'fragment.

[0005]

Patent literatures 2, 3, and 4 disclose inventions relating to a stable pharmaceutical composition containing an anti-human NGF antibody or human NGF, but it is not an invention relating to a PEGylated anti-human NGF antibody Fab' fragment.

CITATION LIST

PATENT LITERATURE

[0006]

[Patent literature 1] WO 2013/022083
[Patent literature 2] WO 2010/032220
[Patent literature 3] WO 95/05845
[Patent literature 4] WO 2011/116090

SUMMARY OF INVENTION

TECHNICAL PROBLEM

[0007]

An object of the present invention is to provide a stable pharmaceutical composition comprising the PEGylated anti-human NGF antibody Fab' fragment.

More particularly, an object of the present invention is to provide a stable pharmaceutical composition comprising the PEGylated anti-human NGF antibody Fab' fragment, capable of inhibiting the generation of degradation products, multimers, acidic related substance, and basic related substances, which increase with, for example, heat, temperature conditions, or the like. Another object of the present invention is to provide a stable pharmaceutical composition comprising the PEGylated anti-human NGF antibody Fab' fragment, capable of inhibiting the generation of foreign insoluble matters, which increase with, for example, freeze-thaw, physical vibration, or the like.

SOLUTION TO PROBLEM

[0008]

The present inventor found that a stable pharmaceutical composition could be prepared by adjusting the pH of a solution to a specific range, and formulating the PEGylated anti-human NGF antibody Fab' fragment (Example 1 described below), and that a further stable pharmaceutical composition could be provided by adding specific isotonic agents (Example 2 described below), by adding a surfactant (Example 3 described below), or the like, and completed the present invention.

[0008a]

In one aspect, there is provided a stable pharmaceutical composition comprising a PEGylated anti-human NGF antibody Fab' fragment and a pharmaceutically acceptable

buffer,
wherein pH is 4 to 5.5;
wherein the anti-human NGF antibody Fab' fragment is selected from:
(1) an anti-human NGF antibody Fab' fragment comprising a heavy chain fragment consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain consisting of the amino acid sequence of SEQ ID NO: 3, and
(2) an anti-human NGF antibody Fab' fragment that is a Fab' fragment generated by a post-translational modification of the anti-human NGF antibody Fab' fragment of (1),
wherein the post-translational modification of an anti-human NGF antibody Fab'fragment is pyroglutamylation at the N-terminus of a heavy chain variable region; and
wherein the PEGylation is a covalent bond of a thiol reactive group of a PEG derivative, to which the thiol reactive group is bonded, to a thiol group of cysteine in a hinge region of the anti-human NGF antibody Fab' fragment,
and wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof.

[0008b]

In another aspect, there is provided a method of stabilizing a PEGylated anti-human NGF antibody Fab' fragment, characterizing by adjusting a pH to 4 to 5.5 and by using a pharmaceutically acceptable buffer,
wherein the anti-human NGF antibody Fab' fragment is selected from:
(1) an anti-human NGF antibody Fab' fragment comprising a heavy chain fragment consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain consisting of the amino acid sequence of SEQ ID NO: 3, and
(2) an anti-human NGF antibody Fab' fragment that is a Fab' fragment generated by a post-translational modification of the anti-human NGF antibody Fab' fragment of (1),
wherein the post-translational modification of an anti-human NGF antibody Fab'fragment is pyroglutamylation at the N-terminus of a heavy chain variable region; and
wherein the PEGylation is a covalent bond of a thiol reactive group of a PEG derivative, to which the thiol reactive group is bonded, to a thiol group of cysteine in a hinge region of the anti-human NGF antibody Fab' fragment,
and wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof.

