RAPID RECONSTITUTION FOR LYOPHILIZED-PHARMACEUTICAL SUSPENSIONS

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A method of preparing and reconstituting a sterile, lyophilized pharmaceutical active for rapid reconstitution by evacuating a lyophilized pharmaceutical active-containing container until the pressure within the container is less than about 300 Torr and hermetically sealing the evacuated container. The sterile, lyophilized pharmaceutical active can be prepared by flash freezing a pharmaceutical active-containing composition then lyophilizing the composition. The hermetically sealed lyophilized pharmaceutical active can be reconstituted by adding at least the total volume of liquid necessary for reconstitution of the sterile, lyophilized pharmaceutical active to the sterile, lyophilized pharmaceutical active, sealed under a pressure of less than about 300 Torr, in less than about 10 seconds to yield, within about 5 minutes, an administrable pharmaceutical active-containing composition. One aspect of the herein described sterile, lyophilized pharmaceutical active is a packaged sterile pharmaceutical active comprising an evacuated, hermetically sealed container having disposed therein a sterile, lyophilized pharmaceutical active, sealed under a pressure of less than about 300 Torr.
RAPID RECONSTITUTION FOR LYOPHILIZED-PHARMACEUTICAL SUSPENSIONS

CROSS-REFERENCE TO RELATED APPLICATION


FIELD OF THE DISCLOSURE

[0002] The invention relates to the pharmaceutical and medical field and provides a packaged lyophilized pharmaceutical active and a method of producing the packaged lyophilized pharmaceutical active. Specifically, the invention provides for the rapid reconstitution of a lyophilized pharmaceutical active with minimal foaming.

BACKGROUND

[0003] Lyophilization is used to prepare pharmaceutical actives with higher stability, broader temperature tolerance, and longer shelf-life than comparable aqueous solutions. Typically, pharmaceutical actives are dried to water contents of less than 5 wt. % through sublimation and desorption.

[0004] The reconstitution of lyophilized pharmaceutical actives that contain proteins or polypeptides by the addition of water, leads to the formation of a foam. The foam is thought to occur from the interaction of the amphiphilic protein or polypeptide with the reconstituting solvent, typically water. The foaming of the lyophilized pharmaceutical active poses problems for medical practitioners and researchers. For example, in double blind studies placebo of lyophilized pharmaceuticals need to appear identical to the active therefore a placebo must foam identically to the active. See e.g., U.S. Pat. No. 6,242,423. The reduction or elimination of foaming would benefit both the medical practitioner by saving time and the researcher by reducing the complexity of formulating a placebo for a double blind study.

SUMMARY OF THE INVENTION

[0005] Described herein, in the preferred embodiment, is a lyophilized pharmaceutical active stored under a pressure of less than 500 Torr (40 kPa) that can be rapidly reconstituted for in vivo use.

[0006] One aspect of the materials and methods described herein is a process for making a sterile, lyophilized pharmaceutical active. This process includes evacuating a container that contains the sterile, lyophilized pharmaceutical active and hermetically sealing the container.

[0007] Another aspect of the materials and methods described herein is a process for preventing Ostwald ripening growth during the preparation of a sterile, lyophilized pharmaceutical active. This process includes flash freezing a sterile pharmaceutical active containing composition, lyophilizing the composition, and sealing the sterile, lyophilized pharmaceutical active under a pressure of less than about 300 Torr (40 kPa).

[0008] Yet another aspect of the materials and methods described herein is a process for reconstituting a sterile, lyophilized pharmaceutical active. This process includes adding a sterile liquid to the sterile, lyophilized pharmaceutical active to yield an administrable pharmaceutical active-containing composition within about 5 minutes.

[0009] Still another aspect of the materials and methods described herein is a packaged sterile pharmaceutical active. This package includes a sterile, lyophilized pharmaceutical active hermetically sealed within a container.

