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(54) Benævnelse: **ANVENDELSE AF EN OLIESAMMENSÆTNING OMFATTENDE SILIKONEOLIE TIL STABILISERING AF OPBEVARING AF HYDROGENPEROXID**

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EP-A1- 3 378 514
EP-A1- 3 437 678

DESCRIPTION

TECHNICAL FIELD

[0001] The present invention relates to a use of an oil composition comprising silicone oil for stabilizing storage of hydrogen peroxide, wherein the oil composition is applied to an inner surface of a container or syringe.

BACKGROUND

[0002] A hydrogen peroxide solution is used industrially as a bleaching agent, and as a disinfectant in the food industry. A hydrogen peroxide solution containing 2.5 to 3.5% (w/v) hydrogen peroxide (known as "oxydol" in the Japanese Pharmacopoeia) is used for medical purposes as a disinfectant.

[0003] This hydrogen peroxide solution can be used as a radiosensitizer by mixing it with a solution of hyaluronic acid or a salt thereof such as sodium hyaluronate in a pre-determined ratio, and then injecting the mixture into a tumor just before the therapeutic radiation dose (Patent Document 1). Decomposition of hydrogen peroxide is accelerated by an increase in liquid temperature thereof due to its thermal decomposition. Non-Patent Document 1 discloses a material suitable for hydrogen peroxide.

[0004] EP3437678 discloses a prefilled syringe containing a hydrogen peroxide solution for teeth whitening. EP3378514 discloses silicone oil used to coat the inner surface of the barrel of a syringe in order to reduce the sliding resistance of the plunger when dispensing contents, which are typically protein preparations.

PRIOR ART DOCUMENTS

PATENT DOCUMENT

[0005] Patent Document 1: WO2008/041514

NON-PATENT DOCUMENT

[0006] Non-Patent Document 1: Ryo KUSAKABE, "Production, Properties, and Handling of Hydrogen Peroxide", Japan TAPPI journal, Vol. 52, No. 5, May 1998.

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0007] As disclosed in Non-Patent Document 1, there are few types of storage container materials that can be used for storing a hydrogen peroxide solution, and thus there are few choices of materials for the storage container.

[0008] Because hydrogen peroxide decomposes rapidly when removed from a special storage container that shields it from light, it must be drawn out in the appropriate volume or weight and then mixed with the sodium hyaluronate solution just before injection, when used as a radiation sensitizer as in Patent Document 1. This places an extra burden on the medical personnel treating the patient. Either the hospital pharmacy must draw out the hydrogen peroxide solution and mix it with the sodium hyaluronate, or a physician must do so at the patient's bedside. In the former case, the pharmacy personnel are burdened and there is risk of delay in transporting the injection mixture from the pharmacy to the patient's bedside. In the latter case, medical personnel at the patient's bedside, who are preparing the patient for radiotherapy, are burdened. In both cases, the complications of drawing out and mixing the solutions increase risks of mistakes that might compromise medical treatment or endanger the patient.

[0009] In addition, if the hydrogen peroxide solution is prefilled using a syringe made of conventional glass (for example, borosilicate glass), the glass syringe expands during storage of the hydrogen peroxide solution and the gasket thereof is pushed back. This might interfere with the long-term storage of the hydrogen peroxide solution in such a glass syringe.

MEANS FOR SOLVING THE PROBLEMS

[0010] The present invention is directed to the subject-matter as defined in the claims.

[0011] The present inventor has made intensive studies and found that an oil composition containing silicone oil has an effect of stabilizing the storage of hydrogen peroxide, and thus completed the present invention. In order to solve this problem, the present invention provides the use of an oil composition comprising silicone oil in accordance with claim 1 for stabilizing the storage of hydrogen peroxide.

[0012] One object of the present invention is the use of an oil composition to provide a pre-filled syringe having at least a barrel thereof made of a material having high decomposition capability with respect to hydrogen peroxide, including: a hydrogen peroxide solution therein;

and an oil composition applied to an inner wall of the barrel, the oil composition containing silicone oil.

[0013] By using the oil composition, it is possible to stabilize storage of hydrogen peroxide in the hydrogen peroxide solution. Thus, by applying the oil composition to the inner wall of the syringe, the hydrogen peroxide solution prefilled in the syringe can be stored for a long time.

[0014] Another object of the present invention is the use of an oil composition containing silicone oil, in which the oil composition is for stabilizing storage of hydrogen peroxide.

[0015] By using the oil composition, it is possible to stabilize storage of hydrogen peroxide in a hydrogen peroxide solution and to store the hydrogen peroxide solution for a long time, regardless of the material of the container or the syringe that stores the hydrogen peroxide solution.

