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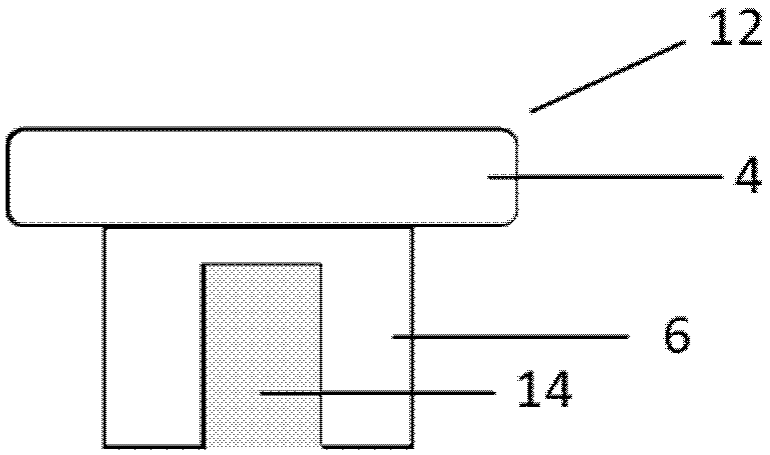
(54) **LYOPHILIZATION STOPPER COMPRISING A MEMBRANE**

(57) The invention relates to a stopper comprising a stopper body and a water vapor-permeable membrane.

Figure 3:



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Description

Field of the invention

[0001] The present invention is directed to a lyophilization stopper comprising a water vapor-permeable membrane.

Background of the invention

[0002] Lyophilization, i.e. freeze-drying, is a process that has become prominent in the pharmaceutical industry for drying sensitive pharmaceutical compositions. During lyophilization, the solvent is removed by sublimation. For this purpose, several containment systems are known in the prior art.

[0003] WO 2019/012512 A1 describes a container that has been designed to protect product from contamination during lyophilization. The container has at least one water vapor-permeable side through which water vapor can escape during lyophilization. However, such a container is unsuitable for long-term storage, as water can re-hydrate the product in the container in a humid environment. In addition, such a container is unsuitable for easy handling, as a needle pierceable region for reconstitution is missing.

[0004] Vials with rubber stoppers are commonly used, wherein the stopper has a first configuration that allows the sublimation of the solvent and a second configuration for sealing the vial with the stopper. However, during the lyophilization process there is a risk of contamination from the environment with the stoppers of the prior art. In addition, the product itself may potentially be hazardous and may contaminate the process facility. Such a risk of contamination is in particular worrisome for crosscontamination between batches of different products, wherein trace amounts of a first product may cross-contaminate a batch of a second product. It is, in particular for lyophilization in vials, a drawback that contamination can occur when the stopper is the above-mentioned first configuration and the vial is not yet sealed.

[0005] There is growing pressure in the pharmaceutical industry from regulatory agencies to minimize the risk of e.g. microbacterial contamination in sterile products. Lyophilization products are especially concerned given the need for the vial to be partially open ("pre-plugged") during the lyophilization process in order to allow the water that sublimates during the process to escape the vial. The lyophilization can take several days in those products that require long freeze-drying cycles, thereby increasing the risk for contamination.

[0006] In the case of facilities that do not have an automatic transport process from the filling of the vials to the entrance of the lyophilizer, there is also the need for the intervention of a human operator who moves the trays with the pre-plugged vials from the end of the filling machine to the freeze dryer. Human intervention is one of the main reasons for contamination of sterile products in the pharmaceutical industry.

[0007] Therefore, it is an object of the present invention to provide a stopper that minimizes the risk of contamination, in particular the risk of microbiological contamination. In addition, it is a further object to provide a stopper for lyophilization that is easy to use and allows for an efficient lyophilization process.

Summary of the invention

[0008] These objects have been solved by a stopper comprising a stopper body and a water vapor-permeable membrane.

[0009] It has surprisingly been found that this stopper allows the sublimation of solvent, such as water, during a lyophilization process while at the same time providing a barrier that lowers the risk of contamination. The membrane used in the stopper of the present invention is permeable to water vapor, thereby allowing the water that sublimates during the lyophilization process to escape the vial. The membrane used in the stopper of the present invention is furthermore impermeable to liquid water and impermeable to microorganisms, thereby reducing, preferably avoiding the risk of contamination such as microbiological contamination with microorganisms, such as bacteria, viruses, and fungi, in particular bacteria, of the lyophilized product. Furthermore, the stopper of the present invention can maintain the container closure integrity (CCI) of the prior art container systems.

[0010] In addition, it has been found that the stopper can be used with a vial for ready-to-use formulations, wherein the stopper can be pierced by a needle without interference of the water vapor-permeable membrane.

[0011] In another aspect, the invention relates to a kit of parts comprising the stopper of the present invention, a lyophilization container, and preferably a cap assembly.

[0012] In another embodiment, the present invention relates to the use of the stopper of the present invention for lyophilization.

[0013] In yet another embodiment, the present invention relates to a method for preparing the stopper of the present invention, comprising the steps of

(a) providing a stopper body by extrusion or compression molding; and

(b) connecting a water-vapor permeable membrane to the stopper body to provide the stopper.

