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(54) **METHOD FOR TESTING THE RESULT OF A FILLING PROCESS OF VIALS**

(57) The invention relates to a method which employs a dye for testing the result of a filling process of vials with a liquid formulation, and to the use of a dye for testing the result of a filling process of vials with said liquid formulation.

Figure 2



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Description

FIELD OF THE INVENTION

[0001] The invention relates to a method which employs a dye for testing the result of a filling process of vials with a liquid formulation, and to the use of a dye for testing the result of a filling process of vials with said liquid formulation.

BACKGROUND OF THE INVENTION

[0002] Lyophilized formulations have become an important part of pharmaceutical development and production. In particular, lyophilized formulations offer significant advantages with respect to stability and storage over solutions or other liquid formulations.

[0003] It is often undesirable to store pharmaceutical formulations in a liquid form due to potential stability problems. Some liquid formulations must be stored at low temperatures. Other formulations deteriorate during storage in a liquid form. One possibility to overcome these issues is to freeze-dry the pharmaceutical formulation. A freeze-dried formulation can be transported and stored in a dry form which can then be reconstituted prior to use.

[0004] However, the freeze-drying process itself can result in a deterioration of the properties of the formulation, in particular if the active agent is a protein. Lyoprotectants such as certain sugars as well as surfactants are commonly added to the pharmaceutical formulation to avoid degradation of active agents and improve overall stability. In addition, surfactants are typically used to ensure adequate drug product stability, processing and compatibility with administration materials and devices. Surfactants within the meaning of the invention means any substance that shows surface activity, so the terms "surfactant" and "surface active agent" can be used synonymously within the meaning of the invention.

[0005] It has been observed that in some cases a liquid pharmaceutical formulation can creep up the inner surface of the walls of a container (e.g., a vial) above the meniscus of the liquid pharmaceutical formulation after it has been filled in. This creeping results in an undesired appearance that is in essence a material causing the undesired appearance, for example, in the form of a contamination of the inner surface of the wall of a container above the meniscus and can take the form of a haze or cloud or fog or haziness of different patterns, or even of droplets, on the inner wall of the vial above the meniscus of the liquid pharmaceutical formulation.

[0006] So for the purpose of this invention, the term "undesired appearance" encompasses also contamination or defect of the inner surface of the wall of a container above the meniscus of the content of the container, such as a liquid pharmaceutical formulation.

[0007] Another source of such a defect of the inner wall of the vial above the meniscus of the liquid pharmaceutical formulation can also be a "dirty" filling process or a

shaking of the vial after filling, leaving splashes on the inner wall of the vial above the meniscus of the pharmaceutical formulation. After lyophilization, the defect takes on a form of a residue on the inner wall surface of the container. This residue may be considered a cosmetic defect, yet it is undesirable because it can impact the visual inspection of the containers and its appearance may be questioned by patients and doctors alike.

[0008] Aside from the cosmetic side, it is possible that such a defect provides risks for container closure integrity if the material causing the defect, such as dried material, is in between container and stopper. This increases the likelihood of microbiological contamination, which may present a risk for adverse reactions in patients. Further risks include the possibility that the material making up the defect is air-dried instead of lyophilized, which could result in different reconstitution kinetics or, depending on the formulation, might cause changes in the formulation, e.g. in the form of protein denaturation.

[0009] The creeping of the liquid on the container walls can for example occur, if the liquid formulation comprises a surfactant; however, it has also been observed for liquid formulations without surfactant. The creeping can also depend on the properties of the glass container.

[0010] The creeping of the liquid on the container walls has been explained with the Marangoni flow or Marangoni convection and can be influenced by the parameters of the glass containers used (Abdul-Fattah, A.M., et al.; *European Journal of Pharmaceutics and Biopharmaceutics*, 85 (2013) 314-326). To avoid creeping (also called "fogging"), it has been suggested to utilize glass containers with a defined contact angle (see for example WO 2010/115728 A2). Contact angle measurement also allows for an estimation of the overall hydrophobicity of a glass surface (Rödel, E., et al.; *Pharm. Ind.* 75 (2013), 328-332).

[0011] The use of hydrophobic coatings (e.g., silyconized coatings) in glass containers has also been suggested to prevent creeping in glass vials of lyophilisates. However, the inventors found that not every container with a hydrophobic coating is equally suitable and such containers may introduce further quality defects, such as an increased amount of sub-visible particles. The inventors found that, in particular, the difference between the actual surface tension of the liquid, compared to the actual surface energy of the glass container, is relevant for the avoidance of creeping.

[0012] Manufacturers of glass containers with hydrophobic coatings even promote their hydrophobic coated vials by suggesting a Lotus effect caused by the hydrophobic coating, which means that any material making up the defect of the inner wall of the vial above the meniscus of the liquid formulation in the vial after filling flows down and back into the liquid formulation, but also this was found by the inventors not to occur in all instances; instead the material making up the defect occasionally remained on the inner wall surface of the vial above the meniscus of the liquid formulation in the vial after filling.

[0013] As such, there is a need for a new method to allow for an optimized selection of glass containers for lyophilized formulations, to allow for an optimized selection of a "clean" filling process of vials with a liquid drug formulation, and for control, improvement and optimization of a filling process of vials with liquid formulations in order to minimize or even to avoid any material making up the defect on the inner wall surface of the vial above the meniscus of the liquid formulation in the vial.

[0014] The present invention is based on the finding that the use of a dye in a liquid drug formulation provides an accurate and reliable test method for determining whether material making up the defect occurs during the filling process of vials with a liquid drug formulation. Advantageously, the method according to the invention allows one to determine both a vial and a filling process which avoids material making up the defect, thereby providing significant improvements in lyophilized drug formulation quality, in particular in mass production, and associated cost savings.

