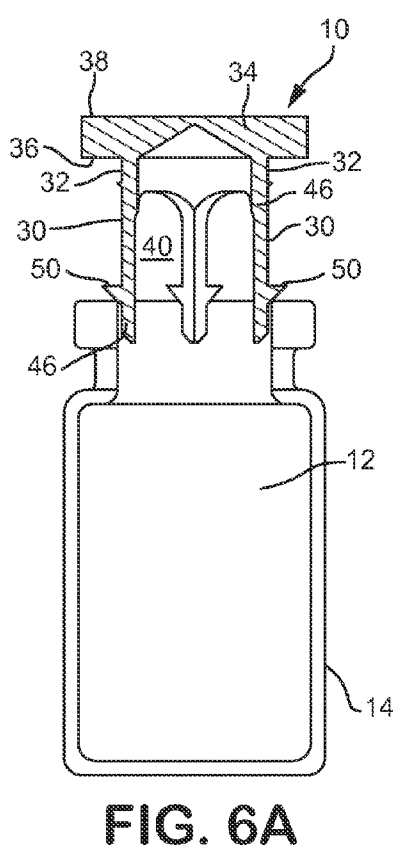
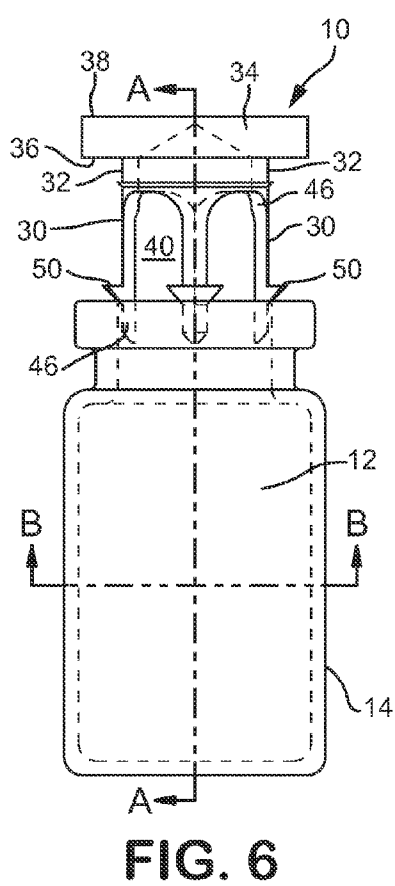