Brief description of the figures

[0014]

Figure 1 depicts the cross section of a prior art two-legged stopper 2. The stopper 2 comprises a stopper head 4, and two stopper legs 6 that are essentially orthogonal to main surface area 7 of the stopper head 4. The stopper comprises an outer surface 3 and an inner surface 5. The stopper comprises a vent passageway 9. The two stopper legs form a vent area 8 on the outer surface 9 of the stopper through which gases can flow when the stopper is partially inserted into a vial.

Figure 2 depicts the top view of a stopper, wherein stopper head 4 comprises a needle penetration region 10. This region is in the center of the main surface area of the stopper head. The needle penetration region allows the piercing of the stopper with a needle for reconstitution and removal of the reconstituted product without having to remove the stopper.

Figure 3 shows the cross section of a two-legged stopper 12 of the present invention, wherein the stopper body 12 comprising a stopper head 4 and two stopper legs 6 that are essentially orthogonal to the stopper head, wherein the two stopper legs form a vent area, and the vent area is covered by a water vapor-permeable membrane 14. In this embodiment, the vent area is completely covered by the water vapor-permeable membrane 14. The water vapor-permeable membrane 14 is connected to the surface of the stopper legs 6.

Figure 4 depicts the cross section of a two-legged stopper 22 of the present invention, wherein the water vapor-permeable membrane 14 does only partially cover the vent area 8. Such a construction still prevents contamination during lyophilization, provided the stopper is inserted into the vial so that the area not covered by the water vapor-permeable membrane is inside the vial.

Figure 5 depicts the cross section of a two-legged stopper 32 of the present invention, wherein the water vapor-permeable membrane 16 is essentially orthogonal to the stopper legs 6 and the vent area 8.

Figure 6 depicts a three-dimensional view of a two-legged stopper of the present invention comprising a stopper head 4 and two stopper legs 6 that are essentially orthogonal to the stopper head, wherein the two stopper legs form a vent area, and the vent area is covered by a water vapor-permeable membrane 14. The stopper legs 6 comprise nubs 18 that fasten the stopper and prevent the stopper from slipping off.

Figure 7 depicts the cross section of a bunker stopper 42 of the present invention, wherein the vent area of the stopper 8 is completely covered by the water vapor-permeable membrane 16.

Figure 8 depicts the cross section of a bunker stopper 52 of the present invention, wherein the stopper comprises a sealing ring 19. The sealing ring 19 is ring shaped and surrounds stopper legs 6. The sealing ring facilitates fastening of the stopper in the "open" configuration and stabilizes the legs of the stopper. In addition, the sealing ring prevents microcanals or crevices between the stopper and the vial from forming in the open configuration and helps to stabilize the legs during the insertion of the stopper into a vial. Thus, the sealing ring further minimizes contamination during lyophilization.

Detailed description

[0015] The following definitions are relevant in connection with the embodiments of the present invention.

[0016] The term "pharmaceutical" refers to compositions, wherein the active ingredient fulfils all necessary pharmaceutical standards/monographs of the USP-NF (United States Pharmacopoeia National Formulary) or Ph. Eur. (European Pharmacopoeia) reference standard with regard to purity of the active ingredient and/or amount of pathogens and/or bacterial contamination.

[0017] The term "stopper body" refers to the part of the stopper of the present invention not comprising a water vapor-permeable membrane.

[0018] The term "stopper" generally refers to a device for closing a container or vial.

[0019] The term "stopper head" refers to the part of the stopper body that is configured to not be inserted into the lyophilization vial. The stopper head has a larger diameter than the stopper leg and a larger diameter than the vial opening.

[0020] The term "stopper leg" refers to the part of the stopper body that is configured to be pushed into the lyophilization vial. The stopper leg preferably protrudes essentially orthogonal to the main surface area of the stopper head.

[0021] The term "water vapor-permeable" refers to a water vapor permeability of 1000 g/m^2/24 h or more.

[0022] The term "essentially orthogonal" refers to an angle of 70° to 110°. The term "essentially parallel" refers to an angle of -20° to +20°.

[0023] The meaning of the term "comprising" is to be interpreted as encompassing all the specifically mentioned features as well optional, additional, unspecified ones, whereas the term "consisting of" only includes those features as specified. Therefore, "comprising" includes as a limiting case the composition specified by "consisting of".

[0024] The term "wt.-%" refers to the amount of the respective ingredient by weight based on the total amount of the element it refers to, unless noted otherwise.

[0025] As used herein, the singular forms "a", "an", and "the" include both singular and plural referents unless the context clearly dictates otherwise. By way of example, "a stopper leg" means one stopper leg or more than one stopper leg.

[0026] The term "vent area" is to be understood as the area on the outer surface of the stopper of a vent passageway. The vent passageway is a passageway for gas that goes through the stopper and is used for venting gas during the lyophilization process.

[0027] The vial is "pre-plugged" when the stopper is not completely inserted into the vial. With conventional stoppers, this configuration leaves vent areas allowing water vapor resulting from sublimation to escape the vial during lyophilization.

[0028] Preferred embodiments according to the invention are defined hereinafter. The preferred embodiments are preferred alone or in combination. Further, it is to be understood that the following preferred embodiments refer to all aspects of the present invention, i.e. the stopper, the kit of parts, the use of the stopper, and the method for preparing the stopper.