DETAILED DESCRIPTION

[0010] Herein, ranges may be expressed as from “about” or “approximately” one particular value and/or to “about” or “approximately” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. Additionally, compilations of parts of or areas in devices are at times designated specific regions, these regions are described based on the theorized primary event occurring in the designated region. Regions can and often overlap and other events can and likely occur within the specifically designated regions.

[0011] The article and methods described herein generally relates to the preparation, storage and reconstitution of pharmaceutical actives. An aspect of the reconstitution of pharmaceutical actives is the amount of time necessary for the reconstitution, with multi-step and/or prolonged reconstitution processes being burdensome on an administrating medical practitioner. Embodiments of the herein described methods and article can be selected to reduce the medical practitioner’s time commitment to the reconstitution process and thereby the medical practitioner can more readily care for the patient.

[0012] One aspect of the herein described article and methods is the preparation of a sterile, lyophilized pharmaceutical active (“LPA”) for rapid reconstitution, comprising evacuating a lyophilized pharmaceutical active-containing container until the pressure within the container is less than about 25 Torr (333 Pa); and hermetically sealing the evacuated container. Another aspect of the herein described methods is the prevention of Ostwald ripening growth by flash freezing during the preparation of the sterile, LPA. Still another aspect of the herein described methods is the rapid reconstitution of the sterile, LPA. Yet another aspect of the herein described article is the packaged sterile, LPA, for example, prepared by any one of the methods described herein.

[0013] Generally, the preparation of the sterile, LPA described herein involves the lyophilization and storage of a pharmaceutical active-containing composition, containing a solvent or liquid, e.g., water. In addition, the pharmaceutical active can be in the form of a solution, a suspension, or an emulsion. The pharmaceutical active can be lyophilized by placing a pharmaceutical active-containing composition in a freeze dryer or a lyophilizer, and lyophilizing. One procedure for lyophilizing a pharmaceutical active-containing composition includes continuously pulling a vacuum (e.g. to less than about 1 Torr (133 Pa), preferably about 0.01 to about 1 Torr, preferably about 0.1 to about 100 mTorr (8 to 40 Pa), even more preferably about 0.01 to about 100 mTorr (13 Pa) or less) on a pharmaceutical active-containing composition that was precooled and maintained at a temperature of less than about -20°C, more preferably a temperature of about -20°C to about -70°C, for example a temperature of about -40°C.
A lyophilization of a pharmaceutical active-containing composition can be divided into a plurality of drying cycles, e.g., the drying cycles can include a primary drying cycle and a secondary drying cycle. The primary drying cycle can be a period of time that depends on the removal of an amount of frozen solvent, e.g., the majority, from the pharmaceutical active-containing composition. The plurality of drying cycles can include a primary to secondary drying cycle transition which can include raising the temperature of the pharmaceutical active-containing composition, e.g., at about 0.5°C per minute to about −20°C, while continuously pulling a vacuum. The secondary drying cycle can be a period of time that depends on the removal of an amount of residual solvent in the pharmaceutical active-containing composition, e.g., that not removed in the primary drying cycle, if any, and which would be apparent to one of ordinary skill. The plurality of drying cycles can further include a secondary to tertiary drying cycle transition that can include raising the temperature of the pharmaceutical active-containing composition, at about 0.5°C per minute to about 30°C, while continuously pulling a vacuum. A tertiary drying cycle can be a period of time, that is apparent to one of ordinary skill, that includes continuously pulling vacuum at a temperature above the melting point of a solvent that was included in the pharmaceutical active-containing composition prior to lyophilization.