FIG. 5B



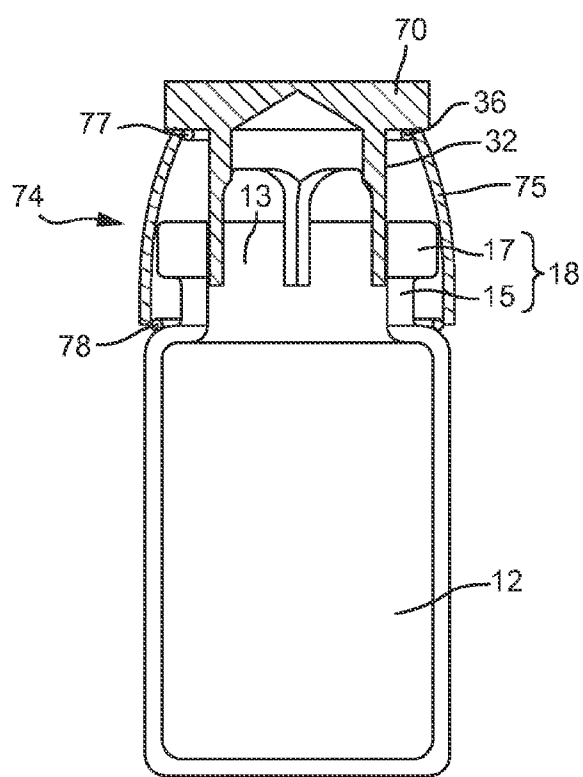


FIG. 7

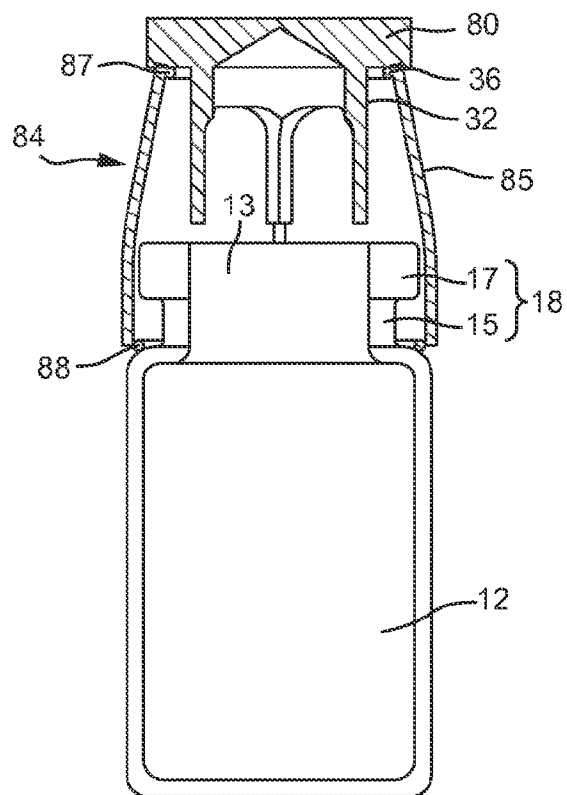


FIG. 8

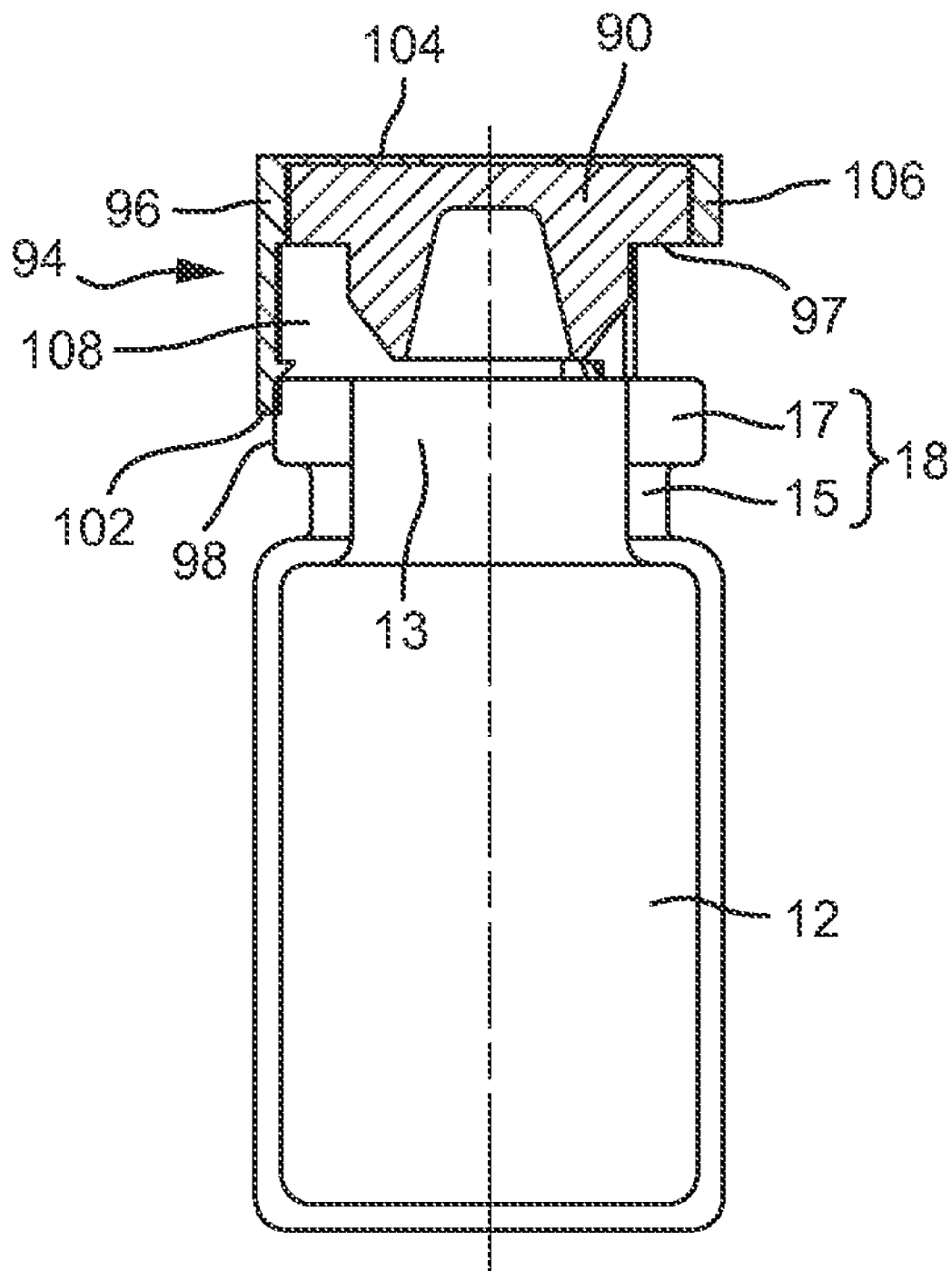


FIG. 9

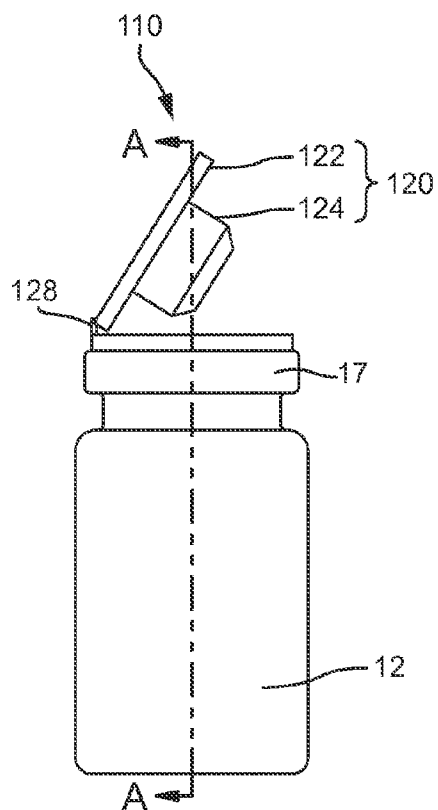


FIG. 10

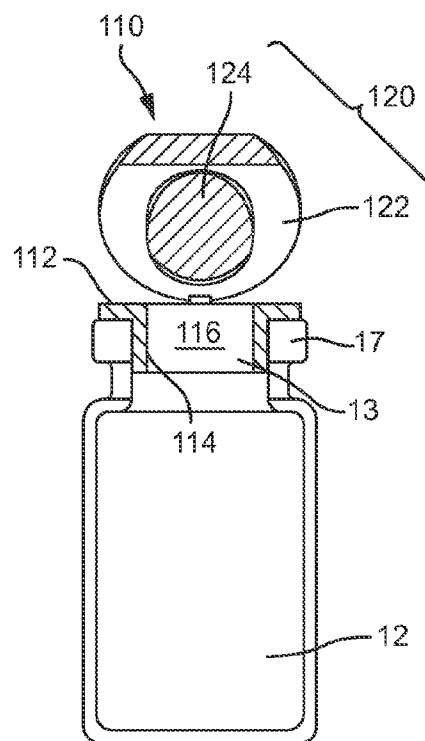


FIG. 10A

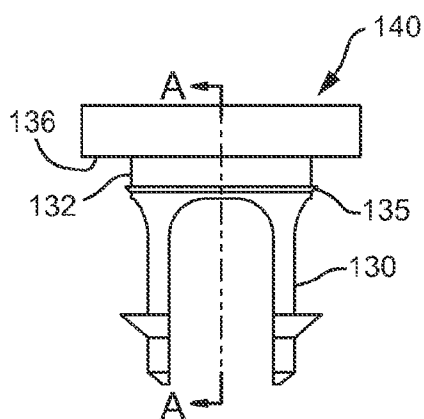


FIG. 11

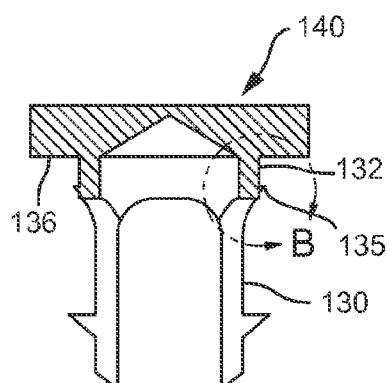


FIG. 11A

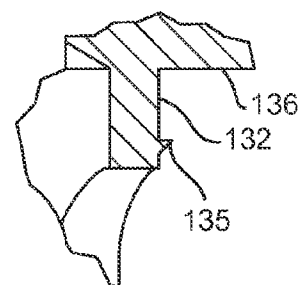


FIG. 11B

CONTAINER-CLOSURE SYSTEM FOR USE IN LYOPHILIZATION APPLICATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent application Ser. No. 60/937,232, filed on Jun. 26, 2007.

FIELD OF THE INVENTION

[0002] The present invention relates to a container closure system for use in lyophilization applications, and more particularly, to vial or container stoppers useful in advanced lyophilization processes.

BACKGROUND

[0003] Lyophilization, or freeze-drying, is a process used in manufacturing various pharmaceutical, veterinary, medical, or diagnostic products. In a broad sense, a typical lyophilization process includes a material loading phase, a freezing phase, one or more drying phases, and a post-drying handling phase. In many lyophilization processes, the material to be lyophilized is a solution placed into a container such as a glass vial or bottle. This container is generally equipped with a special closure, or stopper, that provides both a path for solvent removal during the drying phases of the lyophilization process and a method for sealing the container during the post-drying phase to protect the lyophilized material from contamination or degradation during its specified shelf-life.

[0004] Closures are often manufactured out of polymeric materials that provide a flexible seal capable of conforming to potential irregularities in the container dimensions and being penetrated by a needle to reconstitute the lyophilized material or withdraw the reconstituted material. The combination of a container and a closure is commonly referred to as a "container-closure system." The container-closure system is generally supplemented by an aluminum crimp seal that overlays the junction between the container and closure.

[0005] FIG. 1A depicts a prior art stopper or closure whereas FIG. 1B and FIG. 1C show the prior art container-closure system using the closure of FIG. 1A. As seen therein, the stopper or closure is a two-leg configuration. The two legs allow the closure to stand in the container in an open position during the lyophilization process and act as guides when the closure is pushed or pressed downward from the open or unsealed position (FIG. 1B) into the closed or sealed position (FIG. 1C) after lyophilization is complete. FIG. 2 depicts a prior-art one-leg closure configuration, and FIG. 3 illustrates a three-leg closure configuration also found in the prior art.

[0006] In all three prior art closures, the closure includes a vertical sealing surface located above the legs that seals against the inside wall of the container mouth when the closure is oriented in the closed position. In addition, each of the closures also includes a continuous horizontal sealing surface disposed above the vertical sealing surface. The horizontal sealing surface provides a seal that is pressed against the rim of the container mouth when the closure is oriented in the closed position.