[0029] In an embodiment, the stopper is a lyophilization stopper. In an embodiment the stopper is a stopper for lyophilization, i.e. the stopper is for sealing and venting a lyophilization container, preferably a vial. In a preferred embodiment, the stopper of the present invention is a vial stopper.

[0030] In an embodiment, the stopper of the present invention is a two-legged stopper, a three-legged stopper or an Igloo stopper. These stoppers (not comprising a water vapor-permeable membrane) are commercially available, e.g. from West Pharmaceutical Services Inc. or DWK life Sciences Co. Ltd. A two-legged stopper of the prior art is schematically depicted in Figures 1 and 2. Igloo stoppers comprise a vent area comprising one vent portion through which gas can be removed during the lyophilization process. Two-legged stoppers comprise a vent area consisting of two vent portions through which gas can be removed during the lyophilization process. Three-legged stopper comprise a vent area consisting of three vent portions through which gas can be removed during the lyophilization process. These stoppers are typically sold having an outer diameter of the stopper leg of e.g. 12 mm, 13 mm, 15 mm or 20 mm. These stoppers are advantageous due to the large vent area that allows efficient and fast lyophilization. In addition, such stoppers are compatible with automated loading unloading systems (ALUS). The compatibility with automated systems, such as ALUS, is beneficial, since the use of automated systems increases production efficiency and further minimizes the risk of contamination before and after freeze-drying.

[0031] In an embodiment, the stopper of the present invention is a bunker stopper. A bunker stopper is schematically depicted in Figure 7. Bunker stoppers comprise a vent area on the stopper leg, preferably near the stopper head. In the present invention, the vent area is completely covered by the water vapor-permeable membrane. In the pre-plugged state, the bunker stopper is configured so that the water vapor-permeable membrane is not in the vial and is not in contact with the surface of the vial. After lyophilization, the bunker stopper is fully inserted so that the vent area and the water vapor-permeable membrane is inside the vial and the vial is sealed by the stopper. It is preferred that the vent area is near the stopper head to minimize the amount of surface exposed to the outside in the pre-plugged state to further minimize the risk of contamination. This configuration is particularly preferred, as there is even less risk of contamination, as there is no contact point between the water vapor-permeable membrane and the vial's surface in the pre-plugged state. The bunker stopper is configured in that the water-vapor permeable membrane is essentially orthogonal to the stopper head and/or the needle penetration area.

[0032] In an embodiment, the stopper body comprises a stopper head. The stopper head is configured to prevent the stopper from sliding or falling into a vial. The stopper head comprises a main surface area. Said main surface area is preferably circular. The stopper head preferably comprises a needle penetration region, i.e. a needle pierceable area. The needle penetration area is configured so that a needle can penetrate through the stopper. This region is preferably centrally located on the stopper head, i.e. the stopper comprises a centrally located needle penetration region. This is useful for reconstituting the lyophilized product and emptying the vial without removing the stopper. The stopper comprises a vent passageway for venting gas during the lyophilization process. The stopper body may further comprise a stopper leg that protrudes essentially orthogonal to the main surface area of the stopper head. The leg is configured to be inserted into the vial. The leg is configured to span a vent area on the outer surface of the stopper that allows gas to flow through the vent passageway through the stopper when the stopper is only partially inserted into a vial. It is preferred that the water vapor-permeable membrane is not parallel to the main surface area of the stopper head or the needle penetration

area. It is preferred that the water vapor-permeable membrane is essentially orthogonal, i.e. horizontal, to the main surface area of the stopper head and/or the needle penetration area. In an embodiment, the water vapor-permeable membrane covers the vent passageway. Thus, the water vapor-permeable membrane is placed in the path of any gas traveling through the vent passageway. It is preferred that the water vapor-permeable membrane completely or partially covers the vent area.

[0033] In a particularly preferred embodiment, the stopper of the present invention is a lyophilization vial stopper comprising a stopper body and a water vapor-permeable membrane, wherein

the water vapor-permeable membrane comprises ePTFE,
the stopper body comprises a vent passageway, and
the water vapor-permeable membrane covers the vent passageway.

[0034] In an embodiment, the stopper comprises nubs and/or recesses. Nubs and/or recesses facilitate fastening of the stopper to the vial and prevent the stopper from slipping off the vial. When the stopper is inserted into the vial, the stopper needs to be in a proper position. The nubs and/or recesses prevent angled or misplaced positioning of the stopper.

[0035] In an embodiment, the stopper comprises a sealing ring. The sealing ring facilitates fastening of the stopper in the "open" configuration and stabilizes the legs of the stopper. In addition, the sealing ring prevents microcanals between the stopper and the vial from forming in the open configuration and helps to stabilize the legs during the insertion of the stopper into a vial. Thus, the sealing ring further minimizes contamination during lyophilization. The sealing band comprises preferably the same rubber as the stopper.

[0036] It is preferred that the stopper does not comprise any moving parts. The absence of moving parts leads to a more stable and reliable stopper. In addition, the absence of moving parts decreases the probability of errors due to malfunctioning of the moving parts during the lyophilization process. As many lyophilized products are complex molecules that are difficult to manufacture, even a small decrease in errors during the lyophilization process results in substantial cost savings.

[0037] In an embodiment, the stopper of the present invention comprises a stopper body that is laminated with a fluoropolymer or a silicone polymer. Such a laminated stopper can reduce the migration of leachables from the stopper and can facilitate the insertion of the stopper into the vial.