SUMMARY OF THE INVENTION

[0015] Subject of the invention is a method METHTEST for testing the result of a filling process of vials with a liquid formulation DYE-FORM, comprising the steps (a), (b) and (c):

- (a) filling a vial with DYE-FORM resulting in a filled vial;
- (b) allowing the filled vial to stand upright for a period of time; and
- (c) determining whether DYE-FORM is present or not on the inner wall surface of the filled vial above the meniscus line of DYE-FORM;

with DYE-FORM comprising two components (1) and (2), component (1) being a dye, component (2) being a liquid or a liquid formulation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016]

Figure 1 is a representative photograph of a TopLyo® vial with a "clean" vial wall, after having been filled with DYE-FORM by the filling process of Example 1; a "clean" vial means a vial without any of the defects mentioned herein, such as no DYE-FORM is observed on the inner wall surface above the meniscus line of the DYE-FORM.

Figure 2 is a representative photograph of a TopLyo® vial with small droplets on the inner wall surface above the meniscus line of the DYE-FORM, after having been filled with DYE-FORM by the filling

process of Example 1.

Figure 3 is a representative photograph of a Fiolax® vial showing a defect ("fogging") on the inner wall surface above the meniscus line of the DYE-FORM, after having been filled with DYE-FORM by the filling process of Example 2.

Figure 4 is a representative photograph of a Fiolax® vial showing a defect ("fogging") on the inner wall surface above the meniscus line of the DYE-FORM, after having been filled with DYE-FORM according to formulation 1 by the filling process of Example 3.

Figure 5 is a representative photograph of a TopLyo® vial with a "clean" vial wall, after having been filled with DYE-FORM according to formulation 1 by the filling process of Example 3; a "clean" vial means a vial without any of the defects mentioned herein, such as no DYE-FORM is observed on the inner wall surface above the meniscus line of the DYE-FORM.

DETAILED DESCRIPTION

[0017] The testing of a filling process of a vial comprises, for example, testing whether fogging occurs once a vial has been filled with liquid formulation. This can also be used to predict fogging, for example using a test liquid formulation to simulate the filling of an actual drug formulation. Furthermore, testing a filling process of a vial comprises verification that the filling of the vial with the liquid formulation was done in a clean way essentially keeping the inner surface of the wall above the meniscus of the liquid formulation in the vial in a clean state, for example, the filling of the vial was done without any splashing to the inner surface of the wall having occurred. The result of the filling process of vials can be determined as being negative or unsatisfactory when any of the mentioned defects or undesired appearances occur, caused for example, when the filling process itself fails to meet expectations, such as when splashing occurs during the filling process, or caused for example when after the filling process for other reasons any of the mentioned defects or undesired appearances occur, such as due to fogging or creeping.

[0018] Preferably, the vial is a glass vial. For example, one type of glass that is suitable is borosilicate glass. Borosilicate glass vials are commercially available inter alia under the trade designations Duran®, Pyrex®, Ilmabor®, Simax®, Fiolax®, TopLyo®, Ompi Alba® and BORO-8330™. The surface of the glass can optionally be modified. Examples of modifications are hydrophobic coatings, siliconization or methylation of the surface.

[0019] The dye may be selected from the group consisting of fluorescein, methylene blue, rhodamine, Congo red, acridine orange, crystal violet, cyanine, methyl orange, Coomassie blue, methyl red, ethidium bromide, Victoria blue, Orange G, BODIPY, Alexa Fluor, Texas

red, indocyanine green, cyanine, phtahlocyanine, and derivatives thereof.

[0020] Preferably, the dye is a fluorescent dye.

[0021] In a particular embodiment, the dye is fluorescein.

[0022] In some embodiments, DYE-FORM comprises a surfactant. In the case that DYE-FORM comprises a surfactant, component (2) of DYE-FORM can comprise the surfactant. In the case that DYE-FORM comprises a surfactant, preferably the surfactant is a polysorbate or a poloxamer. In specific embodiments, the surfactant is selected from the group consisting of polysorbate 20, polysorbate 80 and poloxamer 188.

[0023] DYE-FORM can be prepared by mixing the two components (1) and (2) in any order. In one embodiment, component (1) is added to component (2).

[0024] Preferably, the dye is dissolved in component (2) thereby obtaining DYE-FORM with the dye in a dissolved state.

[0025] The dissolving can be done by any conventional means known to the skilled person in the art, such as shaking, stirring, application of ultrasonic sound. Devices which can be used for the shaking, stirring or for application of ultrasonic sound are also known to the skilled person, stirring can for example be done with appliances such as stirring rods or magnetic stirrers.

[0026] Preferably, the dissolving is performed during a time of from 1 second to 12 hours, more preferably of from 2 minutes to 6 hours, even more preferably of from 10 minutes to 4 hours, especially of from 30 minutes to 3 hours, more especially of from 1.5 hours to 2.5 hours.

[0027] Preferably, the dissolving is done at a temperature of from 0°C to 100°C, more preferably of from 2°C to 80°C, even more preferably of from 5°C to 50°C, especially of from 10°C to 35°C, more especially of from 15°C to 25°C.

[0028] DYE-FORM can be filtered before it is filled into the vial, this is for example done to remove any undissolved particles, such as undissolved dye. The filtering can be performed by any means known in the art. For example, the filtering may be performed using a PVDF filter. The pore size can range preferably from 50 nm to 50 micrometer, more preferably from 100 nm to 10 micrometer, even more preferably from 100 nm to 5 micrometer. In one particular embodiment, the pore size is 0.2 micrometer.

[0029] Preferably, the liquid is water.

[0030] Preferably, the liquid formulation is an aqueous formulation.

[0031] Preferably, the liquid formulation comprises a drug product.

[0032] The drug product can be any drug product known to the skilled person, such as small molecule drug products, large molecule drug products, such as proteins, antibodies, antibody-drug conjugates, peptides, RNA, DNA, oligonucleotides, or polynucleotides.