[0007] The size and shape of the closure legs and the manner in which they are positioned relative to the container dictate the size and shape of the openings through which fluids may enter or leave the container (e.g., solvent vapor being removed during drying). These openings are commonly referred to as the vents. Most container-closure sys-

tems used for lyophilizing various pharmaceutical, veterinary, medical, or diagnostic products are designed such that the vents do not present a significant resistance to vapor flow out of the container during the primary or secondary drying processes. Conventional lyophilization container-closure systems are designed to minimize the size of the vents without significantly impeding the upper range of solvent vapor flow rates that are typically encountered in the drying phases of lyophilization. The vents are traditionally minimized in an effort to control manufacturing costs, reduce product contamination risks when the container closure system is in the open position, and ensure an acceptable seal when the container closure system is oriented in the closed position.

[0008] A recent advancement in lyophilization processes, as set forth in U.S. patent application Ser. No. 11/702,472, involves changes in the pressure in the lyophilization chamber during the freezing phase so as to initiate nucleation of the solution to be lyophilized in a controlled and uniform manner. What is needed is an improved closure or stopper for use in lyophilization processes that optimizes the vent area yet does not present significant resistance to changes in the lyophilization environment during either the freezing phase or the drying phases of lyophilization processes, and ensures an acceptable seal when the container closure system is oriented in the closed position.

SUMMARY OF THE INVENTION

[0009] In one aspect, the present invention may be characterized as a container-closure system comprising: a container having an upper section defining an opening having a cross-sectional area and the container having a top surface and an interior surface adjacent to the opening; the container further comprising a body section defining a cavity in fluid communication with the opening; a closure element disposed proximate to the container and adapted for sealing the opening of the container when in a closed position, the closure element having a first sealing surface adapted for sealably contacting the interior surface of the container when in the closed position, the closure element having a second sealing surface adapted for sealably contacting the top surface of the container when in the closed position, and the closure element having a plurality of closure legs extending from the first or second sealing surface toward the body section; wherein the closure legs define a plurality of side vents between each of the closure legs when the container closure system is in an open position and the cumulative area of the side vents is greater than or equal to 50% of the cross-sectional area of the opening; and wherein the side vents define a fluid path between the cavity within the container and an atmosphere surrounding the container to facilitate nucleation of freezing of a material disposed within the cavity of the container upon depressurization of the atmosphere surrounding the container.