[0038] In an embodiment, the water vapor-permeable membrane comprises expanded polytetrafluoroethylene (ePTFE) and/or a polymer selected from the group consisting of polyether esters, polyether amides, polyether urethanes, and mixtures thereof. It is preferred that the water vapor-permeable membrane comprises ePTFE. In an embodiment, the membrane comprises 50 to 100 wt.-% of ePTFE, preferably 70 to 100 wt.-% of ePTFE, and more preferably 90 to 100 wt.-% of ePTFE. In an embodiment, the water vapor-permeable membrane consists of ePTFE. The above materials are further advantageous as these polymers are inert so that the membrane does not pose any risk to contaminate the lyophilized product with extractables and leachables from the membrane. Extractables are chemical entities that may be released from container systems under stressed conditions with various solvents. Leachables are chemical entities that can migrate from the container system into the drug product under standard conditions.

[0039] ePTFEis obtained by the steps of extrusion of a PTFE resin with a lubricant, usually a naptha solvent. After extrusion to provide a film, the film is calendared, dried to evaporate the lubricant and subsequently expanded (either uniaxially or biaxially) at elevated temperatures, to provide a ePTFE membrane. Such a ePTFE membrane is porous. The size of the pores are larger than molecules of water molecules but significantly smaller than water droplets, thus making the ePTFE membrane water vapor-permeable but impermeable to liquid water. In an embodiment, the expanded polytetrafluoroethylene is an uniaxially expanded membrane. An uniaxially expanded membrane is obtainable by calendaring in the machine direction (MD). In a preferred embodiment, the expanded polytetrafluoroethylene is a biaxially expanded membrane. A biaxial expanded membrane is obtainable by calendaring in the machine direction (MD) and in transverse or cross direction (CD). The ePTFE membrane preferably has a microstructure of nodes and fibrils, wherein the fibrils connect the nodes.

[0040] In another embodiment, it is preferred that the water vapor-permeable membrane comprises a polyether polyester copolymer or a polyester polymer. Such membranes are commercially available as Sympatex® and Futurelight™. In another embodiment, the water vapor-permeable membrane is a polyurethane. Suitable polyurethanes are described in US 6,790,926 B1.

[0041] In an embodiment, the water vapor-permeable membrane has a thickness of 0.1 to 500 μm, preferably of 1 to 200 μm, more preferably of 5 to 100 μm. When the membrane has a thickness of less than 0.1 μm, the processing can be difficult and the stability of the membrane suffers. When the thickness of the membrane exceeds 500 μm, the water vapor permeability may decrease leading to a less efficient lyophilization process.

[0042] In an embodiment, the water vapor-permeable membrane has a water vapor permeability of 1000 to 65000 g/m^2/24 h, preferably of 3000 to 50000 g/m^2/24 h. The water vapor permeability can be measured according to ASTM E-96-95, procedure B. In an embodiment, the water vapor-permeable membrane has a water vapor permeability of 500

to 100000 g/m^2/24 h, of 2000 to 40000 g/m^2/24 h or of 4000 to 20000 g/m^2/24 h.

[0043] The membrane can comprise one or more layers. In an embodiment, the membrane consists of a single layer. In a preferred embodiment, the membrane consists of a single layer and the membrane comprises 70 to 100 wt.-% expanded polytetrafluoroethylene.

[0044] In another embodiment, the membrane is a multi-layer construction, comprising, two, three, four or more layers. The layers can be attached to each other by lamination. In an embodiment, the membrane comprises polyethylene, polyethylene terephthalate, and/or mixtures thereof.

[0045] In an embodiment, the stopper body comprises a rubber. In a preferred embodiment, the rubber is selected from the group consisting of natural rubber, isoprene rubber, ethylene propylene diene rubber, butyl rubber, bromobutyl rubber, chlorobutyl rubber and mixtures thereof as well as copolymers thereof.

[0046] In order to prevent moisture absorption, the rubber stopper may be coated by a hydrophobic coating agent, such as silicone polymers or may contain a desiccant. In a preferred embodiment, the rubber stopper is coated with a polytetrafluoroethylene (PTFE) coating. The coating is preferable on the inside of the stopper.

[0047] In an embodiment, the stopper body comprises a filler, an accelerator, an activator, a plasticizer, a pigment, and/or a stabilizer.

[0048] In an embodiment, the stopper is sterile in accordance with the European Pharmacopoeia 5.1.1, edition 10.0, 2019.

[0049] In an embodiment, the invention relates to a kit of parts comprising the stopper of the present invention, a lyophilization container, and preferably a cap assembly. It is preferred that the lyophilization container is a vial. The vial can be a plastic or a glass vial. Examples for glass are soda-lime glass and borosilicate. In an embodiment, the vial has a hole opening with an inner diameter of 5 to 100 mm, preferably of 10 to 50 mm. For optimal container closure integrity (CCI), it is preferred that the stopper has an outer diameter that is slightly larger of the inner diameter of the vial. The outer diameter of the stopper refers to the diameter of the portion of the stopper that is inserted into the vial, i.e. the outer diameter does not refer to the diameter of the stopper head. In a preferred embodiment, the outer diameter of the stopper refers to the outer diameter of the stopper legs, i.e. the portion of the stopper that is inserted into the vial. Thus, for a vial with a hole opening with an inner diameter of 12 mm, a rubber stopper with an outer diameter of e.g. 13 mm can be used.