An added benefit can be obtained if Ostwald ripening growth is prevented during the preparation of the sterile, LPA. Preferably, the pharmaceutical active-containing composition is flash frozen prior to lyophilization. The pharmaceutical active-containing composition can be flash frozen by, for example, submerging a container holding the composition in a cryogenic liquid, e.g., liquid nitrogen. Alternative methods exist for the flash freezing of the composition and will be available to one of ordinary skill. Preferably, the composition is frozen at a sufficient rate (e.g. within about 60 seconds) to prevent Ostwald ripening growth. When the pharmaceutical active-containing composition is cryogenically flash frozen the composition can be subsequently warmed within the lyophilization chamber (e.g. to a temperature of about −40°C) while exposed to a vacuum (e.g. to less than about 1 Torr (133 Pa), preferably about 0.01 to about 1 Torr, more preferably about 60 to about 300 mTorr (8 to 40 Pa), even more preferably to about 100 mTorr (13 Pa) or less.

Generally, the storage of the LPA involves disposing the LPA in a sealable container and preferably sealing the container. Preferably, after lyophilization, the LPA is disposed within a hermetically sealable container; the container is evacuated, preferably, to a pressure less than about 300 Torr, more preferably less than about 200 Torr, even more preferably less than about 100 Torr, still more preferably less than about 50 Torr, even still more preferably less than about 25 Torr (3333 Pa), yet more preferably less than about 10 Torr (1333 Pa), and yet still more preferably less than about 5 Torr (667 Pa) or 4 Torr (533 Pa); and the container is then hermetically sealed. One of ordinary skill will comprehend methods for storing a material within a container. These methods include and are not limited by the methods of 1) storing the LPA in a sealable container, evacuating the container, and then hermetically sealing the container; 2) sealing the LPA in a container, evacuating the container, and then applying a hermetic seal; or 3) evacuating a chamber containing the LPA and the container; and then hermetically sealing the LPA inside the container. Optionally, the sealed container contains a dissolution aid, for example a dissolution aid can be a impeller, a magnetic stirrer, and/or other inert solids like glass beads, polyethylene beads, and ceramic beads.

The sealable container can be a rigid container, a non-rigid container, or a variable-volume container. Examples of rigid containers include ampoules, vials, tubes, bottles, and the like; for example made of glass, plastic, and the like. Non-rigid containers include hermetically sealable plastic bags. When the sealable container is a non-rigid container one of ordinary skill would recognize that the pressure within the container will equilibrate to the same pressure as when the container was evacuated, e.g., the container deforms to equilibrate the external pressure and the internal pressure; a non-rigid container sealed under a pressure of less than about 25 Torr (3333 Pa) will equilibrate to a higher internal pressure, approaching or achieving the external pressure. Variable-volume containers include for example syringes. While syringes hermetically sealed under vacuum may decrease the internal volume within the syringe, syringes with barrel-locking mechanisms may be used to maintain a minimum volume within the syringe and thereby a known internal pressure. One of ordinary skill in the art will comprehend how to hermetically seal the sealable container. Rigid containers are preferred.

The methods described above will yield a packaged sterile, LPA. Preferably, the packaged sterile, LPA comprises a LPA disposed within a hermetically sealable container. More preferably, the LPA is sealed within the container at a pressure of less than about 300 Torr, more preferably less than about 200 Torr, even more preferably less than about 100 Torr, still more preferably less than about 50 Torr, even still more preferably less than about 25 Torr (3333 Pa), yet more preferably less than about 10 Torr (1333 Pa), and yet still more preferably less than about 5 Torr (667 Pa) or 4 Torr (533 Pa). One of ordinary skill in the art will recognize that the pressure in the hermetically sealed container is dependent on the rigidity of the container, therefore the pressure within the container may be different from the pressure at which the container was sealed.

The reconstitution of the pharmaceutical active by the addition of a solvent for the pharmaceutical active is preferably carried out under reduced pressure. One of ordinary skill in the art will recognize that there are multiple methods for the addition of a solvent to a material stored under a reduced pressure. Herein, all methods for the addition of the solvent to the pharmaceutical active are applicable so long as the addition occurs with minimum addition of a gas. These methods include the cannula transfer of the solvent, the syringe transfer of the solvent, addition of the solvent in a vacuum chamber, vacuum distillation of the solvent into the pharmaceutical active containing container, and the like. More preferably, the addition of the solvent occurs without the formation of bubbles or foam in the pharmaceutical active-containing container. Still more preferably, the solvent is degassed prior to the addition to the pharmaceutical active.