[0033] In case the liquid formulation is an aqueous formulation, it can comprise a buffer. The buffer can, for

example, be used to stabilize the pH of the solution.

[0034] In case the liquid formulation is an aqueous formulation, it can have a pH of 2 to 12, preferably of 2.5 to 10, more preferably of 3.5 to 8, and even more preferably of 4 to 7.

[0035] Suitable buffers are well known in the art. Such buffers are for example histidine-buffers, citrate-buffers, succinate-buffers, acetate-buffers, phosphate-buffers, and mixtures thereof. Preferred buffers are citrate, L-histidine or mixtures of L-histidine and L-histidine hydrochloride. Independently from the buffer used, the pH can be adjusted with an acid or a base known in the art, e.g. hydrochloric acid, acetic acid, phosphoric acid, sulfuric acid, citric acid, sodium hydroxide or potassium hydroxide.

[0036] The liquid formulation can comprise, besides a drug product, further components typically found in pharmaceutical formulations, such as carriers, excipients, stabilizers, preservatives, lyoprotectants or other components.

[0037] Carriers can be any carrier known to the skilled person in the art such as for example aqueous liquids; dextrose solutions; glycerol solutions; microemulsions; nanoparticles; liposomal suspensions; oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, and sesame oil; isopropyl alcohol, gaseous fluorocarbons, ethyl alcohol, polyvinyl pyrrolidone, propylene glycol, a gel-producing material, stearyl alcohol, stearic acid, spermaceti, sorbitan monooleate, and methylcellulose; as well as combinations thereof.

[0038] Excipients can be any excipient known to the skilled person in the art such as for example starch, glucose, lactose, sucrose, gelatin, silica gel, sodium stearate, glycerol, glycerol monostearate, talc, sodium chloride, propylene glycol, and ethanol; as well as combinations thereof.

[0039] Stabilizers can be any stabilizers known to the skilled person in the art such as for example amino acids; ascorbic acid; surfactants such as a polysorbate or a poloxamer; polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol, mannitol and sucrose; as well as combinations thereof.

[0040] Preservatives can be any preservative known to the skilled person in the art, such as for example octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl or benzyl alcohol, alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol.

[0041] Lyoprotectants are pharmaceutically acceptable excipients which protect a labile active ingredient (e.g., a protein) against destabilizing conditions during the freeze-drying process, subsequent storage and reconstitution. Lyoprotectants comprise, but are not limited to, the group consisting of sugars, polyols (e.g. sugar alcohols) and amino acids. Preferably, lyoprotectants are

selected from the group consisting of sugars (such as sucrose, trehalose, lactose, glucose, mannose, maltose, galactose, fructose, sorbose, raffinose, and neuraminic acid), amino sugars (such as lucosamine, galactosamine, and N-methylglucosamine ("Meglumine")), polyols (such as mannitol and sorbitol), and amino acids (such as arginine and glycine). Preferably, lyoprotectants are present in the liquid formulation in an amount of 1 to 500 mM, more preferably 10 to about 300 mM and even more preferably in an amount of about 100 to about 200 mM.

[0042] Yet other components in the liquid formulation can be hydrophilic polymers such as polyethylene glycol (PEG); monosaccharides; disaccharides; including mannose and trehalose; oligosaccharides, polysaccharides, and other carbohydrates including dextrans or dextrans; chelating agents such as EDTA; salt-forming counterions such as sodium; metal complexes (e.g. Zn-protein complexes); and fatty acid esters, fatty acid ethers or sugar esters.

[0043] In the case that DYE-FORM comprises a surfactant, then DYE-FORM preferably comprises the surfactant in an amount of from 0.000001 to 50%, more preferably from 0.000001 to 10%, even more preferably from 0.00001 to 1%, especially from 0.0001 to 0.5%, more especially from 0.00015 to 0.2%, even more especially from 0.001 to 0.1%, of surfactant; the percentages are weight of surfactant/volume of DYE-FORM.

[0044] Preferably, DYE-FORM comprises from 0.01 to 100 mg/ml, more preferably from 0.05 to 50 mg/ml, even more preferably from 0.1 to 20 mg/ml, especially from 0.5 to 12 mg/ml, more especially from 1 to 10 mg/ml, even more especially from 2 to 8 mg/ml, of dye in DYE-FORM.

[0045] In step (a) of the method, the vial is typically filled according to a pre-determined volume. Preferably, DYE-FORM fills 1 to 99%, more preferably 5 to 95%, even more preferably 10 to 90%, especially 15 to 80%, more especially 20 to 70%, even more especially 25 to 60%, in particular 30 to 60%, more in particular 40 to 60%, of the volume of the vial. The filling of vials is preferably automated.

[0046] In step (b) of the method, the period of time that the filled vial is allowed to stand upright may depend on the type of liquid or liquid formulation, on the type of vial and, in case a surfactant is present, on the type of surfactant. Preferably, the vial is allowed to stand upright for 1 second to 1 week, more preferably for 10 seconds to 1 day, even more preferably for 10 seconds to 12 hours, especially for 1 minute to 6 hours, more especially for 2 minutes to 3 hours, even more especially for 3 minutes to 1 hour, in particular for 5 minutes to 30 minutes.

[0047] During the period of time that the filled vials are allowed to stand upright, potential creeping of DYE-FORM up the inner wall surface of the vials could occur.

[0048] Preferably, the filled vials are allowed to stand upright for said period of time to observe potential creeping of DYE-FORM up the inner wall surface of the vials

at a temperature of 0°C to 100°C, more preferably 2°C to 80°C, even more preferably 5°C to 50°C, especially 10°C to 35°C, more especially 15°C to 25°C.

[0049] In step (c) of the method, the meniscus line of the DYE-FORM is to be understood to correspond to the height which the DYE-FORM would be expected to reach in the vial based on the volume of DYE-FORM.