[0050] In an embodiment, the stopper is configured to have

(i) a first position for lyophilization, wherein the vial is hermetically sealed by the stopper except for an area that allows water vapor through the water vapor-permeable membrane of the stopper; and
(ii) a second position for storage, wherein the vial is hermetically sealed by the stopper.

[0051] In the first configuration (i), the water vapor can vent through the vent area. In this configuration, the vent area is completely covered by the water vapor-permeable membrane. This configuration is used during the lyophilization process. Usually, this configuration is achieved by inserting the stopper into an intermediate position into the vial. In the second configuration (ii), the vial is hermetically sealed by the stopper. This position is used for storage. Usually, this configuration is achieved by inserting the stopper further into the vial until the stopper head touches the vial.

[0052] It is in particular preferred that the water vapor-permeable membrane is configured to substantially only cover the area on the outer surface of the stopper in the first position that allows water vapor through, i.e. the water vapor-permeable membrane covers the opening of the stopper body (the vent area), when inserted into the vial. Thus, it is preferred that the water vapor-permeable membrane is not coated continuously over the surface of the stopper body or the stopper leg. In a preferred embodiment, the stopper is configured so that the stopper body can be pierced to reconstitute the lyophilized product by a needle without piercing the water vapor-permeable membrane. Put differently, it is preferred that the water-permeable membrane is not connected in such a way to the stopper body that the water vapor-permeable membrane can be pierced by a needle.

[0053] In an embodiment, the water-permeable membrane is not essentially parallel to the main surface area of the stopper head. Such a configuration, as depicted in Figures 3, 4, and 6, is preferred, as the membrane is not damaged by the piercing with the needle. Thus, a thin membrane can be used and the stopper can be re-used. In Figure 5, the water vapor-permeable membrane is parallel to the main surface area of the stopper head and is pierced when the lyophilized product is reconstituted. Thus, the membrane may be damaged, in particular if the membrane is too thin. In addition, this configuration, wherein the water-permeable membrane is not parallel to the main surface area of the stopper head, improves safety during reconstitution. In case the needle penetration region on the stopper head as well as the water-vapor-permeable membrane need both to be pierced, then the different pressure required to pierce the membrane and to withdraw the needle from the membrane may surprise the user and lead to slipping off and other accidents.

[0054] In addition, these configurations are preferred, as the vent area that is covered by the water vapor-permeable membrane has a large surface area and therefore results in a time-efficient lyophilization process. It is preferred that the vent area has a surface of 0.01 cm^2 to 10 cm^2, of 0.05 cm^2 to 5 cm^2, of 0.1 cm^2 to 5 cm^2, of 0.25 cm^2 to 5 cm^2, of

0.5 cm^2 to 5 cm^2, of 0.75 cm^2 to 5 cm^2, of 1 cm^2 to 4 cm^2, or of 1.5 cm^2 to 3 cm^2. It is to be understood that the surface area of the vent area corresponds to the surface of the membrane which completely covers the vent area. Thus, the membrane of the present invention likewise has a surface area of preferably 0.01 cm^2 to 10 cm^2, of 0.05 cm^2 to 5 cm^2, of 0.1 cm^2 to 5 cm^2, of 0.25 cm^2 to 5 cm^2, of 0.5 cm^2 to 5 cm^2, of 0.75 cm^2 to 5 cm^2, of 1 cm^2 to 4 cm^2, or of 1.5 cm^2 to 3 cm^2

[0055] In an embodiment, the kit of parts of the present invention comprises a cap system. The cap system, also known as crimp seal, can comprise a metal seal, such as aluminum, and preferably a polymer button, and is configured to surround both the stopper and a neck of the vial in a sealed position. In an embodiment, the cap system comprises a plastic cap, the plastic cap preferably comprising polypropylene. In an embodiment the cap comprises a polymer selected from the group of PE (polyethylene), PET (polyethylene terephthalate), PETG (polyethylene terephthalate glycol), PEHD (polyethylene high-density), PP (polypropylene), ABS (acrylonitrile butadiene styrene) polymer, and mixtures thereof. Cap systems act as an additional seal (the contact between stopper and vial acting as the primary seal) and are advantageous for further sealing the vial and increasing the container closure integrity (CCI). The cap system can then be removed prior to use.

[0056] In an embodiment, the stopper of the present invention is used for lyophilization. Preferably, the stopper is used to lyophilize a pharmaceutically active agent or a pharmaceutical composition, which typically comprises one or more pharmaceutically acceptable excipients besides the pharmaceutically active agent(s).

[0057] It is preferred that the use of the stopper comprises the step of filling a pharmaceutical composition in a syringe, cartridge, vial or container. The stopper can then be inserted into the syringe, cartridge, vial or container so that gas can vent through the vent passageway. After the lyophilization process is completed, the syringe, cartridge, vial or container is hermetically sealed with the stopper. It is preferred that a cap system is additionally used for sealing the syringe, cartridge, vial or container.

[0058] The pharmaceutical composition can be reconstituted with solvent prior to use. This allows for the administration by intravenous infusion or injection as well as subcutaneous injection. However, it is also possible to provide the pharmaceutical composition as a suspension which is used for subcutaneous injection.