The reconstitution of the pharmaceutical active is preferably rapid. In the reconstitution of known pharmaceutical actives preferably occurs in 50% less time than the time necessary under the current and accepted procedures for the reconstitution of the same pharmaceutical actives. More preferably, the reconstitution of the pharmaceutical active occurs as a single step through the addition of the total volume of solvent necessary for reconstitution of the pharmaceutical active. Preferably, the total volume of solvent is added in less than about 60 seconds, more preferably less than about 30
seconds, even more preferably less than about 20 seconds, and still more preferably less than about 10 seconds; thereaf-
ter the reconstituted pharmaceutical active-containing com-
position is preferably administrable within about 10 minutes,
more preferably within about 5 minutes, and even more pre-
ferably within about 2.5 minutes.

The pharmaceutical active is one that can be lyo-
philized and reconstituted. In one embodiment, the pharma-
ceutical active includes an albumin. Typically, lyophilized 
albumin compositions foam upon reconstitution with water 
due to the interaction of the amphiphilic albumin and the 
water. The foaming of lyophilized albumin forces prolonged 
reconstitution procedures to prevent the injection or biologi-
cal application of the foam albumin, thereby preventing 
rapid reconstitution and administration. The foaming of the 
reconstituted albumin is especially detrimental to the rapid 
reconstitution and administration of pharmaceutical actives 
intended for human use. When intended for human use the 
albumin is preferably a human serum albumin. More prefer-
ably the pharmaceutical active has nanoparticles of human 
serum albumin. The amount of albumin in the pharmaceutical 
active can vary. Preferably, the pharmaceutical active has at 
least about 50 wt. % of the albumin, more preferably about 75 
wt. %, and even more preferably about 85 wt. %. When the 
pharmaceutical active comprises an albumin the active can 
further comprise a drug or drugs that bind to an albumin. 
Examples of drugs that bind to human serum albumin are 
known to one of ordinary skill and include ontological, imag-
ing, anti-inflammatory, and antiallergic drugs. A preferable 
ontological drug that binds to human serum albumin is pacli-
taxel.

EXAMPLES

Several lyophilization and reconstitution studies were performed to test the invention using: 1) ABRAXANE 
vials, 2) homogenized 0.3% paclitaxel/albumin formulation, 
3) 5% BSA (bovine serum albumin), and 4) 3% BSA. 
ABRAXANE is a nanoparticle suspension containing 
approximately 4.5% HSA (human serum albumin) and 0.5% 
paclitaxel after reconstituted with 20 mL of the diluent. Thus, 
90% of the content of the ABRAXANE vials is HSA which is a 
protein. As such, HSA contributes the major physical char-
acteristics, such as texture of the lyophilized vial, reconstitu-
tion rate, and foaming, of the ABRAXANE product. Thus 
placebo vials, i.e. vials containing HSA without paclitaxel, 
will give a close representation of the above physical char-
acteristics. For convenience, BSA was used as the placebo for 
the testing, since pure BSA in solid form is more available 
than HSA. The 5% BSA was used to mimic the ABRAXANE 
with 20 mL of fill volume for lyophilization, and 3% BSA was 
used as the placebo to mimic 35 mL fill volume for lyophiliza-
tion. The studies were performed per the following experi-
mental designs:

1) Reconstituted the original ABRAXANE vial with 20 mL.
2) Pulled a vacuum on the ABRAXANE vial, to 
approximately 4 Torr (533 Pa) using a LYOSTAR II 
dryer, followed by reconstitution with 33 mL water to 
study the effect of vacuum on the reconstitution rate.
3) Divided the above reconstituted vial into 4 
vials, 4 mL each into 10 mL vials, followed by lyo-
philization and sealing under a high vacuum of 4 Torr 
(533 Pa) to 5 Torr (667 Pa). Studied the reconstitution 
time of the resulting vials. The purpose of dividing the 
content in the ABRAXANE vial was due to the high cost 
of ABRAXANE. The results from these small vial stud-
ies gave a close indication of the physical characteristics 
of the actual size of the ABRAXANE vial.