[0050] The determination of whether DYE-FORM is present on the inner wall surface of the filled vial above the meniscus line of the DYE-FORM can be made by a machine. In preferred embodiments, the determination of whether DYE-FORM is present on the inner wall surface of the filled vial above the meniscus line of the DYE-FORM is made by automated photographic analysis of the vial wall.

[0051] Another subject of the invention is a method METHSELECT for selecting a vial which shows no defects after the filling of the vial with a drug product, comprising the steps (a), (b), (c) and (d):

20 steps (a), (b) and (c) as defined herein, also with all their embodiments; and
step (d) selecting a vial for which it has been determined that no DYE-FORM is present on the inner wall surface of the filled vial above the meniscus line of the DYE-FORM;

25 with DYE-FORM as defined herein, also with all its embodiments.

[0052] Another subject of the invention is a kit KITDYE for analyzing the susceptibility to fogging of a vial containing a component (2), wherein the kit comprises a component (1);

30 with component (1) and component (2) as defined herein, also with all their embodiments.

[0053] Preferably, the kit additionally comprises a member selected from the group consisting of:

- 40 (i) a surfactant;
- (ii) a buffer;
- (iii) a filter;
- (iv) a positive control vial;
- (v) a negative control vial;

45 and a combination thereof;
with the surfactant, the buffer and the filter as defined herein, also with all their embodiments.

[0054] In some embodiments, component (1) is present in the kit in the form of a solution, preferably in the form of an aqueous solution.

[0055] The positive control vial can be a vial type which has been tested by METHTEST, and for which it has been determined that DYE-FORM is present on the inner wall surface of the filled vial above the meniscus line of the DYE-FORM;

55 the negative control vial can be a vial type which has been tested by METHTEST, and for which it has been determined that DYE-FORM is not present on the inner

wall surface of the filled vial above the meniscus line of the DYE-FORM;
with METHTEST as defined herein, also with all its embodiments.

[0056] Another subject of the invention is a method METHCOMP for increasing patient compliance, wherein a drug product is provided to the patient in a vial selected by METHSELECT, with METHSELECT as defined herein, also with all its embodiments.

[0057] Preferably, METHCOMP is for increasing patient compliance for a patient who is self-administering a drug product.

[0058] Another subject of the invention is a method METHRED for reducing waste of drug product dosed from a vial and/or for reducing waste of vials, comprising selecting the vial by METHSELECT, with METHSELECT as defined herein, also with all its embodiments.

[0059] Another subject of the invention is a method METHSTAND for standardizing the dosage and/or administration of drug product administered to a patient from a vial, comprising filling a vial with drug product, wherein said vial is selected by METHSELECT, with METHSELECT as defined herein, also with all its embodiments.

[0060] Another subject of the invention is the use of a dye in METHTEST, KITDYE, METHSELECT, METHCOMP, METHRED, and/or METHSTAND, with METHTEST, KITDYE, METHSELECT, METHCOMP, METHRED, and METHSTAND as defined herein, also with all their embodiments.

[0061] The definitions of the words or drawing elements described herein are meant to include not only the combination of elements which are literally set forth, but all equivalent structure, material or acts for performing substantially the same function in substantially the same way to obtain substantially the same result. In this sense, it is therefore contemplated that an equivalent substitution of two or more elements may be made for any one of the elements described and its various embodiments or that a single element may be substituted for two or more elements in a claim.

[0062] Changes from the claimed subject matter as viewed by a person with ordinary skill in the art, now known or later devised, are expressly contemplated as being equivalents within the scope intended and its various embodiments. Therefore, obvious substitutions now or later known to one with ordinary skill in the art are defined to be within the scope of the defined elements. This disclosure is thus meant to be understood to include what is specifically illustrated and described herein, what is conceptually equivalent, what can be obviously substituted, and also what incorporates the essential ideas.

EXAMPLES

Example 1

[0063] A simulated "dirty" fill-in procedure causing

creeping of non-lyophilized formulations was performed to evaluate the extent of solution creeping up the inner vial surface, before actual freeze drying. The filling process and any material making up the defect was characterized through the use of a fluorescent dye.

Method:

[0064] An aqueous solution of 5 mg/mL fluorescein (Fluka Analytical) and polysorbate 20 0.02 % weight/volume (= 0.2 g per 1 L water) was prepared by mixing fluorescein with a respective aqueous solution of polysorbate 20 and stirring the mixture for 2 h at room temperature. The obtained aqueous solution was subsequently filtered using a Millipore 0.22 micrometer PVDF (polyvinylidene difluoride) filter.

[0065] 50 SCHOTT TopLyso® vials (size 2R, ca. 2 mL of volume) were filled with 0.7 mL of this filtered aqueous solution. The vials were allowed to stand for 10 min at ambient temperature before being assessed for any changes on the inner wall of the vials above the meniscus of the aqueous solution. The assessment was conducted in an Apollo II liquid viewer (Adelphi manufacturing, Haywards heath, UK) with the least possible movement of the vials during assessment.

Results:

[0066] Of the 50 vials, 35 vials did not show any fogging or creeping; rather, the inner wall surfaces of the vials were "clean", that is without any defect on the inner wall surface above the meniscus of the aqueous solution of the vial. This can be seen from Figure 1, which is a representative photograph of the 35 vials with a "clean" vial wall.

[0067] The other 15 vials of the 50 vials showed dots or small droplets on the inner wall surface above the meniscus of the aqueous solution. This can be seen from Figure 2, which is a representative photograph of the 15 vials with such small droplets on the inner wall surface above the meniscus of the aqueous solution. These small droplets remained on the inner wall surface and did not flow down back into the solution.

Example 2

[0068] To illustrate the use of the method for predicting fogging, an aqueous solution of 5 mg/mL fluorescein and polysorbate 20 0.02 % weight/volume (= 0.2 g per 1 L water) was prepared by mixing fluorescein with a respective aqueous solution of polysorbate 20 and stirring the mixture for 2 h at room temperature. The obtained aqueous solution was subsequently filtered using a Millipore 0.22 micrometer PVDF filter.