[0010] The invention may also be characterized as a lyophilization stopper comprising: a sealing element defining an annular sealing surface; a cap section disposed adjacent to the sealing element and having a second sealing surface disposed in an orthogonal orientation relative to the annular sealing surface; and a plurality of closure legs extending from the annular sealing surface, each of the closure legs further defining an outwardly facing surface and the plurality of closure legs further defining a plurality of side vents between each of the closure legs; wherein the cumulative area of the plurality

of side vents is equal to or greater than the cumulative area of the outwardly facing surfaces of the closure legs.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The above and other aspects, features, and advantages of the present invention will be more apparent from the following, more descriptive description thereof, presented in conjunction with the following drawings, wherein:

[0012] FIG. 1A is a perspective view of a prior art stopper used in lyophilization applications;

[0013] FIG. 1B is a cross-sectional view of a container with the stopper of FIG. 1A shown in the open or unsealed position;

[0014] FIG. 1C is a cross-sectional view of a container with the stopper of FIG. 1A shown in the closed or sealed position;

[0015] FIG. 2 is a perspective view of another prior art stopper typically used in lyophilization applications;

[0016] FIG. 3 is a perspective view of yet another prior art stopper typically used in lyophilization applications;

[0017] FIG. 4 is a side view of a container-closure arrangement in accordance with an embodiment of the present invention;

[0018] FIG. 4A is a cross-sectional view of the container-closure arrangement of FIG. 4 taken along line A-A.

[0019] FIG. 4B is a cross-sectional view of the container-closure arrangement of FIG. 4 taken along line B-B.

[0020] FIG. 5 is a side view of a container-closure arrangement in accordance with another embodiment of the present invention;

[0021] FIG. 5A is a cross-sectional view of the container-closure arrangement of FIG. 5 taken along line A-A.

[0022] FIG. 5B is a cross-sectional view of the container-closure arrangement of FIG. 5 taken along line B-B.

[0023] FIG. 6 is a side view of a container-closure arrangement in accordance with another embodiment of the present invention;

[0024] FIG. 6A is a cross-sectional view of the container-closure arrangement of FIG. 6 taken along line A-A;

[0025] FIG. 6B is a cross-sectional view of the container-closure arrangement of FIG. 6 taken along line D-D;

[0026] FIG. 7 is a side cross-sectional view of a container-closure arrangement employing a suspension device in accordance with yet another embodiment of the present invention;

[0027] FIG. 8 is a side cross-sectional view of a container-closure arrangement employing a suspension device in accordance with still another embodiment of the present invention;

[0028] FIG. 9 is a side cross-sectional view of a container-closure arrangement employing a suspension device in accordance with still another embodiment of the present invention;

[0029] FIG. 10 is a side view of a container-closure arrangement in accordance with yet another embodiment of the present invention;

[0030] FIG. 10A is a cross-sectional view of the container-closure arrangement of FIG. 10 taken along line A-A;

[0031] FIG. 11 is a side view of a container-closure arrangement in accordance with still another embodiment of the present invention;

[0032] FIG. 11A is a cross-sectional view of the container-closure arrangement of FIG. 11 taken along line A-A; and

[0033] FIG. 11B is a cross-sectional view of the container-closure arrangement of FIG. 11A detailing area B-B.

DETAILED DESCRIPTION

[0034] The advanced lyophilization process described in U.S. patent application Ser. No. 11/702,472, and incorporated by reference herein, involves depressurization of the lyophilization chamber to controllably induce nucleation of freezing in the solution during lyophilization. Conventional container-closure designs tend to inhibit the efficacy of the depressurization method for inducing nucleation. The present container-closure systems, disclosed herein, allow the controlled nucleation via depressurization to occur with less interference and in a more precisely controlled manner.

[0035] Turning now to FIG. 4, there is shown an embodiment of the present container-closure system. The container closure system includes a closure element or stopper 10 adapted for sealing a container 12 when depressed into the top mouth or opening 13 of the container 12. The container 12 includes a generally cylindrical body section 14 adapted to contain a solution to be lyophilized, a neck portion 15 which defines an opening 16 into the body section 14, and a rim section 17 adapted for sealably engaging the closure or stopper 10 when the container 12 is sealed. Collectively the neck portion 15 and rim section 17 of the container 12 are referred to as the top section 18 of the container 12. As seen in the drawings, the rim section 17 includes a rim inner surface 21, a rim outer surface 22, and a top surface 23. The rim section 17 also defines an opening or mouth 13 of the container 12 having a prescribed diameter. The neck portion 15 of the container 12 also defines a neck inner surface 24 generally aligned with the rim inner surface 21 and adapted to receive and guide the closure element 10 into place during sealing. The neck portion 15 also includes a neck outer surface 26 that defines an annular shoulder 28 that facilitates handling the container 12 with and without the closure element 10.

[0036] Similar to conventional closures, the closure element or stopper 10 illustrated in FIGS. 4, 4A, and 4B possesses a set of legs 30; a first, vertically or nearly vertical oriented sealing surface 32; and a cap section 34 that defines a second, horizontally or nearly horizontal oriented sealing surface 36 and a top surface 38. As with the prior art stoppers, the closure legs 30 function to align and stand the closure element 10 inside the rim section 17 of the container 12 in an open position during the lyophilization process. The closure legs 30 also function as guides when pushing or pressing the closure element 10 into the closed position after lyophilization is complete. The four legs 30 for the closure element 10 illustrated in FIG. 4, FIG. 4A, and FIG. 4B each possess a triangular cross-section, although various other leg cross-section configurations are equally suitable within the present container-closure system. The vertically or nearly vertical oriented sealing surface 32 of the closure element 10 is an annular surface located above the closure legs 30 and beneath the cap section 34. The horizontally or nearly horizontal oriented sealing surface 36 of the cap section 34 is adjacent to and generally orthogonal to the annular vertically oriented sealing surface 32.

[0037] When the container-closure system is oriented in the open position, the closure element 10 stands upright within the container mouth 13 and is held in such stationary position as a result of the friction forces between the legs 30 and the inside surface 21 of the rim section 17 of the container 12. When the container-closure system is oriented in the closed

position, the vertical sealing surface 32 functions to seal the closure against the inside surface 21 of the rim section 17 proximate the mouth 13 of the container 12. Concurrently, the horizontal sealing surface 36 forms a seal against the top surface 23 of the rim section 17 of the container 12 proximate the mouth 13 of the container 12.