EFFECT OF THE INVENTION

[0016] According to the use of the present invention, it is possible to provide a prefilled syringe capable of storing a hydrogen peroxide solution for a long period of time until it can be used as a radiosensitizer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017]

FIG. 1 shows a schematic view of a prefilled syringe containing a hydrogen peroxide solution according to the present embodiment.

FIG. 2 shows a graph of residual rates of hydrogen peroxide of each container material in the example.

DESCRIPTION OF THE EMBODIMENTS

Definition

[0018] For convenience, certain terms employed in the context of the present disclosure are collected here. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of the ordinary skilled in the art to which

this invention belongs. The singular forms "a", "and", and "the" are used herein to include plural referents unless the context clearly dictates otherwise.

[0019] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are described as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in the respective testing measurements. Also, as used herein, the term "about" generally means within 10%, 5%, 1%, or 0.5% of a given value or range. Alternatively, the term "about" means within an acceptable standard error of the mean when considered by one of ordinary skill in the art.

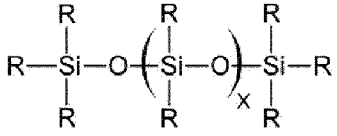
Oil composition

[0020] In the present embodiment, the oil composition contains silicone oil for stabilizing the storage of hydrogen peroxide. The oil composition can be used as an agent for stabilizing the storage of hydrogen peroxide. The oil composition may contain a pharmaceutically acceptable component (such as sterilized water) in addition to the silicone oil. The oil composition can be to be applied to an inner surface of a container or a syringe. The oil composition can suppress decomposition of hydrogen peroxide by a material having high decomposition capability with respect to hydrogen peroxide (e.g., glass, plastic having the high decomposition capability with respect to the hydrogen peroxide such as polyethylene terephthalate, and stainless steel). Thus, a container or a syringe may be made of the material having the high decomposition capability with respect to the hydrogen peroxide.

[0021] The silicone oil may have a kinematic viscosity of 20 to 40,000 cSt, preferably 500 to 30,000 cSt, more preferably 800 to 20,000 cSt, and further preferably 1,000 to 15,000 cSt at 25 °C.

[0022] The kinematic viscosity at 25 °C of the silicone oil can be measured according to JIS Z8803.

[0023] Preferably, a linear silicone represented by the following formula (1) can be used as the silicone oil.



(1)

[0024] In the above formula (1), R independently represents an organic functional group not containing a functional group involved in a hydrosilylation reaction such as an alkenyl group or a SiH group, a monovalent hydrocarbon group or a hydroxyl group. R may be the same as or different from each other. x represents an integer of 10 to 1200. R preferably represents an alkyl group or an aryl group, and more preferably represents a methyl group, an ethyl group,

or a phenyl group.

[0025] The linear silicone represented by the above formula (1) includes polydiorganosiloxane having both ends blocked with triorganosilyl groups, which is preferably polydialkylsiloxane, polydiarylsiloxane, polyalkylarylsiloxane, or a copolymer thereof, more preferably polydimethylsiloxane or polymethylphenylsiloxane, further preferably polydimethylsiloxane in which R are all methyl groups.

Syringe

[0026] FIG. 1 shows a schematic diagram of a prefilled syringe (1) filled with hydrogen peroxide solution (50) according to the present embodiment. In the present embodiment, a syringe (10), particularly a barrel (20) of the syringe (10), has generally cylindrical shape. In the present embodiment, the syringe (10) has, at one end thereof, a needle mounting part (30) from which the hydrogen peroxide solution (50) is discharged. In the present embodiment, the syringe (10) has, at the other end thereof, an opening (80) for inserting a plunger rod (70). In the present embodiment, the syringe (10) has a flange (90) provided around the opening (80). In the prefilled syringe (1) shown in FIG. 1, a silicone oil is applied to an inner wall of the syringe (10). In order to seal the filled hydrogen peroxide solution (50), the prefilled syringe (1) shown in FIG. 1 has a cap (40) provided on the needle mounting part (30) and the plunger rod (70) inserted from the opening (80), the plunger rod (70) having a gasket (60).