[0069] 10 SCHOTT Fiolax® vials (size 2R, ca. 2 mL of volume) were filled with 0.7 mL of this filtered aqueous solution. The vials were allowed to stand for 10 min at ambient temperature before being assessed for any

changes on the inner wall of the vials above the meniscus of the aqueous solution. The assessment was conducted in an Apollo II liquid viewer (Adelphi manufacturing, Haywards heath, UK) with the least possible movement of the vials during assessment.

Results:

[0070] Of the 10 vials, all 10 vials showed a defect in the form of a contamination ("fogging") of the inner wall surface above the meniscus of the aqueous solution. This can be seen from Figure 3, which is a representative photograph of the 10 vials with such defect on the inner wall surface above the meniscus of the aqueous solution. This defect remained on the inner wall surface and did not flow down back into the solution.

Example 3

[0071] In this experiment, the method for predicting fogging was tested using two different formulations in two vial types. Both formulations contained a model protein (BSA) at a concentration of 20 mg/ml. One formulation was prepared containing polysorbate 20 (PS20), and one formulation was prepared containing polysorbate 80 (PS80), as follows:

Formulation 1: 20 mg/ml BSA, 0.03% w/v PS20, 248 mM Sucrose, 20 mM Histidine/Histidine HCl at pH 5.75.

Formulation 2: 20 mg/ml BSA, 0.03% w/v PS80, 248 mM Sucrose, 20 mM Histidine/Histidine HCl at pH 5.75.

[0072] The vials used were the following:

Two types of vials were used, each in a 2 ml configuration. For vial type 1 a Fiolax® vial (SCHOTT AG, Germany) was used, which had a hydrophilic inner wall glass surface. For vial type 2 a TopLyso® vial (SCHOTT AG, Germany) was used, which had a hydrophobic inner wall glass surface. Prior to filling, vials type 1 and 2 were washed with a Belimed PH810 vial washer (Belimed AG, Zug, Switzerland) at 80°C using deionized water.

[0073] Fluorescein was added to formulations 1 and 2 in a concentration of 5 mg/ml and the formulations were stirred for 2 h at room temperature and subsequently filtered using a Millipore 0.22 micrometer PVDF filter. The filtered aqueous solutions were used for simulated fogging.

[0074] 10 vials each from the two different vial types were slowly filled with 1 ml of the filtered aqueous solution according to formulation 1, and 10 vials each were slowly filled with 1 ml of the filtered aqueous solution according to formulation 2. The vials were assessed for any changes related to solution creeping up the inner surface of the vial wall, both after 10 seconds and after 60 minutes at ambient temperature. The assessment was conducted in an Apollo II liquid viewer (Adelphi manufacturing, Haywards heath, UK) with the least possible movement of the vials during assessment.

Results:

[0075] The method showed that there were distinct differences in the extent of fluorescence solution creeping up the inner wall surface of the two different vial types. While both formulations 1 and 2 formed a concave meniscus in the type 1 vials (see Figure 4), they formed a planar surface in type 2 vials (see Figure 5). No significant differences between formulations 1 and 2 were visible.

[0076] When formulation 1 was filled into the type 1 vials, the method showed after 10 seconds a defect in the form of a contamination ("fogging") of the inner wall surface above the meniscus of the aqueous solution (see the area pointed to by the arrow in Figure 4). The defect appeared equally in formulation 2. No fogging was observed within 10 seconds in type 2 vials (see Figure 5), or even within 60 minutes, regardless of the formulation used.

Claims

1. A method METHTEST for testing the result of a filling process of vials with a liquid formulation DYE-FORM, comprising the steps (a), (b) and (c):

(a) filling a vial with DYE-FORM resulting in a filled vial;

(b) allowing the filled vial to stand upright for a period of time; and

(c) determining whether DYE-FORM is present or not on the inner wall surface of the filled vial above the meniscus line of DYE-FORM;

with DYE-FORM comprising two components (1) and (2), component (1) being a dye, component (2) being a liquid or a liquid formulation.

2. Method according to claim 1, wherein the vial is a glass vial.

3. Method according to claim 1 or claim 2, wherein the dye may be selected from the group consisting of fluorescein, methylene blue, rhodamine, Congo red, acridine orange, crystal violet, cyanine, methyl orange, Coomassie blue, methyl red, ethidium bromide, Victoria blue, Orange G, BODIPY, Alexa Fluor, Texas red, indocyanine green, cyanine, phtahlocyanine, and derivatives thereof.

4. Method according to one or more of claims 1 to 3, wherein the dye is a fluorescent dye.

5. Method according to one or more of claims 1 to 4, wherein the dye is fluorescein.

6. Method according to one or more of claims 1 to 5, wherein DYE-FORM comprises a surfactant.

7. Method according to claim 5, wherein the surfactant is a polysorbate or a poloxamer.
8. Method according to one or more of claims 1 to 7, wherein the liquid is water. 5
9. Method according to one or more of claims 1 to 7, wherein the liquid formulation comprises a drug product. 10
10. A method METHSELECT for selecting a vial which shows no defects after the filling of the vial with a drug product, comprising the steps (a), (b), (c) and (d): 15
- step (a), (b) and (c) as defined in claims 1 to 9; and
- step (d) selecting a vial for which it has been determined that no DYE-FORM is present on the inner wall surface of the filled vial above the meniscus line of the DYE-FORM; 20
- with DYE-FORM as defined in claim 1.
11. A kit KITDYE for analyzing the susceptibility to fogging of a vial containing a component (2), wherein the kit comprises a component (1); with component (1) and component (2) as defined in claim 1. 25
- 30
12. A method METHCOMP for increasing patient compliance, wherein a drug product is provided to the patient in a vial selected by METHSELECT, with METHSELECT as defined in claim 10. 35
13. A method METHRED for reducing waste of drug product dosed from a vial and/or for reducing waste of vials, comprising selecting the vial by METHSELECT, with METHSELECT as defined in claim 10. 40
- 45
14. A method METHSTAND for standardizing the dosage and/or administration of drug product administered to a patient from a vial, comprising filling a vial with drug product, wherein said vial is selected by METHSELECT, with METHSELECT as defined in claim 10. 50
15. A dye in METHTEST, KITDYE, METHSELECT, METHCOMP, METHRED, and/or METHSTAND, with METHTEST, KITDYE, METHSELECT, METHCOMP, METHRED, and METHSTAND as defined in any one of claims 1 to 14. 55

