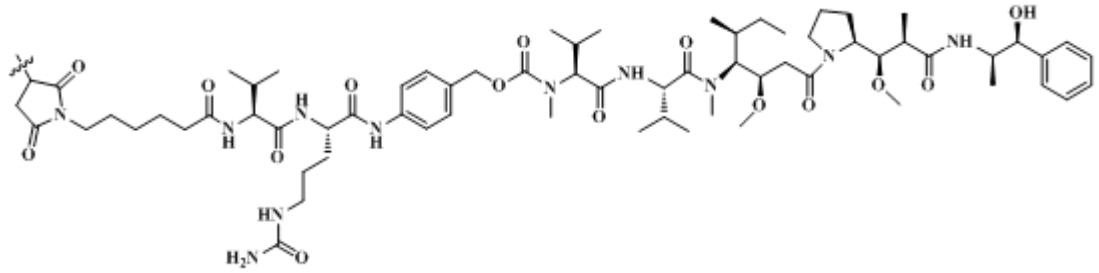
the non-reducing sugar is selected from mannitol, sucrose, ~~trehalose,~~ and a combination thereof,

the amino acid is selected from histidine, ~~alanine, arginine, glycine, glutamic acid, a~~ histidine hydrochloride ~~of the above amino acids~~, and a combination thereof, and

the solubilizer is polysorbate 80~~selected from glycerol, Tween 80, and a combination thereof~~,

wherein the antibody-drug conjugate is an anti-HER2 monoclonal antibody-vc-MMAE, wherein the anti-HER2 monoclonal antibody is connected to MMAE via a linker vc, and the structure of the linker and MMAE after connection is:



, and

wherein the antibody of the antibody-drug conjugate comprises a heavy chain and a light chain, wherein the heavy chain comprises CDRs 1-3 having amino acid sequences as shown in SEQ ID NO: 1, 2 and 3, respectively, and wherein the light chain comprises CDRs 1-3 having amino acid sequences as shown in SEQ ID NO: 4, 5 and 6, respectively.

[0011b] In another aspect, the present disclosure refers to a lyophilized pharmaceutical formulation of an antibody-drug conjugate, wherein the lyophilized pharmaceutical formulation is obtained by lyophilization of the aqueous liquid pharmaceutical formulation disclosed herein.

[0011c] In yet another aspect, the present disclosure refers to a use of the pharmaceutical formulation disclosed herein in the manufacture of a medicament for treating a disease caused by abnormal expression of Her2~~, preferably cancer, further preferably Her2 positive cancer, and most preferably breast cancer, ovarian cancer, gastric cancer, urothelial cancer, gastroesophageal cancer, oesophageal cancer, endometrial cancer, lung cancer, or bladder cancer~~.

[0011d] In a further aspect, the present disclosure provides a pharmaceutical formulation disclosed herein, for use in therapy.

[0011e] In ~~a further~~another aspect, the present disclosure refers to a method for preparing a pharmaceutical formulation of an antibody-drug conjugate, comprising:

(1) preparing the formulation disclosed herein; and

(2) evaluating the stability of the antibody-drug conjugate in the formulation.

[0012] The present disclosure provides an aqueous liquid pharmaceutical formulation of an antibody-drug conjugate, wherein the formulation comprises the antibody-drug conjugate, a non-reducing sugar, an amino acid, and a solubilizer; wherein the non-reducing sugar is selected from mannitol, sucrose, trehalose, and a combination thereof; the amino acid is selected from

CLAIMS

1. An aqueous liquid pharmaceutical formulation of an antibody-drug conjugate, wherein

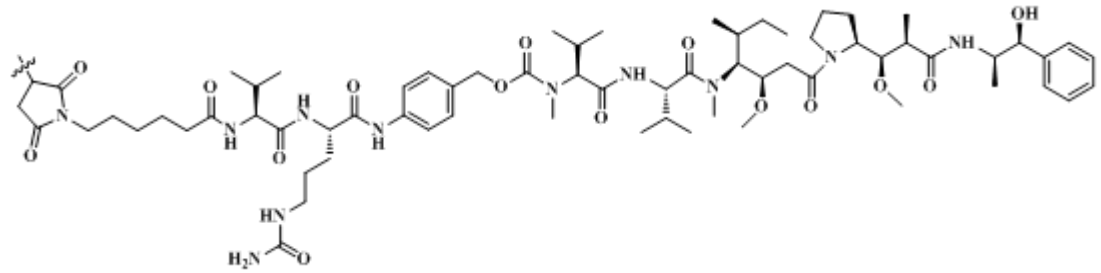
the formulation comprises the antibody-drug conjugate, a non-reducing sugar, an amino acid, and a solubilizer,

the non-reducing sugar is selected from mannitol, sucrose, ~~trehalose,~~ and a combination thereof,

the amino acid is selected from histidine, ~~alanine, arginine, glycine, glutamic acid, a~~ histidine hydrochloride ~~of the above amino acids~~, and a combination thereof, and

the solubilizer is polysorbate 80~~selected from glycerol, Tween-80, and a combination thereof,~~

wherein the antibody-drug conjugate is an anti-HER2 monoclonal antibody-vc-MMAE, wherein the anti-HER2 monoclonal antibody is connected to MMAE via a linker vc, and the structure of the linker and MMAE after connection is:



, and

wherein the antibody of the antibody-drug conjugate comprises a heavy chain and a light chain, wherein the heavy chain comprises CDRs 1-3 having amino acid sequences as shown in SEQ ID NO: 1, 2 and 3, respectively, and wherein the light chain comprises CDRs 1-3 having amino acid sequences as shown in SEQ ID NO: 4, 5 and 6, respectively.