[0027] In the present embodiment, the syringe for hydrogen peroxide solution means a syringe having a low decomposition capability with respect to the hydrogen peroxide in the hydrogen peroxide solution. In the present embodiment, the hydrogen peroxide solution means a solution in which a solvent (for example, water) contains hydrogen peroxide and if necessary, additives (for example, phosphoric acid and phenacetin). In the present embodiment, the syringe may be manufactured from a single material or may be made with a plurality of materials (including a multilayer structure such as a coating). In the case of a syringe manufactured from the single material, the entire syringe is made of a material having high decomposition capability with respect to hydrogen peroxide (e.g., glass, plastic having the high decomposition capability with respect to the hydrogen peroxide such as polyethylene terephthalate, and stainless steel). In the case of a syringe made with a plurality of materials, aside from the part where an inner wall of the syringe is made of glass, the remaining parts may be made of a material having high or law decomposition capability with respect to hydrogen peroxide. However, all parts of the inner wall of the syringe need to be made of the material having the high decomposition capability with respect to the hydrogen peroxide. Thus, main parts, such as the inner surface of the barrel of the syringe, need to be made of the material having the high decomposition capability with respect to the hydrogen peroxide. In other words, parts that may come into contact with the hydrogen peroxide solution, such as a plunger rod, luer lock, cap and gasket, need to be made of the material having the high decomposition capability with respect to the hydrogen peroxide. In the present embodiment, the syringe may be for a radiosensitizer.

[0028] The decomposition capability of hydrogen peroxide can be determined from the ratio of the concentration of hydrogen peroxide in the hydrogen peroxide solution after start of storage to the concentration of hydrogen peroxide in the hydrogen peroxide solution before the start of the storage under specific temperature condition (residual rate of hydrogen peroxide). The storage is performed in a sealed state. The temperature condition is not limited, but may be 35 °C, 37 °C, 40° C, or 60 °C. A period of the storage is not limited, but may be one week, two weeks, three weeks, or four weeks, or four weeks or more. The concentration of hydrogen peroxide in the hydrogen peroxide solution before the start of the storage may be any concentration, for example in the range of 0.01 to 40% (w/v). In an embodiment, the decomposition capability of hydrogen peroxide to the plastic is lower than that of a glass. The residual rate of hydrogen peroxide in the plastic may be 70% or more, preferably 75% or more, more preferably 78% or more, still more preferably 80% or more under the condition that a solution containing 2.5 to 3.5% (w/v) hydrogen peroxide is hermetically stored at 60 °C for 4 weeks. The amount of hydrogen peroxide in the hydrogen peroxide solution can be determined by titration with a potassium permanganate solution according to an oxydol determination method described in Japanese Pharmacopoeia.

[0029] In the present embodiment, the syringe is provided as a hydrogen peroxide solution pre-filled syringe. The hydrogen peroxide solution pre-filled syringe includes a gasket slidably provided with the syringe. Furthermore, a needle mounting portion of the hydrogen peroxide solution pre-filled syringe is sealed with, for example, a cap or the like.

[0030] In the present embodiment, the concentration of hydrogen peroxide in the hydrogen peroxide solution in the prefilled syringe is, for example, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.5, 1, 5, 10, 15, 20, 25, 30, 35 or 40%, or may be in the range between any two of the numerical values exemplified herein, for example, 0.01 to 40% (w/v), preferably, 0.05 to 30% (w/v).

Application

[0031] The oil composition used in accordance with the present embodiment can be applied using a spray or the like. Upon the application, the oil composition may be dissolved in a suitable solvent. When applying the oil composition to the inner wall of the syringe, the oil composition can be applied to the inner wall of the syringe at an application amount of 0.02 to 0.2 mg/cm^2 by spraying. After the application to the inner wall of the syringe, the oil composition may be made uniform in thickness thereof by using a device such as a squeegee or by softening the silicone oil in the oil composition by a heat treatment (for example, an autoclave treatment).

EXAMPLE

Hydrogen peroxide solution stability test

[0032] Stability test of a hydrogen peroxide solution was performed using a glass container coated with silicone oil and a glass container not coated with the silicone oil. The silicone oil was purchased from Dow Coming (product name: Dow Corning 360 Medical Fluid (12,500 cSt)). The hydrogen peroxide solution was added to each container, sealed, and then stored at 60 °C for 4 weeks. The residual rates of hydrogen peroxide in the hydrogen peroxide solutions after storage were measured. Oxydol "KENEI" (containing 2.5 to 3.5%(w/v) hydrogen peroxide, phosphoric acid and phenacetin) manufactured by Kenei Pharmaceutical Co., Ltd. was used as the hydrogen peroxide solution. The amount of hydrogen peroxide in the hydrogen peroxide solution was detected by titration with a potassium permanganate solution according to oxydol determination method described in the Japanese Pharmacopoeia. The results are shown in FIG. 2.