[0038] In most commercial lyophilization processes, numerous individual container-closure systems are processed simultaneously within the freeze-dryer. The containers are loaded onto temperature-controlled shelves within the freeze-dryer with the container-closure system placed in the open position. The container-closure systems are maintained in the open position during the freezing and drying phases of the lyophilization process. Upon completion of the drying phase, the container-closure systems are moved from the open position to the closed position. Most commercial freeze-dryers are equipped with automatic closure systems that push or depress the closure elements into the container mouth once the lyophilization process is complete. The closure step generally occurs in the presence of an inert gas like nitrogen between approximately 10 mTorr and atmospheric pressure. Automatic closure is typically accomplished by raising or lowering the shelves so that all closures on a given shelf are pushed into their respective containers by contact with the shelf above.

[0039] As discussed above, the size and shape of the closure legs and the position of the closure element relative to the container define the size and shape of openings through which fluids may enter or leave the container when the container-closure system is in the open position. As depicted in FIGS. 4, 4A, and 4B, there are shown two different vents created by the engagement of the closure legs 30 with the container 12. As used herein, side vents 40 are the openings between each of the closure legs 30 above the rim section 17 of the container 12 and below the annular vertical sealing surface 32. In addition the mouth vent is the generally circular opening of the container mouth 13 that is not obstructed by the closure legs 30. The size, shape, and number of the side vents 40 together with the size and shape of the mouth vent are important features of the present container-closure system. For purposes of describing the present container-closure system, it is convenient to characterize the size and shape of a vent using a parameter referred to as hydraulic diameter (D_H), as follows:

$$D_H = 4A/P$$

[0040] where A is the open area of a vent at its minimum cross-section and P is the linear perimeter of the vent at its minimum cross-section. The hydraulic diameter characterizes an effective vent area (A_E) of a side vent or a mouth vent as follows:

$$A_E = \frac{\pi D_H^2}{4}$$

[0041] Since the side vents are often plural in number, it is also useful to define a "total side vent area" ($A_{T,S}$) as follows:

$$A_{T,S} = \sum N_S A$$

[0042] where N_S is the number of side vents. Likewise, the effective total side vent area ($A_{ET,S}$) can be defined as follows:

$$A_{ET,S} = \sum N_S A_E$$

[0043] The present container-closure systems are characterized in that both the effective total side vent area and the effective mouth vent area are maximized and each are preferably at least 50% of the cross-sectional area of the mouth of the container. Alternatively, the length, thickness, number, and shape of the legs are chosen to produce an effective total side vent area that is greater than the cumulative surface area of the outwardly facing surface of the closure legs. Preferred embodiments of the present container closure system include one or more vents.

[0044] Turning now to FIG. 5, FIG. 5A, and FIG. 5B there is shown another embodiment of the present container-closure system. Many of the elements of the container and the upper portion of the closure element are the same or similar to the embodiment described with reference to FIG. 4 and will not be repeated here. The difference in this embodiment is that the cross-sectional shape of the closure element 10 is non-uniform along the length of the closure legs 30. At the upper end 44 of the closure legs 30 proximate the vertical sealing surface 32 and cap section 34 of the closure element 10, the four legs 30 are relatively thin to provide greater effective total side vent area 40. Towards the distal end 46 of the closure legs 30, the four legs transition into an annular lower ring 48 that provides a very stable base to support the closure element 10 or stopper standing in the container 12 when the container closure system is in the open position. The lower ring 48, however, is dimensioned so as to maximize the effective mouth vent area and, in particular maintain the effective mouth vent area greater than 50% of the container mouth area.

[0045] The closure shown in FIG. 6, FIG. 6A, and FIG. 6B differ from the closures previously described by the shape and features of the closure legs. The illustrated container-closure system maintains the effective total side vent area 40 and sealing features of the previously described designs including a set of four closure legs 30 and the annular vertically oriented sealing surface 32 and the horizontally oriented sealing surface 36 above the legs 30 necessary to provide a pharmaceutically acceptable seal with the container-closure system. Again, many of the elements of the container and the upper portion of the closure element are the same or similar to the embodiments described with reference to FIG. 4 and FIG. 5 and thus will not be repeated here. However, the illustrated closure element 10 includes one or more outwardly directed protrusions 50 located at or near the distal end 46 of the closure legs 30. These protrusions 50 enable the closure element 10 to sit or rest on the top surface 23 of the rim section 17 of the container 12 when the container closure system is in the open position. When the container closure system is to be closed, the protrusions 50 and legs 30 are pushed through the mouth 13 and into the neck portion 15 of the container 12 so the vertical or nearly vertical sealing surface 32 can sealably mate with the inner surface 21 of the rim section 17 and the horizontal or nearly horizontal sealing surface 36 can sealably mate with the top surface 23 of the rim section 17 of the container 12.

[0046] The material and dimensions of the protrusions 50 and legs 30 are selected to allow them to properly compress upon entering the mouth 13 of the container 12 during the closure process. As seen in the drawings, the protrusions 50 should be sufficiently long to accommodate the variability of mouth diameters for a given container style. Again, the length, thickness, number, and shape of the legs and protrusions are chosen to optimize the effective total side vent area

40 and an effective mouth vent while maintaining stability of the container closure system when in the open position.

[0047] As can be appreciated when considering the embodiments described above, the shape and surface features of the closure element, and in particular, the closure legs, can be modified to enhance the stability of the container closure system in the open position and the sealing properties of the container closure system in the closed position while maintaining the desired effective vent areas.