Prepared 5% BSA and filled 4 mL each into 10 
vials, followed by lyophilization and reconstitution, 
and compared the results with those in Step 2.
Prepared approximately 30 mL of 0.3% 
paclitaxel/albumin nanoparticle suspension in 50 mL 
vials, followed by lyophilization and reconstitution.
Prepared 5% BSA and filled 33 mL each into 
50 mL vials, followed by lyophilization and reconstruc-
tion, and compared the results with those in Step 4.

The results of the above studies are presented below.

Example 1

Lyophilization and Reconstitution Studies for 5% 
BSA (Bovine Serum Albumin), 5 mL Fill into 10 mL 
Vials

The purpose of using 4 mL fill of ABRAXANE in 10 
vials was due to the high cost of ABRAXANE. The small 
vial studies generated more replicates for data analysis.

The lyophilization cycle parameters are:

1) Cool the shelf to −40°C and hold for 80 
2) Pull vacuum to 100 mTorr (133 Pa).
3) Hold at −40°C, 100 mTorr (133 Pa) for 30 
4) Ramp 0.5°C to −20°C, 100 mTorr (133 Pa).
5) Primary drying: Hold at −20°C, 100 mTorr 
(133 Pa) for approximately 2300 minutes.
6) Ramp 1°C/min to 30°C, 100 mTorr (133 Pa).
7) Secondary drying: Hold at 30°C, 100 mTorr 
(133 Pa) for approximately 330 minutes.

After lyophilization, the vials were sealed at 
approximately 5 Torr (667 Pa). The reconstitution was 
performed by pointing the needle at the cake to allow water to 
quickly absorbed by the cake.

It was observed minimal amount of foam produced, 
probably due to the fact that the vials were sealed at a high 
vacuum of approximately 5 Torr (667 Pa). The vial was gently 
rotated by fingers, and it was observed complete dissolution 
of the cake approximately 4 minutes from the time when 
water was injected into the vial.

Comparative Example 1

Reconstitution of the Original ABRAXANE Vial 
with 20 mL Water

The purpose of the study was to determine the 
reconstitution time and foaming phenomenon of the 
ABRAXANE vial which contained very little vacuum.

<table>
<thead>
<tr>
<th>Reconstitution time</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately 20 min</td>
<td>The reconstitution procedure</td>
</tr>
<tr>
<td></td>
<td>provided in the package</td>
</tr>
<tr>
<td></td>
<td>insert was carefully followed</td>
</tr>
<tr>
<td></td>
<td>to avoid foaming.</td>
</tr>
</tbody>
</table>
As seen, approximately 20 minutes was required to reconstitute the vial with a very careful control of the reconstitution procedure described in the package insert.

Example 2
Lyophilization and Reconstitution Studies for Reconstituted ABRAXANE Vial (4 mL Filled into 10 mL vials) and 5% BSA (5 mL Fill into 10 mL Vials)

The purpose of the study was to investigate the lyophilization and reconstitution characteristics of the reconstituted ABRAXANE vials and the placebo vials of 5% BSA.

The lyophilization cycle parameters are:

1) Cool the shelf to -40°C. and hold for 90 minutes.
2) Pull vacuum to 100 mTorr (133 Pa).
3) Hold at -40°C., 100 mTorr (133 Pa) for 20 minutes.
4) Ramp at 0.5°C./min to -20°C., 100 mTorr (133 Pa).
5) Hold at -20°C., 100 mTorr (133 Pa) for approximately 2400 minutes.
6) Ramp at 0.5°C./min to 30°C., 100 mTorr (133 Pa).
7) Hold at 30°C., 100 mTorr (133 Pa) for approximately 300 minutes.