[0033] In the case of the glass container not coated with the silicone oil, the residual ratio of hydrogen peroxide was about 70%. The residual ratio of the glass container coated with the silicone oil was 78% or more. As a result, the glass container coated with the silicone oil was able to suppress the decomposition of hydrogen peroxide more than the glass container not coated with the silicone oil.

EXPLANATION OF REFERENCES

[0034]

1
: Prefilled syringe

10
: Syringes

20
: Barrel

30
: Needle mounting part

40
: Cap

50
: Hydrogen peroxide solution

60
: Gasket

70
: Plunger rod

80

Opening

90

Flange

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- EP3437678A [0004]
- EP3378514A [0004]
- WO2008041514A [0005]

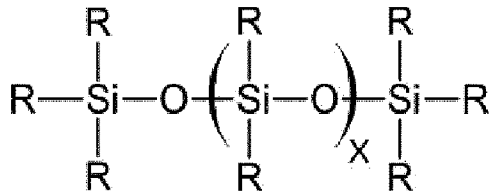
Non-patent literature cited in the description

- **RYO KUSAKABE**Production, Properties, and Handling of Hydrogen PeroxideJapan TAPPI journal, 1998, vol. 52, 5 [0006]

Patentkrav

1. Anvendelse af en oliesammensætning, der omfatter silikoneolie, til stabilisering af opbevaring af hydrogenperoxid,
hvilken oliesammensætning påføres på en indvendig overflade af en beholder eller en sprøjte.

2. Anvendelse ifølge krav 1, hvor silikoneolien er en lineær silikone repræsenteret ved følgende formel (1):



(1)

hvor det i ovenstående formel (1) gælder, at

R betegner uafhængigt en organisk funktionel gruppe, der ikke indeholder en funktionel gruppe, som er involveret i en hydrosilyleringsreaktion, en monovalent carbonhydridgruppe eller en hydroxylgruppe,
R kan være det samme som eller adskille sig fra hinanden, og
x betegner et heltal fra 10 til 1200.

3. Anvendelse ifølge krav 2, hvor R uafhængigt betegner en alkylgruppe eller en arylgruppe.

4. Anvendelse ifølge krav 3, hvor R uafhængigt betegner en methylgruppe, en ethylgruppe eller en phenylgruppe.

5. Anvendelse ifølge et hvilket som helst af kravene 2 til 4, hvor den lineære silikone repræsenteret ved ovenstående formel (1) er polydiorganosiloxan, der har begge ender blokeret med triorganosilylgrupper.

6. Anvendelse ifølge krav 5, hvor polydiorganosiloxanen er polydialkylsiloxan, polydiarylsiloxan, polyalkylarylsiloxan eller en copolymer deraf.

7. Anvendelse ifølge krav 6, hvor polydiorganosiloxanen er polydimethylsiloxan eller polymethylphenylsiloxan.

8. Anvendelse ifølge krav 7, hvor polydiorganosiloxanen er polydimethylsiloxan, og R er alle methylgrupper.

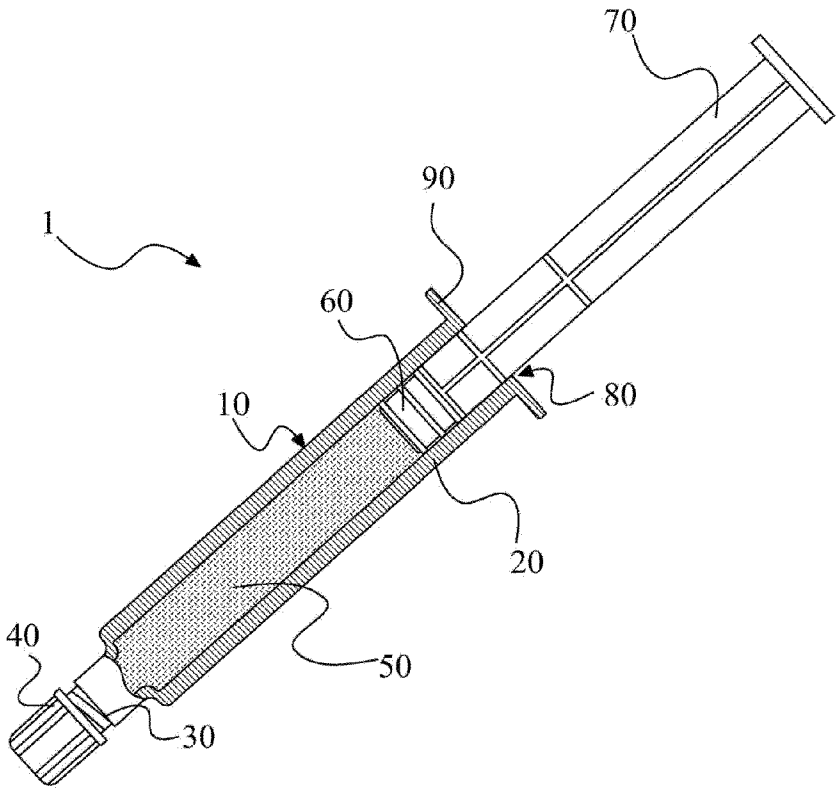
9. Anvendelse ifølge et hvilket som helst af kravene 1 til 8, hvor koncentrationen af hydrogenperoxid i hydrogenperoxidopløsningen er på 0,01 til 40 vægt/volumen-procent.

