'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

TECHNICAL PROBLEM

[0007]

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

More particularly, an object of the present disclosure 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 disclosure 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 disclosure.

[0008a]

In one aspect, the present disclosure refers to a stable pharmaceutical composition comprising a PEGylated anti-human NGF antibody Fab'

fragment, a pharmaceutically acceptable buffer and a pharmaceutically acceptable surfactant,
wherein pH is 4.6 to 5.2;
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,
wherein a concentration of the PEGylated anti-human NGF antibody Fab' fragment is 0.1 to 100 mg/mL,
wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof
and wherein the pharmaceutically acceptable surfactant is polysorbate 80.
[0008b]

In another aspect, the present disclosure refers to a method of stabilizing a PEGylated anti-human NGF antibody Fab' fragment, characterizing by adjusting a pH to 4.6 to 5.2, and by using a pharmaceutically acceptable buffer and a pharmaceutically acceptable surfactant,
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,
wherein a concentration of the PEGylated anti-human NGF antibody Fab' fragment is 0.1 to 100 mg/mL,
wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof

and wherein the pharmaceutically acceptable surfactant is polysorbate 80.

[0009]

The present disclosure relates to:

[1] a stable pharmaceutical composition comprising a PEGylated anti-human NGF

the PEGylated anti-human NGF antibody Fab' fragment is 0.1 to 200 mg/mL,
[15] the pharmaceutical composition of [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,
[16] the pharmaceutical composition of [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,
[17] the pharmaceutical composition of [1] or [16], 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,
[18] a method of stabilizing a PEGylated anti-human NGF antibody Fab' fragment, characterizing by adjusting a pH to 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); 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
[19] the method of [18], using a pharmaceutically acceptable buffer, a pharmaceutically acceptable isotonic agent, and a pharmaceutically acceptable surfactant.

ADVANTAGEOUS EFFECTS OF DISCLOSURE

[0010]

According to the present disclosure, a stable pharmaceutical composition comprising the PEGylated anti-human NGF antibody Fab' fragment, more particularly, a stable pharmaceutical composition comprising the PEGylated anti-human NGF antibody Fab' fragment, capable of inhibiting the generation of its degradation products, multimers,

CLAIMS

1. A stable pharmaceutical composition comprising a PEGylated anti-human NGF antibody Fab' fragment, a pharmaceutically acceptable buffer and a pharmaceutically acceptable surfactant,
wherein pH is 4.6 to 5.2;
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,
wherein a concentration of the PEGylated anti-human NGF antibody Fab' fragment is 0.1 to 100 mg/mL,
wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof
and wherein the pharmaceutically acceptable surfactant is polysorbate 80.

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

3. The pharmaceutical composition according to claim 1 or 2, wherein a concentration of the pharmaceutically acceptable buffer is 1 to 200 mmol/L.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the pharmaceutical composition is a liquid preparation or a lyophilized preparation.

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

6. The pharmaceutical composition according to any one of claims 1 to 5, 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.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein a concentration of the pharmaceutically acceptable isotonic agent is 1 to 500 mmol/L.

8. The pharmaceutical composition according to any one of claims 1 to 7, wherein a concentration of the pharmaceutically acceptable surfactant is 0.001 to 1% (w/v).

9. 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.

10. 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.

11. A method of stabilizing a PEGylated anti-human NGF antibody Fab' fragment, characterizing by adjusting a pH to 4.6 to 5.2, and by using a pharmaceutically acceptable buffer and a pharmaceutically acceptable surfactant,
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,
wherein a concentration of the PEGylated anti-human NGF antibody Fab' fragment is 0.1 to 100 mg/mL,
wherein the pharmaceutically acceptable buffer is citric acid or a pharmaceutically acceptable salt thereof
and wherein the pharmaceutically acceptable surfactant is polysorbate 80.

12. The method according to claim 11, using a pharmaceutically acceptable isotonic agent.