After completion of the cycle run, the vials were sealed at approximately 4 Torr (533 Pa) and crimped. The results of reconstitution are discussed below.

(1) Reconstitution Time of 4 mL of Reconstituted ABRAXANE Vials

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Reconstitution time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 min 35.41 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>2</td>
<td>3 min 36.05 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>3</td>
<td>3 min 34.72 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>4</td>
<td>2 min 41.89 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>5</td>
<td>3 min 25.21 sec</td>
<td>foaming was minimal</td>
</tr>
</tbody>
</table>

(2) Reconstitution Time for 5% BSA

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Reconstitution time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>4 min 25.87 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>7</td>
<td>3 min 2.87 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>8</td>
<td>0 min 33.91 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>9</td>
<td>4 min 6.22 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>10</td>
<td>1 min 44.75 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>11</td>
<td>3 min 46.03 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>12</td>
<td>2 min 50.19 sec</td>
<td>foaming was minimal</td>
</tr>
</tbody>
</table>

(3) 5% BSA with Glass Beads

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Reconstitution time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>1 min 39.75 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>14</td>
<td>1 min 55.41 sec</td>
<td>foaming was minimal</td>
</tr>
</tbody>
</table>

The above reconstitution times are even shorter than those of 5% BSA without glass beads in (2).

Example 3
Quick Freezing, Lyophilization and Reconstitution Studies for Reconstituted ABRAXANE Vial (4 mL filled into 10 mL Vials) and 5% BSA (5 mL Filled into 10 mL Vials)

The purpose of quick freezing was to immobilize nanoparticles from aggregation or crystallization due to the Ostwald ripening effect.

Quick Freezing Procedure:

1) Placed the test-tube rack on a metal tray and placed a piece of aluminum foil on the bottom of the test tube rack and lifted the four sides of the foil to cover the bottom half of the rack for holding the liquid nitrogen.
2) Placed the reconstituted vials in the slots of the test tube rack.
3) Placed stoppers on the vials.
4) Poured liquid nitrogen into the test tube rack to quick freeze the vials.
5) Started the LyoStar II freeze dryer to precool the shelf to -40°C.
6) Loaded the frozen vials onto the shelf, and started the following cycle.

Lyophilization Cycle Parameters:

1) Cool the shelf to -40°C. and hold for 90 minutes.
2) Pull vacuum to 100 mTorr (133 Pa).
3) Hold at -40°C., 100 mTorr (133 Pa) for 30 minutes.
4) Ramp at 0.5°C./min to -10°C., 100 mTorr (133 Pa).
5) Primary drying: Hold at -10°C., 100 mTorr (133 Pa) for approximately 1050 minutes.
6) Ramp at 0.5°C./min to 30°C., 100 mTorr (133 Pa).
7) Secondary drying: Hold at 30°C., 100 mTorr (133 Pa) for approximately 530 minutes.

After completion of the cycle, the vials were sealed at approximately 4 Torr (533 Pa) and crimped.

The Results of Reconstitution Studies are Presented Below

(1) ABRAXANE Vials (Injected with 4 mL Pure Water)

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Reconstitution time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>2 min 3.50 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>19</td>
<td>2 min 15.66 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>20</td>
<td>2 min 45.25 sec</td>
<td>foaming was minimal</td>
</tr>
</tbody>
</table>
The above results indicate that the resulting cakes after quick freezing followed by lyophilization also reconstituted rapidly. Thus, the combination of quick freezing and vacuum seal can prevent aggregation (or crystallization) of nanoparticles and give a quick reconstitution of the resulting cakes.

Comparative Example 3

Reconstitution of Vials Sealed Under Ambient Pressure

The purpose of this study was to investigate the reconstitution time for samples prepared by the quick freezing and lyophilization procedure described above wherein the samples were sealed under ambient pressure, approximately 760 Torr (101 kPa).