[0059] In an embodiment the invention relates to a method for preparing the stopper of the present invention, the method comprising the steps of

(a) providing the stopper body by extrusion or compression molding; and
(b) connecting the water-vapor permeable membrane to the stopper body to provide the stopper. The connection of the water-vapor permeable membrane to the stopper body can be achieved by welding at elevated temperatures to fuse the water-vapor permeable membrane and the stopper body. Alternatively, the water vapor-permeable membrane and the stopper body may be connected using a glue.

[0060] In an embodiment, the method further comprises the step of
(c) sterilization of the stopper by gamma ray irradiation, by water vapor sterilization or by chemical sterilization, preferably by using chemical sterilization with ethylene oxide. In an embodiment, the stopper and/or the pharmaceutical composition is sterile in accordance with the European Pharmacopoeia 5.1.1, edition 10.0, 2019. In an embodiment the composition is sterile, i.e. it contains less than 10^{-4} wt.-% of nonsterile material, such as microbial contamination. Sterility of the composition can be ensured by a number of processes, such as thermal, chemical, and radiation steps. In an embodiment, the stopper complies with the good manufacturing practice (GMP) standard for primary packaging materials for medicinal products DIN EN ISO 15378. It is preferred that all steps are performed under aseptic conditions.

[0061] In an embodiment, the stopper is a stopper for a vial, preferably a glass or plastic vial. Any composition contained in the vial may be removed from the vial by puncturing the stopper with a needle.

Examples:

[0062] The following examples were carried out in order to compare stoppers according to the present invention comprising an ePTFE membrane with conventional stoppers (not comprising a membrane) in terms of their ability to evacuate different volumes of water during a freeze-drying cycle.

Experimental Conditions:

[0063] Vials were filled with different filling volume of water (2 mL and 5 mL) and stoppered with a stopper in accordance with the present invention or without a stopper. The vials were then lyophilized using the following freeze-drying cycle, launched in the 100ST freeze dryer (Table 1):

Table 1: Cycle for lyophilization

Phase	Temperature [°C]	Vacuum [mBar]	Time [hours:minutes]
Freezing	-50.0	---	0:10
Freezing	-50.0	---	3:0
Condenser preparation	---	---	0:10
Primary drying	50.0	0.200	0:10
Primary drying	50.0	0.200	10:0
Secondary drying	50.0	---	0:1
Secondary drying	50.0	---	1:0

Results:

[0064] 20 Vials were filled with different filling volume of water (2 mL and 5 mL) and either (i) stoppered with a stopper in accordance with the present invention, comprising an ePTFE membrane covering the vent area using different surface areas between 3.14 mm^2 and 176.63 mm^2 (Vials 1-7, 11-17); or (ii) not stoppered and used as open vials without a stopper (Vials 8-10, 18-20).

[0065] The vials were then lyophilized using the freeze-drying cycle according to Example 1.

[0066] The amount of lyophilized water was measured by measuring the weight of the vial before the lyophilization cycle and after the lyophilization cycle. The results of the lyophilization cycle are stated in Table 2 below.

Table 2:

Vial	Filling volume [ml]	Surface [mm^2]	sublimated water (g)	Visual inspection after lyophilization
1	2	3.14	1.9909	no water observed
2	2	7.07	1.9961	no water observed
3	2	12.56	19934	no water observed
4	2	33.17	1.9942	no water observed
5	2	70.85	1.9962	no water observed
6	2	115.88	1.982	no water observed
7	2	176.63	1.9852	no water observed
8	2	open	1.9851	no water observed
9	2	open	1.9937	no water observed
10	2	open	used for probe	no water observed
11	5	3.14	4.9773	no water observed
12	5	7.07	4.9881	no water observed
13	5	12.56	4.9628	no water observed
14	5	33.17	4.9814	no water observed
15	5	70.85	4.7775	no water observed
16	5	115.88	4.9756	no water observed
17	5	176.63	4.9082	no water observed
18	5	open	5.0051	no water observed
19	5	open	4.9824	no water observed
20	5	open	used for probe	nd

[0067] The following can be concluded in view of the results depicted in Table 2.

(i) The ePTFE membrane is capable of evacuating the sublimated water produced by lyophilization.

(ii) If 2 ml or 5 ml were added to the vial, even the smallest ePTFE membrane tested was capable of evacuating the same water as an open vial (cf. Table 2).

[0068] With the data obtained in Example 2, it can be expected that stoppers of the present invention have a similar capacity to evacuate water than open vials.

[0069] The stoppers of the present invention offer the additional advantage that it will not be necessary to modify established freeze-drying cycles for existing pharmaceutical products, at the same time dramatically reducing the risk of microbiological contamination.

List of reference numbers:

[0070]

2 stopper
3 outer surface
4 stopper head
5 inner surface
6 stopper leg
7 main surface of the stopper head
8 vent area
9 vent passageway
10 needle penetration region
12 stopper
14 water vapor-permeable membrane
16 water vapor-permeable membrane
18 nub
19 sealing ring
22 stopper
32 stopper
42 stopper
52 stopper

Claims

1. A stopper comprising a stopper body and a water vapor-permeable membrane.

2. The stopper according to claim 1, wherein the stopper is a lyophilization stopper.

3. The stopper according to claim 1 or 2, wherein the stopper is a two-legged stopper, a three-legged stopper, a bunker stopper or an Igloo stopper.

