[Non-Patent Literature 1] Nat Med. 2012; 18(10):1570-74
[Non-Patent Literature 2] PLoS One. 2013; 8(2):e57479

[Summary]

[Problems to be Solved]

An objective of the present invention is to provide stable solution formulations comprising Emicizumab (ACE910) which is a bispecific antibody functionally substituting for FVIII that binds to FIX and/or FIXa and FX.

[Means for Solving the Problems]

As a result of dedicated research to accomplish the above-mentioned objective, the present inventors discovered that a solution formulation of pH 4.5 to 6.5 that comprises the aforementioned bispecific antibody at 20 to 180 mg/mL, 10 mM to 40 mM histidine/aspartate buffer, Poloxamer 188 at 0.2 to 1 mg/mL, and 100 mM to 300 mM arginine, can be a stable antibody-containing solution formulation in which aggregate formation and/or components with charge heterogeneity are suppressed, and thereby completed the present invention.

In one example, there is provided an antibody solution formulation of pH 4.5 to 6.5, which comprises: a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequences of H-chain CDRs 1, 2, and 3 of SEQ ID NOs: 1, 2, and 3 (H-chain CDRs of Q499), respectively; the second polypeptide comprises an H chain comprising the amino acid sequences of H-chain CDRs 1, 2, and 3 of SEQ ID NOs: 4, 5, and 6 (H-chain CDRs of J327), respectively; and the third polypeptide and the fourth polypeptide comprise a common L chain comprising the amino acid sequences of L-chain CDRs 1, 2, and 3 of SEQ ID NOs: 7, 8, and 9 (L-chain CDRs of L404), respectively; 20 mM histidine/aspartate buffer; 0.2 to 1 mg/mL Poloxamer 188; and 100 mM to 300 mM arginine.

In another aspect, there is provided an antibody solution formulation of pH 6, which comprises: a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12; 20 mM L-histidine/aspartate buffer; 0.5 mg/mL Poloxamer 188; and 150 mM L-arginine.

In another aspect, there is provided an antibody solution formulation of pH 6, which comprises: a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12; 20 mM L-histidine/aspartate buffer; 0.5 mg/mL Poloxamer 188; and 150 mM L-arginine.

In another aspect, there is provided an antibody solution formulation of pH 6, which comprises: a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12; 20 mM L-histidine-aspartic acid; 0.5 mg/mL Poloxamer 188; and 150 mM L-arginine-aspartic acid.

In another aspect, there is provided the antibody solution formulation of the present disclosure, for use in subcutaneous administration.

In another aspect, there is provided the antibody solution formulation of the present disclosure, for use in the treatment of hemophilia A.

In another aspect, there is provided a method for stabilizing an antibody in an antibody-containing solution formulation, which comprises adding a histidine/aspartate buffer, Poloxamer 188, and arginine to the solution, whereby the concentration of the histidine/aspartate buffer is 20 mM, the concentration of Poloxamer 188 is 0.5 mg/mL, and the concentration of arginine is 150 mM, and pH of the solution is 6, wherein the antibody is a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12.

In another aspect, there is provided a method for suppressing the association (aggregate formation) of an antibody in an antibody-containing solution formulation, which comprises adding a histidine/aspartate buffer, Poloxamer 188, and arginine to the solution, whereby the concentration of the histidine/aspartate buffer is 20 mM, the concentration of Poloxamer 188 is 0.5 mg/mL, and the concentration of arginine is 150 mM, and pH of the solution is 6,
wherein the antibody is a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first

polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12.

In another aspect, there is provided a method for suppressing a component with charge heterogeneity in an antibody-containing formulation, which comprises adding a histidine/aspartate buffer, Poloxamer 188, and arginine to the solution, whereby the concentration of histidine/aspartate buffer is 20 mM, the concentration of Poloxamer 188 is 0.5 mg/mL, the concentration of arginine is150 mM, and pH of the solution is 6, wherein the antibody is a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12.

Specifically, the present disclosure provides the following:

[1] An antibody solution formulation of pH 4.5 to 6.5, which comprises:

a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequences of H-chain CDRs 1, 2, and 3 of SEQ ID NOs: 1, 2, and 3 (H-chain CDRs of Q499), respectively; the second polypeptide comprises an H chain comprising the amino acid sequences of H-chain CDRs 1, 2, and 3 of SEQ ID NOs: 4, 5, and 6 (H-chain CDRs of J327), respectively; and the third polypeptide and the fourth polypeptide comprise a common L chain comprising the amino acid sequences of L-chain CDRs 1, 2, and 3 of SEQ ID NOs: 7, 8, and 9 (L-chain CDRs of L404), respectively;

10 mM to 40 mM histidine/aspartate buffer;

0.2 to 1 mg/mL Poloxamer 188; and

100 mM to 300 mM arginine.

[2] The antibody solution formulation of [1], wherein in the bispecific antibody, the first polypeptide and the third polypeptide form a pair, and the second polypeptide and the fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11, and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12.

[3] The antibody solution formulation of [1] or [2], wherein the concentration of Poloxamer 188

CLAIMS

1. An antibody solution formulation of pH 6, which comprises:

a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12;

20 mM L-histidine/aspartate buffer;

0.5 mg/mL Poloxamer 188; and

150 mM L-arginine.

2. An antibody solution formulation of pH 6, which comprises:

a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12;

20 mM L-histidine-aspartic acid;

0.5 mg/mL Poloxamer 188; and

150 mM L-arginine-aspartic acid.

3. The antibody solution formulation of claim 1 or 2, which does not substantially contain a chloride ion or an acetate ion.

4. The antibody solution formulation of any one of claims 1 to 3, for use in subcutaneous administration.

5. The antibody solution formulation of any one of claims 1 to 4, for use in the treatment of hemophilia A.

6. A method for stabilizing an antibody in an antibody-containing solution formulation, which comprises adding a histidine/aspartate buffer, Poloxamer 188, and arginine to the solution,

whereby the concentration of the histidine/aspartate buffer is 20 mM, the concentration of Poloxamer 188 is 0.5 mg/mL, and the concentration of arginine is 150 mM and pH of the solution is 6,
wherein the antibody is a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12.

7. A method for suppressing the association (aggregate formation) of an antibody in an antibody-containing solution formulation, which comprises adding a histidine/aspartate buffer, Poloxamer 188, and arginine to the solution, whereby the concentration of the histidine/aspartate buffer is 20 mM, the concentration of Poloxamer 188 is 0.5 mg/mL, and the concentration of arginine is 150 mM, and pH of the solution is 6,
wherein the antibody is a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12.

8. A method for suppressing a component with charge heterogeneity in an antibody-containing formulation, which comprises adding a histidine/aspartate buffer, Poloxamer 188, and arginine to the solution, whereby the concentration of histidine/aspartate buffer is 20 mM, the concentration of Poloxamer 188 is 0.5 mg/mL, the concentration of arginine is150 mM, and pH of the solution is 6,
wherein the antibody is a bispecific antibody at 20 to 180 mg/mL, wherein a first polypeptide and a third polypeptide form a pair, and a second polypeptide and a fourth polypeptide form a pair, wherein the first polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 10; the second polypeptide comprises an H chain comprising the amino acid sequence of SEQ ID NO: 11; and the third polypeptide and the fourth polypeptide comprise a common L chain of SEQ ID NO: 12.

9. The antibody solution formulation of claim 1, wherein the concentration of a bispecific antibody is 30 mg/mL or 150 mg/mL.