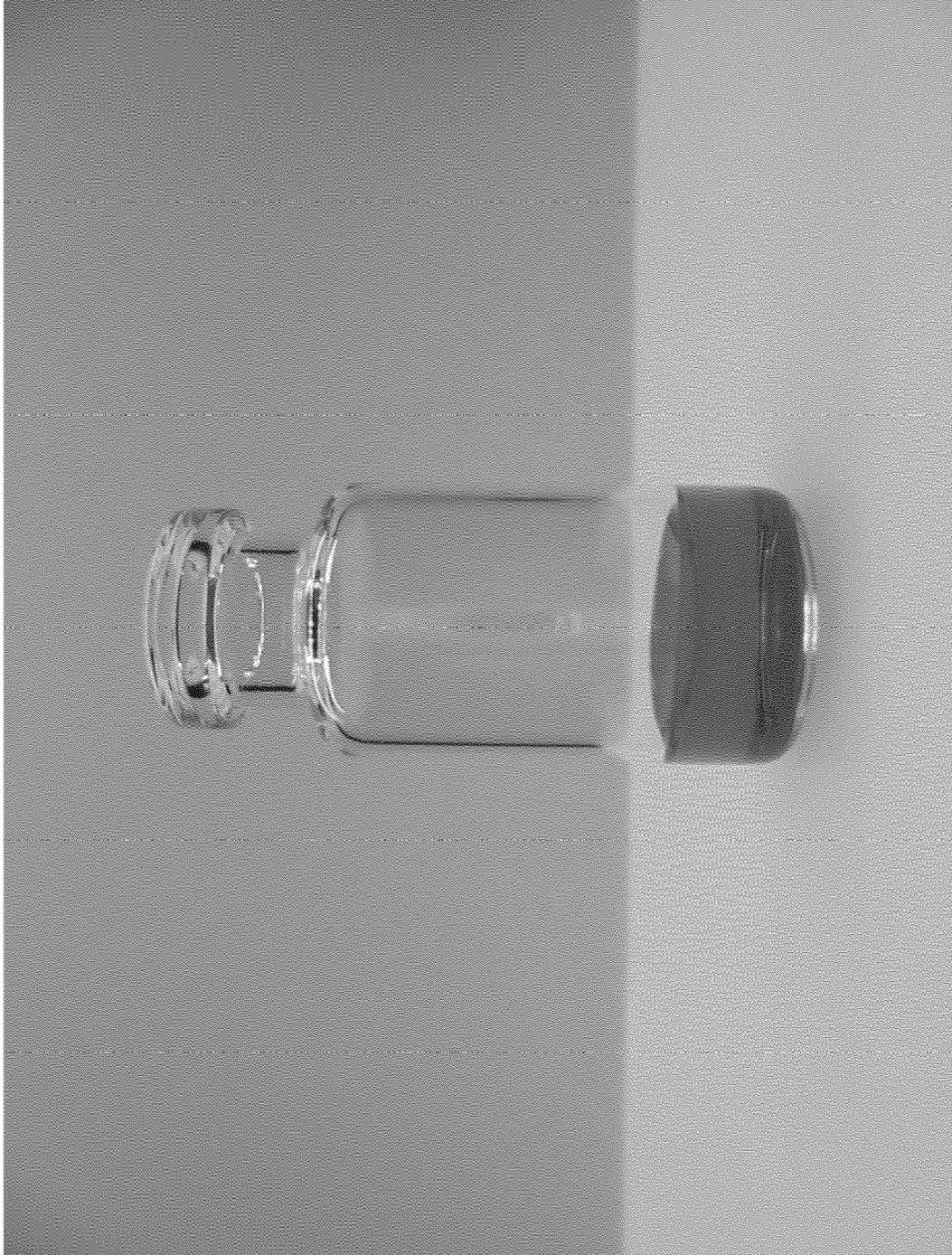


Figure 1

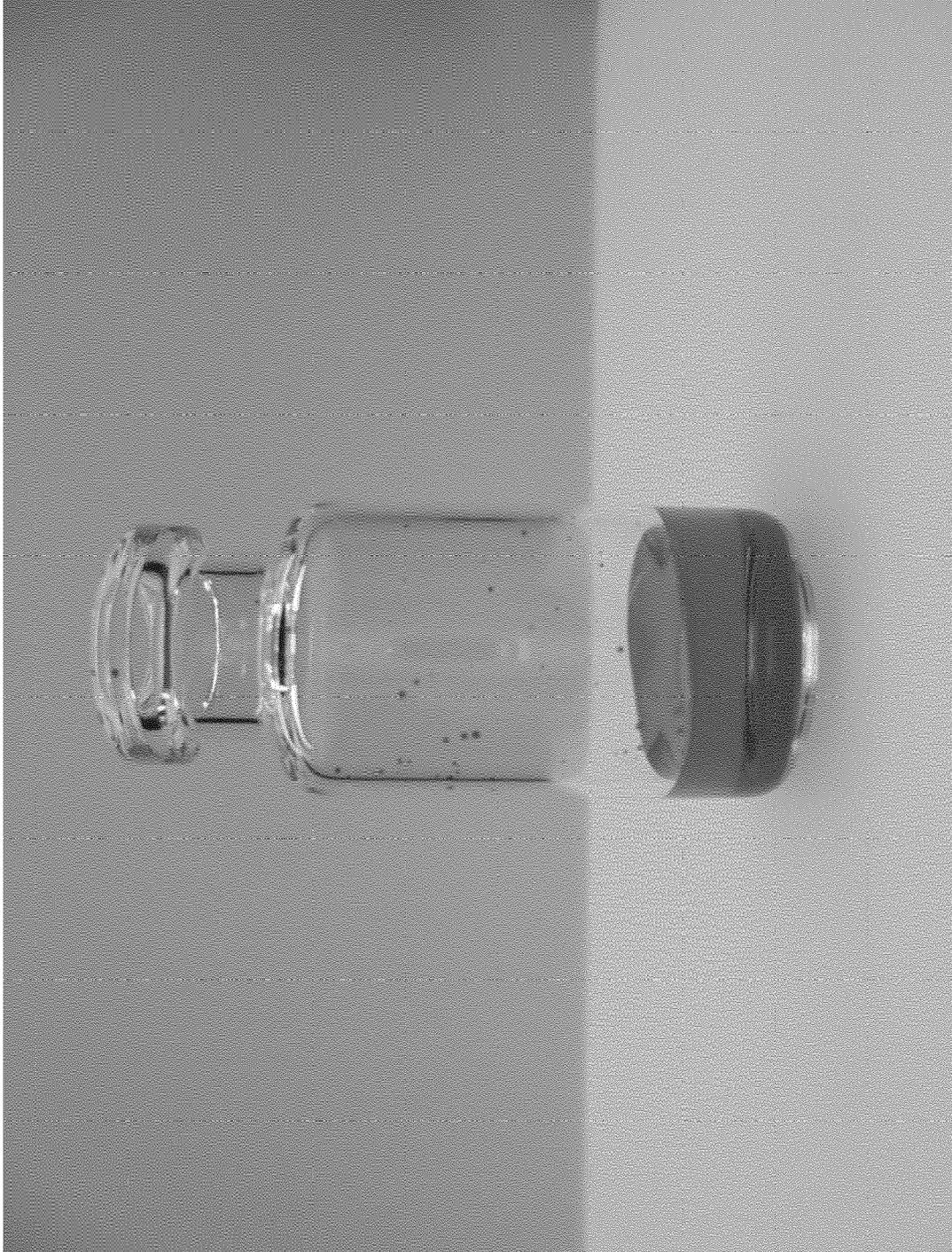


Figure 2

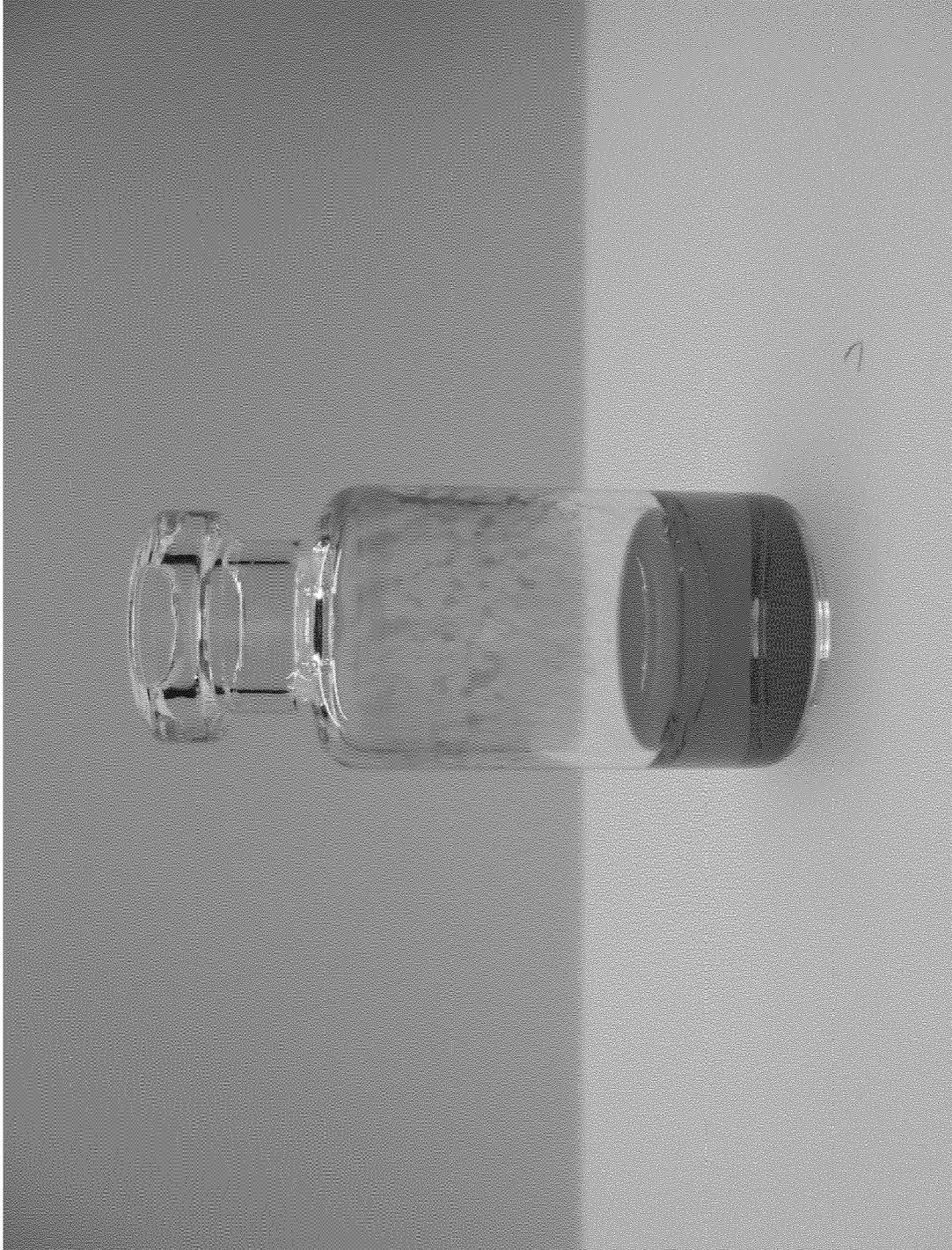


Figure 3

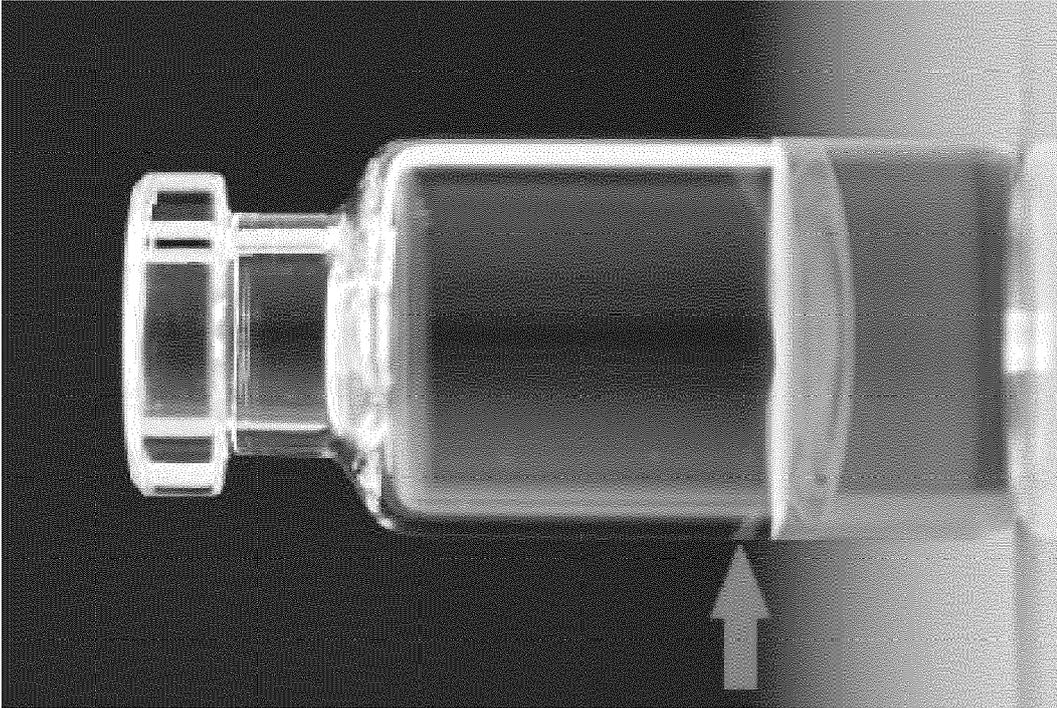


Figure 4