[0048] FIG. 7, FIG. 8, and FIG. 9 show a container-closure system with a stopper or closure element 70, 80, 90 respectively coupled or mounted to a container 12 with the aid of a suspension device 74, 84, 94 respectively. FIG. 7 illustrates a container-closure system in an open position with the closure element 70 partially engaged into the mouth 13 of the container 12 and held in place by collapsible arms 75. FIG. 8 illustrates a container-closure system in an open position with the closure 80 suspended above the container 12 and also held in place by a suspension device 84 such as collapsible arms 85. FIG. 9 illustrates a container-closure system in an open position with the closure 90 suspended above the container 12 and held in place within a suspension device 94, namely a hollow cylindrical sleeve 96. In the three embodiments of FIGS. 7, 8, and 9, the annular suspension device 74, 84, 94 (i.e. collapsible arms or sleeve) is bound at one end 77, 87 to the closure element 70, 80, 90, preferably at or near the horizontally oriented sealing surface. The annular suspension device 74, 84, 94 is also attached at the second end 78, 88, 98 to the outside surface of the top section 18 of the container 12.

[0049] Upon conclusion of the drying phase of the lyophilization process, the suspension device 74, 84, 94 collapses or moves under the closing force to allow the closure element 70, 80, 90 to move downward and seal the container 12 at the generally vertical and horizontal sealing surfaces. The embodiment of FIG. 7 employs the suspension device 74 partially within the mouth 13 of the container 12 to provide enhanced stability of the container-closure system while in the open position. As with the container-closure systems shown and described above, the length, thickness, number, and shape of the legs are chosen to produce an effective total side vent area and an effective mouth vent area greater than 50% of the container mouth area. The embodiments of FIG. 8 and FIG. 9, on the other hand, employ a suspension device 84, 94 that suspends the closure 80, 90 above the container 12, helping maximize the effective vent areas while still providing a facile means of sealing the container 12.

[0050] In the embodiment of FIG. 9, the suspension device 94 takes the form of a hollow cylindrical sleeve 96 where one end, namely the mouth end 102, is open and has an inner diameter designed to fit over the rim section 17 of the container 12 and where the other end, the closure end 104, is open or closed and has an inner diameter sized to hold a closure by friction. Alternatively, the inside wall of the closure end 104 could include grooves or flanges that supplement or replace frictional forces to hold the closure 90 in place. The body 106 of the sleeve 96 between the mouth end 102 and the closure end 104 could take any number of forms as long as side vents 108 are provided with an effective total side vent area greater than 50% of the container mouth area. The mouth end 102 of the cylindrical suspension device 94 would be mounted proximate the container mouth 13 to hold the closure 90 above the container mouth 13. The closure 90 could be sealed within the container mouth 13 by pushing the combined sleeve-closure assembly down until the stopper 90 mates with

the mouth 13 at its horizontal and vertical sealing surfaces. Alternatively for sleeves 96 with open closure ends, the closure 90 only could be pushed down within the sleeve 96 until the closure 90 mates with and seals the container mouth 13.

[0051] It has been found that suspending the closure element above the rim of the container typically eliminates most closure element inhibition effects on the depressurization method outlined in U.S. patent application Ser. No. 11/702, 472. In fact, the additional vent area created by suspending the closure element above the rim of the container can even enable conventional lyophilization closures to work successfully with the depressurization method for most lyophilization applications. Since suspension devices such as the ones described herein hold the closure in the open position, the closure does not strictly require legs, but only the horizontal and vertical sealing surfaces. To exemplify this consideration, the closure in FIG. 9 is depicted without legs.

[0052] The suspension device depicted in FIGS. 7, 8, and 9 need not be bound to the container, as illustrated, but could instead be bound to some part of the freeze-dryer system, such as the shelves. It should be recognized that the idea or concept of suspending the closure element within or above an individual containers can be extrapolated to systems that hold a plurality of closures within or above a plurality of containers. Such systems might be independent of the freeze-dryer or coupled to the freeze-dryer shelves and automatic closure system. Independent closure element suspension systems may take the form of a tray holding the containers in set positions and possessing a set of collapsible arms that hold a manifold of closures in the proper positions within or above the containers. Built-in suspension systems may take the form of a grid holding the containers in set positions on a shelf, a corresponding grid on the underside of the shelf above holding the closure elements in positions aligned with the containers below, and a means of releasing the closures after they are pushed into the containers during the closure process. Still other configurations or designs for a suspension device can be conceived without departing from the scope of the teachings herein.

[0053] The container closure systems depicted in FIG. 10 and FIG. 10A represent an alternate approach to maximizing the effective vent area. As shown in FIG. 10A, the closure element 110 includes an annular vertical sealing surface 112 and a horizontal sealing surface 114, but now these components are disposed in the mouth 13 of the container 12 and define an interior cavity 116. The closure lid 120 includes a circular cap 122 and a plug 124 attached thereto adapted to fit into the interior cavity 116. The illustrated embodiment of the closure element 110 has no legs (and thus no side vents) as the sealing surfaces are always in contact with the rim section 17 of the container 12 proximate the mouth 13. Rather, the lid 120 is disposed in a hinged coupling 128 with the sealing surfaces 112, 114 of the closure element 110 such that the plug 124 can be inserted into the interior cavity 116 when the container closure system is in the closed position or pulled away from the interior cavity 116 and mouth 13 of the container 12 when the container closure system is in the open position. In this embodiment, the open and closed positions are defined by the position of the cap 122 and plug 124 relative to the interior cavity 116.

[0054] As seen in FIG. 10, the lid 120 is preferably maintained at an acute angle with respect to the vertical axis of the container 12 to allow automatic closure systems to push the cap 122 and plug 124 into sealing engagement after the drying

phase of lyophilization is complete. The interior cavity **116** is preferably sized to produce an effective mouth vent area sufficient to allow the depressurization method of inducing nucleation to proceed uninhibited. Other arrangements for sealing the interior cavity are also contemplated including a compression fit or press fit of a stand-alone plug or even a threaded plug and cavity to facilitate closure via rotational motion.