4. The stopper according to any one of claims 1 to 3, wherein the water vapor-permeable seal comprises expanded polytetrafluoroethylene and/or a polymer selected from the group consisting of polyether esters, polyether amides, polyether urethanes, and mixtures thereof.

5. The stopper according to any one of claims 1 to 4, wherein the water vapor-permeable membrane has a thickness of 0.1 to 500 μm, preferably of 10 to 200 μm.

6. The stopper according to any one of claims 1 to 5, wherein the water vapor-permeable membrane has a water vapor permeability of 1000 to 65000 g/m^2/24 h, preferably of 3000 to 50000 g/m^2/24 h.

7. The stopper according to any one of claims 1 to 6, wherein the stopper body comprises a rubber from the group consisting of natural rubber, isoprene rubber, ethylene propylene diene rubber, butyl rubber, bromobutyl rubber,

chlorobutyl rubber and mixtures thereof.

8. The stopper according to any one of claims 1 to 7, wherein the stopper body comprises a filler, an accelerator, an activator, a plasticizer, a pigment, and/or a stabilizer.

9. The stopper according any one of claims 1 to 8, wherein the stopper comprises a vent passageway and the water vapor-permeable membrane covers the vent passageway.

10. A kit of parts comprising the stopper according to any one of claims 1 to 9, a lyophilization container, and preferably a cap assembly.

11. The kit of parts according to claim 10, wherein the lyophilization container is a vial.

12. The kit of parts according to claim 10 or 11, wherein the stopper is configured to have

(i) a first configuration for lyophilization, wherein the vial is hermetically sealed by the stopper except for an area that allows water vapor through the water vapor-permeable membrane of the stopper; and
(ii) a second configuration for storage, wherein the vial is hermetically sealed by the stopper.

13. The kit of parts according to any one of claims 10 to 12, wherein the cap assembly comprises an aluminum crimp, and preferably a polymer button, and is configured to surround both the stopper and a neck of the vial in a sealed position.

14. Use of the stopper according to any one of claims 1 to 9 for lyophilization, preferably for lyophilization of a pharmaceutically active agent or a pharmaceutical composition.

15. A method for preparing the stopper according to any one of claims 1 to 9, comprising the steps of

(a) providing a stopper body by extrusion or compression molding; and
(b) connecting aa water-vapor permeable membrane to the stopper body to provide the stopper.

Figure 1:

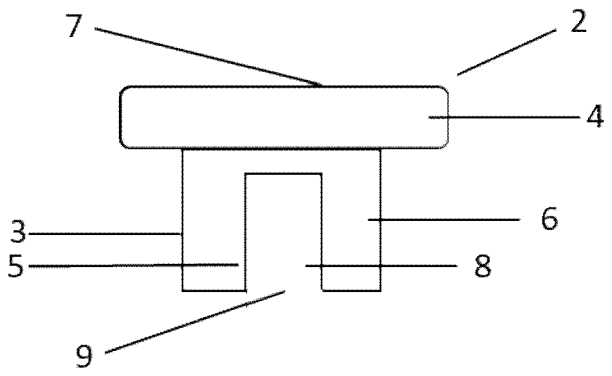


Figure 2:

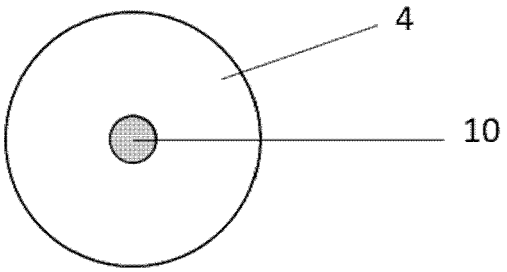


Figure 3:

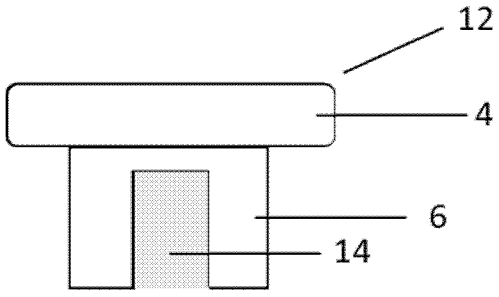


Figure 4:

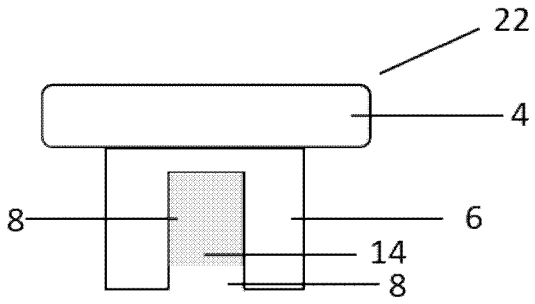


Figure 5:

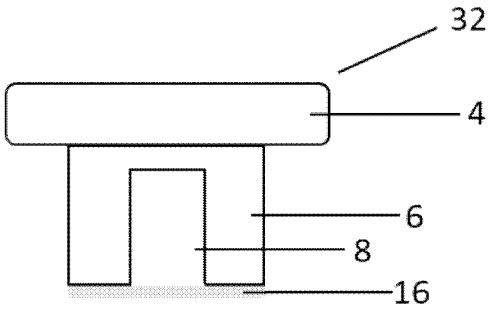


Figure 6:

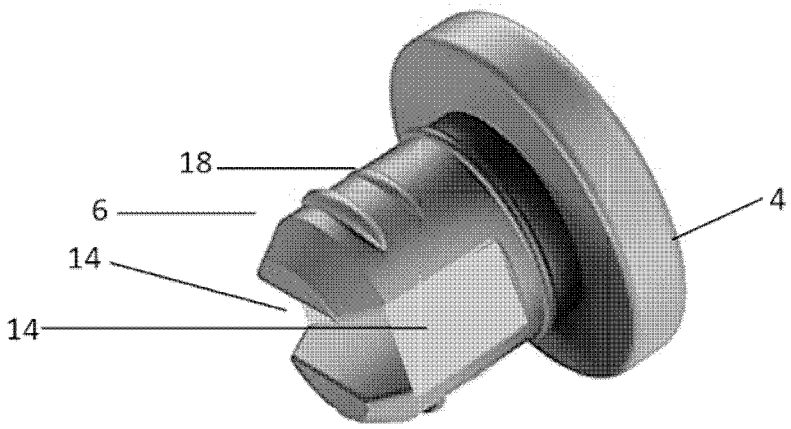


Figure 7:

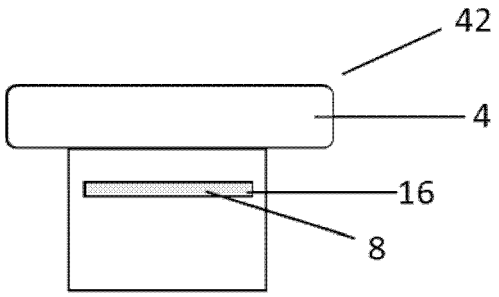
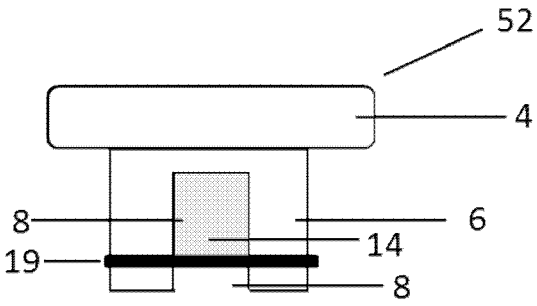


Figure 8:



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EUROPEAN SEARCH REPORT

Application Number
EP 22 20 2491

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X Y	US 5 522 155 A (JONES C BRADFORD [US]) 4 June 1996 (1996-06-04) * the whole document *	1-12,14, 15 13	INV. F26B5/06
X	WO 2007/127286 A2 (MEDICAL INSTILL TECH INC [US]; PY DANIEL C [US]) 8 November 2007 (2007-11-08) * the whole document *	1,2,4,9, 10,14	
X	US 5 596 814 A (ZINGLE RALPH D [US] ET AL) 28 January 1997 (1997-01-28) * the whole document *	1,2,4,9, 10,14	
X	US 2009/175315 A1 (SCHWEGMAN JOHN JEFFREY [US]) 9 July 2009 (2009-07-09) * the whole document *	1,2,4,9, 10,14	
Y	WO 2013/164422 A2 (SCHOTT AG [DE]) 7 November 2013 (2013-11-07) * the whole document *	13	

TECHNICAL FIELDS SEARCHED (IPC)

F26B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	3 April 2023	Villar Fernández, R

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03-04-2023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5522155 A	04-06-1996	AU 678072 B2	15-05-1997
		AU 682294 B2	25-09-1997
		CA 2178496 A1	29-02-1996
		DE 69412291 T2	03-12-1998
		DK 0776297 T3	10-05-1999
		EP 0776297 A1	04-06-1997
		JP H10503993 A	14-04-1998
		US 5522155 A	04-06-1996
		US 5732837 A	31-03-1998
		WO 9606018 A1	29-02-1996
WO 2007127286 A2	08-11-2007	EP 2013113 A2	14-01-2009
		ES 2683919 T3	28-09-2018
		JP 5566101 B2	06-08-2014
		JP 5881767 B2	09-03-2016
		JP 2009534689 A	24-09-2009
		JP 2014160085 A	04-09-2014
		US 2008028632 A1	07-02-2008
		US 2008039773 A1	14-02-2008
		US 2011253250 A1	20-10-2011
		WO 2007127286 A2	08-11-2007
US 5596814 A	28-01-1997	AU 7104796 A	29-05-1997
		CA 2232711 A1	15-05-1997
		EP 0859721 A1	26-08-1998
		JP 3773958 B2	10-05-2006
		JP 2001515435 A	18-09-2001
		US 5596814 A	28-01-1997
		WO 9717265 A1	15-05-1997
US 2009175315 A1	09-07-2009	NONE	
WO 2013164422 A2	07-11-2013	CN 104272049 A	07-01-2015
		EP 2844936 A2	11-03-2015
		EP 2848882 A1	18-03-2015
		WO 2013164422 A2	07-11-2013

EPO FORM P0459

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Patent documents cited in the description

- WO 2019012512 A1 **[0003]**
- US 6790926 B1 **[0040]**

Non-patent literature cited in the description

- European Pharmacopoeia 5.1.1. 2019 **[0060]**