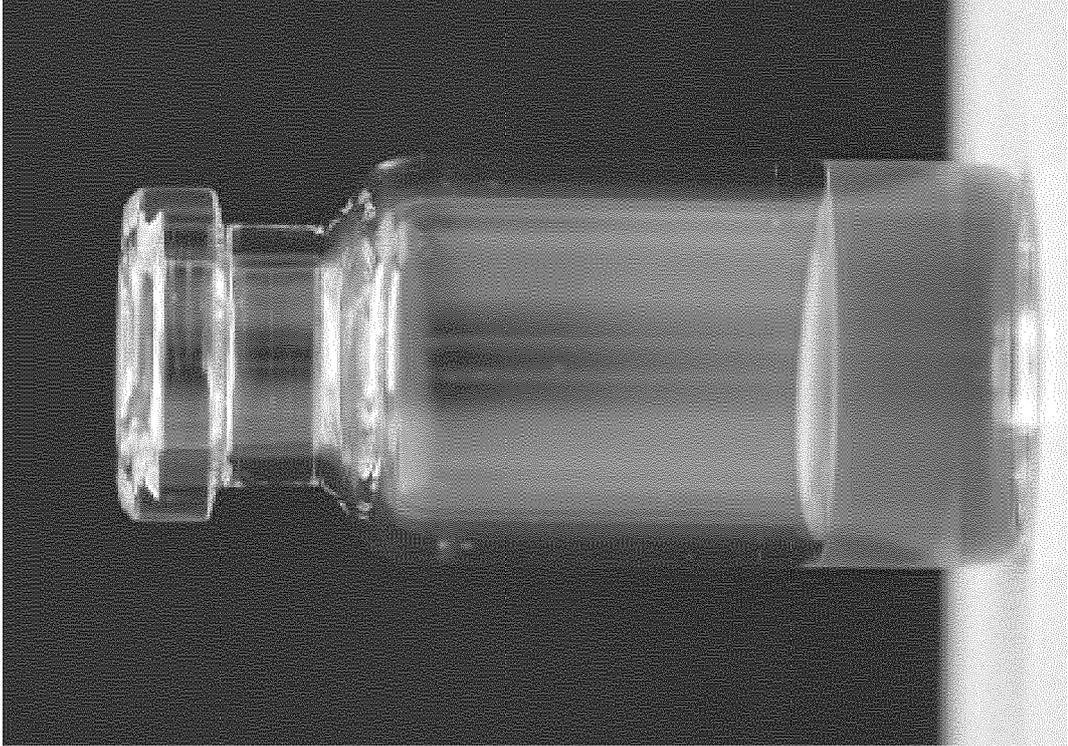


Figure 5



EUROPEAN SEARCH REPORT

Application Number
EP 18 20 8057

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| | | | A22C B65B A47L |
| The present search report has been drawn up for all claims | | | |
| Place of search Munich | | Date of completion of the search 4 March 2019 | Examiner Bigot-Maucher, Cora |
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