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Reconstitution time</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>3 min 41.66 sec</td>
<td>large amount of foaming</td>
</tr>
</tbody>
</table>

Example 4

Vacuum Pull on the Original ABRAXANE Vial, Followed by Reconstitution with 33 mL Water

The purpose of the study was to investigate the effect of vacuum on the reconstitution rate of the original ABRAXANE product vial. The ABRAXANE vial was vacuum pulled to approximately 4 Torr (533 Pa) using LyoStar II dryer and resealed. The purpose of vacuum pull was to minimize foaming during reconstitution. The ABRAXANE vial was then reconstituted with 33 mL of pure water.

<table>
<thead>
<tr>
<th>Vial number</th>
<th>Reconstitution time</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>Approximately 12 minutes and 1.9 sec.</td>
</tr>
</tbody>
</table>

Example 5

Lyophilization and Reconstitution Studies for 0.3% Paclitaxel/Albumin and 3% BSA

The 0.3% paclitaxel/albumin nanoparticle suspension was prepared at Baxter Round Lake facility. The vials contained approximately 30 mL each in 50 mL vials. The placebo of 3% BSA was prepared at Baxter Bloomington facility. The fill volume of the placebo was 33 mL each in 50 mL vials. The vials were lyophilized together using the following cycle parameters:

<table>
<thead>
<tr>
<th>Cycle parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>0088</td>
<td>(1) Precool the shelf to 5° C.</td>
</tr>
<tr>
<td>0089</td>
<td>(2) Load the vials to the shelf and install thermocouples.</td>
</tr>
<tr>
<td>0090</td>
<td>(3) Cool the shelf to −40° C. and hold for approximately 270 min.</td>
</tr>
<tr>
<td>0091</td>
<td>(4) Start vacuum pump at 100 mTorr (133 Pa) and hold at −40° C. for 30 min.</td>
</tr>
<tr>
<td>0092</td>
<td>(5) Primary drying: ramp to −10° C. at 0.5° C/min, at 100 mTorr (133 Pa), and hold for 135 hours and 37 minutes.</td>
</tr>
<tr>
<td>0093</td>
<td>(6) Secondary drying: ramp to 30° C. at 1° C/min, and hold for 10 hours.</td>
</tr>
</tbody>
</table>
After completion of the cycle, the vials were sealed at approximately 4 Torr (533 Pa). The following procedure was used to reconstitute the vials.

(1) Removed the aluminum cap of the vial.
(2) Load the syringe with 20 mL water, and ensure all air is removed by priming.
(3) Stick the needle through the stopper and point at the cake.
(4) The water in the syringe will be automatically and quickly pulled into the vial due to the high vacuum of approximately 4 Torr (533 Pa).
(5) As soon as all water is delivered, pull out the needle quickly to avoid injecting air.
(6) Gently swirl or invert the vial to enhance dissipation of the cake.

As seen, the reconstitution procedure for the vacuum sealed vials is very different than the ABRAXANE product vials, because of foaming can be minimized by the high vacuum.

The following sample IDs are for 3% BSA to mimic the ABRAXANE vials, since the solution in the vials became clear after reconstitution and easier to observe the reconstitution and foam dissipation. The reconstitution times for 3% BSA, 33 mL in 50 mL vials, are presented below:

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Reconstitution time</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>7 min 23.28 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>37</td>
<td>6 min 36.72 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>38</td>
<td>10 min 13.38 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>39</td>
<td>8 min 18.96 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>40</td>
<td>4 min 09.53 sec</td>
<td>foaming was minimal</td>
</tr>
<tr>
<td>41</td>
<td>8 min 26.18 sec</td>
<td>foam was minimal</td>
</tr>
</tbody>
</table>

It was found that the crushed cake in sample 40 reconstituted quicker. The cake was crushed by hand, by end-to-end shaking of the vial for a few minutes. The reconstitution times of the intact cake, samples 36, 37, 38, 39, and 41, are still much shorter than that of the ABRAXANE vial. This result further confirmed the effectiveness of vacuum seal on enhancing the reconstitution and minimizing foaming.