10. Anvendelse ifølge et hvilket som helst af kravene 1 til 9, hvor oliesammensætningen undertrykker nedbrydning af hydrogenperoxid ved hjælp af et materiale af beholderen eller sprøjten.

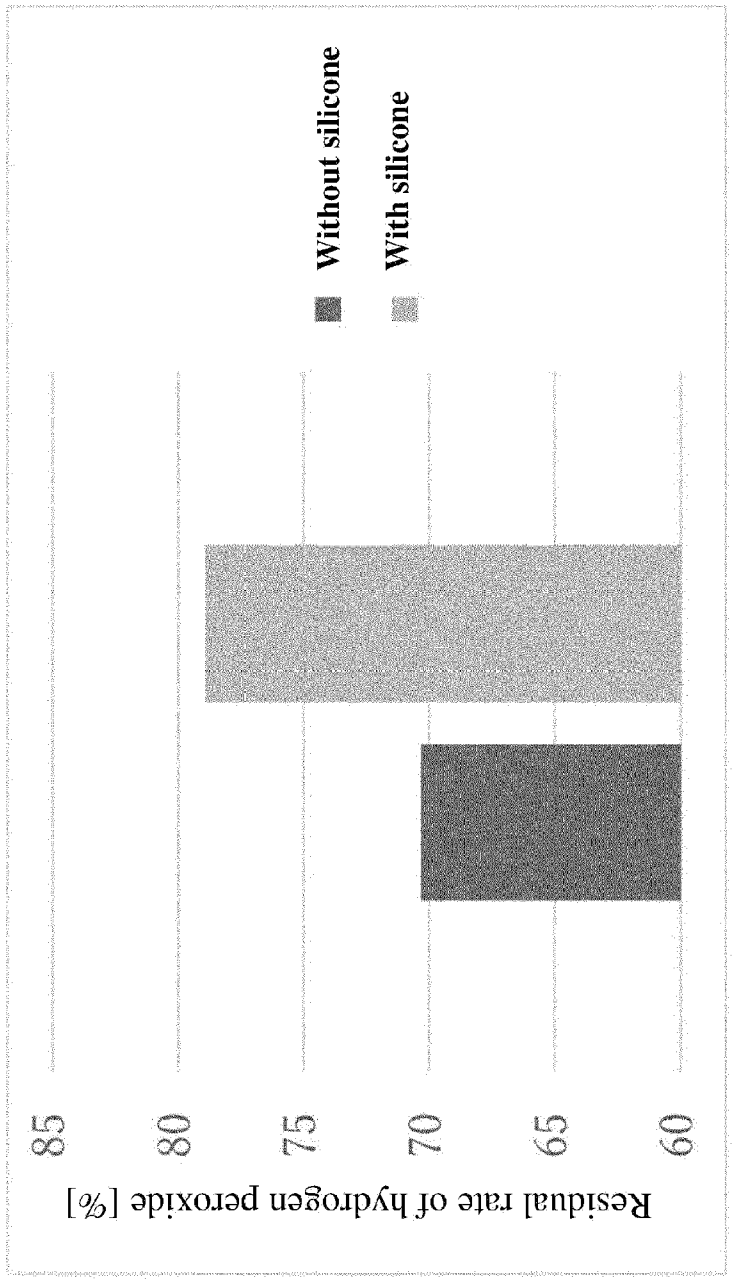
11. Anvendelse ifølge krav 10, hvor materialet er glas.

12. Anvendelse ifølge et hvilket som helst af kravene 1 til 11 til en radiosensibilisator.

DRAWINGS



[Fig. 1]


Without silicone
With silicone
85
80
75
70
65
60
Residual rate of hydrogen peroxide [%]

[Fig. 2]