[0055] It should be understood that the closure elements described herein can be composed of any material that meets the basic demands of a lyophilization process with regards to moisture migration and absorption, oxygen migration, product absorption and adsorption, leaching, coring, fragmentation, reseal, sprayback, handling properties, etc. The material may be a flexible polymer, such as the various butyl rubber formulations employed conventionally. The material may also be a more rigid polymer, such as polytetrafluoroethylene. It may also include polymer blends, block copolymers or coated polymers as well. More rigid polymers may be easier to stabilize in the open position considering the relatively long and thin legs that may be necessary to achieve the vent areas disclosed herein. However, more rigid polymers may face challenges in sealing appropriately with the container mouth. To overcome such challenges, another aspect of this invention is the addition of a narrow sealing flange **135** to the vertical sealing surface **132** above the legs **130** of the closure **140** and below the horizontal sealing surface **136** as shown in FIG. 11, FIG. 11A, and FIG. 11B. The sealing flange **135** should be sized to accommodate the variability of inner mouth diameters for a given container style and to allow the tip of the flange to be compressed during the closure process to achieve the proper seal. All the design concepts disclosed herein permit the addition of such a sealing flange **135**, and all accommodate the conventional aluminum crimp to supplement the container-closure seal. Suspension devices such as the ones described herein can be made of any pharmaceutically acceptable material and should not need to meet the product contact requirements of conventional closure materials.

[0056] More rigid polymers may also prevent injection of needles to directly reconstitute the lyophilized material in the container or withdraw the reconstituted material from the container. To overcome this potential problem, all the closure elements disclosed herein may be executed as composite designs wherein the majority of the closure structure is composed of a rigid polymer for good stability, while a portion of the horizontal surface above the container mouth is composed of a flexible polymer that permits needle injection.

[0057] All of the closure concepts disclosed herein can be coupled to a filter material to minimize any contamination risks associated with the large vent areas as generally disclosed in U.S. Pat. No. 5,732,837. The filter material should not significantly affect the flow of gases between the container and its environment, but should prevent the ingress of bacteria or other non-gaseous contaminants into the vial. The filter material should be positioned within the closure so that anything passing through the vents must pass through the filter material prior to entering the container.

[0058] The novel lyophilization closures disclosed herein overcome the limitations associated with closure elements known in the prior art and significantly extend the range of applicability for using the depressurization method to induce nucleation. To improve the efficacy of depressurization, the size of the vents presented by the closure in the open position

must be expanded substantially beyond the conventional ranges. Conventional lyophilization closures are designed to minimize the size of the vents without significantly impeding the upper range of solvent vapor flow rates that are typically encountered in lyophilization practice. The vents are traditionally minimized to control manufacturing costs, reduce contamination risks when the closure is in the open position, help the closure sit more stably in the open position, and ensure an acceptable seal when the closure is in the closed position. This design strategy is appropriate when one has no reason to increase the size of the vents beyond the standard requirements for drying; the resulting vents are in some cases too small to ensure reliable performance of the depressurization method for inducing nucleation during the freezing step of a lyophilization process.

EXAMPLE

[0059] All tests described herein were performed in a Vir-Tis 51-SRC freeze-dryer having four shelves with approximately 1.0 m² total shelf space and an internal condenser. This unit was retrofitted to hold positive pressures of up to about 15 psig. A 1.5" diameter circular opening also was added to the rear wall of the freeze-drying chamber with 1.5" diameter stainless steel piping extending from the hole through the rear wall insulation to emerge from the back of the freeze-dryer. Two 1.5" full-port, air-actuated ball valves were attached to this tubing via sanitary fittings. One ball valve allowed gas to flow into the freeze-drying chamber and thereby provide positive pressures up to 15 psig. The second ball valve allowed gas to flow out of the freeze-drying chamber and thereby reduce chamber pressure to atmospheric conditions (0 psig). All refrigeration of the freeze-dryer shelves and condenser was accomplished via circulation of Dynalene MV heat transfer fluid cooled by liquid nitrogen using the Praxair NCOOL™-HX system.

[0060] All solutions were prepared in a class **100** clean room. The freeze-dryer was positioned with the door, shelves, and controls all accessible from the clean room while the other components (pumps, heaters, etc.) were located in a non-clean room environment. All solutions were prepared with HPLC grade water filtered through 0.5 μ m membrane. In addition to water, each solution contained a single bulking agent, either mannitol or sucrose, at a concentration of approximately 5 wt %. The final solutions were filtered through a 0.22 μ m membrane prior to filling the vial containers. The argon gas used to pressurize the chamber was supplied via cylinders and was filtered through 0.22 μ m filters to remove particulates. The 5 and 10 mL glass vials were obtained from Wheaton Science Products and pre-cleaned for particulates by a third party (ThermoFisher Scientific). The above steps were taken to ensure the materials and methods met conventional pharmaceutical manufacturing standards for particulates, which act as nucleating agents.

[0061] For the experimental conditions described herein and both lyophilization formulations studied, stochastic nucleation was typically observed to occur at vial temperatures between about -8° C. and -20° C. and occasionally as warm as -5° C. The vials could generally be held at temperatures warmer than -8° C. for long periods of time without nucleating. The onset of nucleation and subsequent crystal growth (i.e., freezing) was determined by temperature measurement as the point at which the vial temperature quickly increased in response to the exothermic latent heat of fusion. The initiation of freezing also could be visually determined

through a sight-glass on the freeze-dryer chamber door or by opening the chamber door immediately after depressurization.

[0062] Table 1 summarizes the results for a set of experimental trials that demonstrate how container-closure systems with vents possessing the features described herein improve the efficacy of the depressurization method for inducing nucleation of the freezing transition in a solution near or below its thermodynamic freezing point. Each tabulated result is based on a minimum of ten vials loaded in close proximity to one another on a freeze-dryer shelf. The temperatures of the vials were monitored using surface mounted thermocouples. The closure style labeled as “prior art” is a traditional, two-legged lyophilization closure supplied by West Pharmaceutical Services, Inc. of Lionville, Pa. that resembles the closure depicted in FIG. 1A. The closure style labeled as Sample A is a four-legged closure similar to the closure element depicted in FIGS. 4, 4A, and 4B. The closure style labeled as Sample B is a four-legged closure similar to the closure element depicted in FIGS. 6, 6A, and 6B. The closure style labeled as Sample C is a four-legged suspension device that holds a conventional legless stopper above the container similar to the closure element depicted in FIGS. 9, 9A, and 9B.