What is claimed:

1. A method of preparing a sterile, lyophilized pharmaceutical active for rapid reconstitution, comprising:
   evacuating a sterile, lyophilized pharmaceutical active-containing container until the pressure within the container is less than about 300 Torr (40 kPa); and
   hermetically sealing the evacuated container.

2. The method of claim 1 further comprising:
   flash freezing a sterile pharmaceutical active-containing composition;
   lyophilizing the flash frozen sterile pharmaceutical active-containing composition to yield the sterile, lyophilized pharmaceutical active; and thereby preventing Ostwald ripening growth.

3. The method of claim 2, wherein the lyophilizing of the flash frozen pharmaceutical active-containing composition comprises:
   storing a flash frozen pharmaceutical active-containing composition in a lyophilization chamber;
   warming the flash frozen pharmaceutical active-containing composition disposed within the lyophilization chamber to a temperature of less than about -20°C;
   pulling a vacuum of less than about 1 Torr (133 Pa) on the lyophilization chamber;
   warming the flash frozen pharmaceutical active-containing composition disposed within the lyophilization chamber to about -20°C; and
   maintaining the vacuum of less than about 1 Torr (133 Pa) on the lyophilization chamber for a period of time constituting a primary drying cycle that corresponds with a removal of a majority of a frozen solvent.

4. The method of claim 3 further comprising:
   after the end of the primary drying cycle, then warming the pharmaceutical active-containing composition to about 30°C and maintaining the vacuum of less than about 1 Torr (133 Pa) for a period of time constituting a secondary drying cycle.

5. A method of reconstituting a sterile, lyophilized pharmaceutical active comprising:
   adding a volume of a sterile liquid to a sterile, lyophilized pharmaceutical active, sealed within an evacuated container wherein the pressure within the evacuated container is less than about 300 Torr (40 kPa), in less than about 10 seconds to yield, within about 5 minutes, an administrable pharmaceutical active-containing composition wherein the volume of liquid added is at least the total volume of liquid necessary for reconstitution of the sterile, lyophilized pharmaceutical active.

6. The method of claim 5, wherein the sterile, lyophilized pharmaceutical active is one having been lyophilized from a first volume of a liquid containing the pharmaceutical active, and wherein the volume of liquid added for reconstitution is equivalent to the first volume.

7. The method of claim 5, wherein the liquid is a solvent for the pharmaceutical active.

8. A packaged sterile pharmaceutical active comprising:
   a sterile, lyophilized pharmaceutical active hermetically sealed within an evacuated container wherein the pressure within the evacuated container is less than about 300 Torr (40 kPa).

9. The package of claim 8, wherein the container is selected from the group consisting of a rigid container, a non-rigid container, and a variable-volume container.

10. The package of claim 8, wherein the container is a lyophilizer chamber within the lyophilization chamber.

11. The package of claim 8, wherein the container, lyophilized pharmaceutical active comprises paclitaxel.

12. The package of claim 11, wherein the pharmaceutical active comprises at least about 50 wt. % of the albumin and wherein the albumin is a human serum albumin.

13. The package of claim 12, wherein the pharmaceutical active comprises at least about 75 wt. % of the human serum albumin.

14. The package of claim 13, wherein the pharmaceutical active comprises at least about 85 wt. % of the human serum albumin.

15. The package of claim 8, wherein the sterile pharmaceutical active-containing composition comprises a nanoparticle of human serum albumin.

16. The package of claim 8, wherein the pressure within the evacuated container is less than about 100 Torr (13 kPa).

17. The package of claim 16, wherein the pressure is less than about 25 Torr (3325 Pa).

18. The package of claim 17, wherein the pressure is less than about 5 Torr (667 Pa).