[0009]

The present invention relates to:
[1] a stable pharmaceutical composition comprising a PEGylated anti-human NGF

CLAIMS

1. A stable pharmaceutical composition comprising a PEGylated anti-human NGF antibody Fab' fragment and a pharmaceutically acceptable buffer,
wherein pH is 4 to 5.5;
wherein the anti-human NGF antibody Fab' fragment is selected from:
(1) an anti-human NGF antibody Fab' fragment comprising a heavy chain fragment consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain consisting of the amino acid sequence of SEQ ID NO: 3, and
(2) an anti-human NGF antibody Fab' fragment that is a Fab' fragment generated by a post-translational modification of the anti-human NGF antibody Fab' fragment of (1),
wherein the post-translational modification of an anti-human NGF antibody Fab'fragment is pyroglutamylation at the N-terminus of a heavy chain variable region; and
wherein the PEGylation is a covalent bond of a thiol reactive group of a PEG derivative, to which the thiol reactive group is bonded, to a thiol group of cysteine in a hinge region of the anti-human NGF antibody Fab' fragment,
and wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition according to claim 1, further comprising a pharmaceutically acceptable isotonic agent, and a pharmaceutically acceptable surfactant.

3. The pharmaceutical composition according to claim 1 or 2, wherein pH is 4.5 to 5.5.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein a concentration of the pharmaceutically acceptable buffer is 1 to 200 mmol/L.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the pharmaceutical composition is a liquid preparation or a lyophilized preparation.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the pharmaceutical composition is a liquid preparation.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the pharmaceutically acceptable isotonic agent is one, or two or more selected from the group consisting of arginine, D-sorbitol, D-mannitol, trehalose, sucrose, xylitol, erythritol, threitol, inositol, dulcitol, arabitol, isomalt, lactitol, and maltitol.

8. The pharmaceutical composition according to any one of claims 1 to 7, wherein a concentration of the pharmaceutically acceptable isotonic agent is 1 to 500 mmol/L.

9. The pharmaceutical composition according to any one of claims 1 to 8, wherein the pharmaceutically acceptable surfactant is at least one of polysorbate or poloxamer.

10. The pharmaceutical composition according to any one of claims 1 to 9, wherein the pharmaceutically acceptable surfactant is polysorbate 80.

11. The pharmaceutical composition according to any one of claims 1 to 10, wherein a concentration of the pharmaceutically acceptable surfactant is 0.001 to 1% (w/v).

12. The pharmaceutical composition according to any one of claims 1 to 11, wherein a concentration of the PEGylated anti-human NGF antibody Fab' fragment is 0.1 to 200 mg/mL.

13. The pharmaceutical composition according to claim 1, comprising, as the PEGylated anti-human NGF antibody Fab' fragment, an anti-human NGF antibody Fab' fragment PEGylated by covalently bonding a thiol reactive group of a PEG derivative, to which the thiol reactive group is bonded, to a thiol group of cysteine in a hinge region of an anti-human NGF antibody Fab' fragment comprising a heavy chain fragment consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain consisting of the amino acid sequence of SEQ ID NO: 3.

14. The pharmaceutical composition according to claim 1, comprising, as the PEGylated anti-human NGF antibody Fab' fragment, an anti-human NGF antibody Fab' fragment PEGylated by covalently bonding a thiol reactive group of a PEG derivative, to which the thiol reactive group is bonded, to a thiol group of cysteine in a hinge region of an anti-human NGF antibody Fab' fragment that is a Fab' fragment generated by a post-translational modification of an anti-human NGF antibody Fab' fragment comprising a heavy chain fragment consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain consisting of the amino acid sequence of SEQ ID NO: 3.

15. A method of stabilizing a PEGylated anti-human NGF antibody Fab' fragment, characterizing by adjusting a pH to 4 to 5.5 and by using a pharmaceutically acceptable buffer,
wherein the anti-human NGF antibody Fab' fragment is selected from:
(1) an anti-human NGF antibody Fab' fragment comprising a heavy chain fragment consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain consisting of the amino acid sequence of SEQ ID NO: 3, and
(2) an anti-human NGF antibody Fab' fragment that is a Fab' fragment generated by a post-translational modification of the anti-human NGF antibody Fab' fragment of (1),
wherein the post-translational modification of an anti-human NGF antibody Fab'fragment is pyroglutamylation at the N-terminus of a heavy chain variable region; and
wherein the PEGylation is a covalent bond of a thiol reactive group of a PEG derivative, to which the thiol reactive group is bonded, to a thiol group of cysteine in a hinge region of the anti-human NGF antibody Fab' fragment,
and wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof.

16. The method according to claim 15, using a pharmaceutically acceptable isotonic agent, and a pharmaceutically acceptable surfactant.