[0063] In each trial, the freeze-dryer was pressurized in an argon environment to about 14 psig. The freeze-dryer shelf was cooled to obtain vial temperatures of between approximately -1°C . and -3°C . ($\pm 1^{\circ}\text{C}$. measurement accuracy of the thermocouples). The freeze-dryer was then depressurized from about 14 psig to about atmospheric pressure in less than five seconds to attempt to induce nucleation of the solution within the vials. The set of depressurization conditions used for the trials summarized in Table 1 were intentionally chosen to provide cases where nucleation efficacy was relatively low for conventional container-closure systems, so the improvement obtained with the container-closure systems disclosed herein could be more obvious.

TABLE 1

Effect of container-closure system on efficacy of inducing nucleation.						
Solution	Vial Size [mL]	Fill Volume [mL]	Closure Style	Ratio of Effective Mouth Vent Area to Container Mouth Area	Ratio of Effective Total Side Vent Area to Container Mouth Area	Percentage of Vials Nucleated [%]
Mannitol	5	2.5	prior art	0.52	0.18	0
Mannitol	10	5.0	prior art	0.52	0.18	0
Sucrose	5	2.5	prior art	0.52	0.18	0
Mannitol	5	2.5	sample A	0.98	0.82	100
Mannitol	10	5.0	sample B	0.98	1.96	100
Sucrose	5	2.5	sample C	1.00	2.81	100

[0064] While the invention herein disclosed has been described by means of specific embodiments and processes associated therewith, numerous modifications and variations can be made thereto by those skilled in the art without departing from the scope of the invention as set forth in the claims or sacrificing all its material advantages.

What is claimed is:

1. A container-closure system comprising:

a container having an upper section defining an opening having a cross sectional area and the container having a top surface and an interior surface adjacent to the open-

ing; the container further comprising a body section defining a cavity in fluid communication with the opening;

a closure element disposed proximate to the container and adapted for sealing the opening of the container when in a closed position, the closure element having a first sealing surface adapted for sealably contacting the interior surface of the container when in the closed position, the closure element having a second sealing surface adapted for sealably contacting the top surface of the container when in the closed position, and the closure element having a plurality of closure legs extending from the first or second sealing surface toward the body section;

wherein the closure legs define a plurality of side vents between each of the closure legs when the container closure system is in an open position and the cumulative area of the side vents is greater than or equal to 50% of the cross sectional area of the opening; and

wherein the side vents define a fluid path between the cavity within the container and an atmosphere surrounding the container to facilitate nucleation of freezing of a material disposed within the cavity of the container upon depressurization of the atmosphere surrounding the container.

2. The container-closure system of claim 1 wherein the cumulative area of the side vents is greater than or equal to 80% of the cross sectional area of the opening.

3. The container-closure system of claim 1 wherein the closure element further defines a mouth vent proximate the distal end of the closure legs when the container closure system is in an open position and the cumulative area of the mouth vent is greater than or equal to 50% of the cross sectional area of the opening.

4. The container-closure system of claim 1 wherein the closure legs have a length and a non-uniform cross-sectional configuration along the length.

5. The container-closure system of claim 1 wherein the closure element is disposed partially within the opening of the container.

6. The container-closure system of claim 1 wherein the closure element is disposed on the top surface of the container and the closure legs are aligned with the opening of the container.

7. The container-closure system of claim 6 wherein the closure legs have one or more protrusions disposed proximate a distal end of the closure legs.

8. The container-closure system of claim 1 wherein the closure element is suspended above the container and the closure legs are aligned with the opening of the container.

9. The container-closure system of claim 8 further comprising a collapsible device attached to the closure element and container, the collapsible device suspending the closure element above the container and aligning the closure legs with the opening of the container.

10. The container-closure system of claim 1 further comprising a sealing flange disposed in the first sealing surface of the closure element.

11. A lyophilization stopper comprising:

a sealing element defining an annular sealing surface;

a cap section disposed adjacent to the sealing element and having a second sealing surface disposed in an orthogonal orientation relative to the annular sealing surface; and

one or more closure legs extending from the annular sealing surface, the closure legs defining an outwardly facing surface and the closure legs further defining vents between the closure legs;

wherein the cumulative area of the vents is equal to or greater than the cumulative area of the outwardly facing surfaces of the closure legs.

12. The lyophilization stopper of claim 11 wherein the cumulative area of the vents is greater than or equal to 80% of the cumulative area of the outwardly facing surfaces of the closure legs.

13. The lyophilization stopper of claim 11 wherein the closure legs have a length and a non-uniform cross-sectional configuration along the length.

14. The lyophilization stopper of claim 11 wherein the closure legs have one or more protrusions disposed proximate a distal end of the closure legs.

15. The lyophilization stopper of claim 11 further comprising a sealing flange disposed in the annular sealing surface of the sealing element.

16. The lyophilization stopper of claim 11 further comprising a suspension structure coupled to the cap section and adapted to suspend the cap section above a lyophilization container.

17. A container-closure system comprising:

a container having an upper section defining an opening having a cross sectional area and the container having a top surface and an interior surface adjacent to the opening; the container further comprising a body section defining a cavity in fluid communication with the opening;

a closure element disposed proximate to the container and adapted for sealing the opening of the container when in a closed position, the closure element having a first sealing surface adapted for sealably contacting the interior surface of the container when in the closed position, the closure element having a second sealing surface adapted for sealably contacting the top surface of the container when in the closed position;

wherein the closure element defines a vent area when the container closure system is in an open position and wherein the vent area defines a fluid path between the cavity within the container and an atmosphere surrounding the container to facilitate nucleation of freezing of a material disposed within the cavity of the container upon depressurization of the atmosphere surrounding the container and wherein the vent area is greater than or equal to 50% of the cross sectional area of the opening.

18. The container-closure system of claim 17 further comprising a suspension structure coupled to the container and the closure element and wherein the closure element is suspended above and aligned with the opening of the container.

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