2. The aqueous liquid pharmaceutical formulation according to claim 1, wherein the concentration of ~~the~~ mannitol is 100-300 mmol/L~~, preferably 190-300 mmol/L, more preferably 200-260 mmol/L, and most preferably 240-260 mmol/L; the concentration of the sucrose is 0-100 mmol/L, preferably 40-100 mmol/L, more preferably 60-100 mmol/L, and most preferably 40-60 mmol/L~~.

3. The aqueous liquid pharmaceutical formulation according to claim 2, wherein the concentration of mannitol is 190-300 mmol/L.

4. The aqueous liquid pharmaceutical formulation according to claim 2, wherein the concentration of mannitol is 200-260 mmol/L.

5. The aqueous liquid pharmaceutical formulation according to claim 2, wherein the concentration of mannitol is 240-260 mmol/L.

6. The aqueous liquid pharmaceutical formulation according to any one of claims 1-5, wherein the concentration of sucrose is 0-100 mmol/L.

7. The aqueous liquid pharmaceutical formulation according to claim 6, wherein the concentration of sucrose is 40-100 mmol/L.

8. The aqueous liquid pharmaceutical formulation according to claim 6, wherein the concentration of sucrose is 60-100 mmol/L.

9. The aqueous liquid pharmaceutical formulation according to claim 6, wherein the concentration of sucrose is 40-60 mmol/L.

~~3~~10. The aqueous liquid pharmaceutical formulation according to ~~claim 1 or 2~~any one of claims 1-9, wherein the ~~histidine~~ amino acid is histidine hydrochloride at a concentration of 0-100 mmol/L ~~, preferably 5-50 mmol/L, more preferably 5-20 mmol/L, and most preferably 10 mmol/L; the arginine is arginine hydrochloride at a concentration of 0-160 mmol/L, preferably 20-100 mmol/L, more preferably 30-90 mmol/L, and most preferably 35 mmol/L~~.

11. The aqueous liquid pharmaceutical formulation according to claim 10, wherein the concentration of histidine hydrochloride is 5-50 mmol/L.

12. The aqueous liquid pharmaceutical formulation according to claim 10, wherein the

concentration of histidine hydrochloride is 5-20 mmol/L.

13. The aqueous liquid pharmaceutical formulation according to claim 10, wherein the concentration of histidine hydrochloride is 10 mmol/L.

14. The aqueous liquid pharmaceutical formulation according to any one of claims 1-9, wherein the amino acid is histidine at a concentration of 0-100 mmol/L.

15. The aqueous liquid pharmaceutical formulation according to claim 14, wherein the concentration of histidine is 5-50 mmol/L.

16. The aqueous liquid pharmaceutical formulation according to claim 14, wherein the concentration of histidine is 5-20 mmol/L.

17. The aqueous liquid pharmaceutical formulation according to claim 14, wherein the concentration of histidine is 10 mmol/L.

18. The aqueous liquid pharmaceutical formulation according to any one of claims 1-9, wherein the amino acid is histidine and histidine hydrochloride at a concentration of 0-100 mmol/L.

19. The aqueous liquid pharmaceutical formulation according to claim 18, wherein the concentration of histidine and histidine hydrochloride is 5-50 mmol/L.

20. The aqueous liquid pharmaceutical formulation according to claim 18, wherein the concentration of histidine and histidine hydrochloride is 5-20 mmol/L.

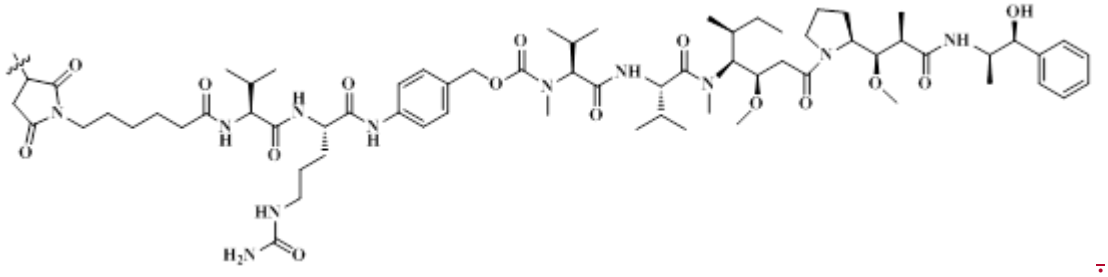
21. The aqueous liquid pharmaceutical formulation according to claim 18, wherein the concentration of histidine and histidine hydrochloride is 10 mmol/L.

~~4~~22. The aqueous liquid pharmaceutical formulation according to any one of claims 1-~~3~~21,

wherein ~~the content of the glycerol is 0-1%, preferably 0.2-0.5% (w/v); the~~ the mass percentage of ~~Tween~~ polysorbate 80 is 0-0.02% (w/v).

~~5~~23. The aqueous liquid pharmaceutical formulation according to any one of claims 1-~~4~~22, wherein the antibody of the antibody-drug conjugate is an anti-HER2 monoclonal antibody; and the drug is MMAE, MMAF, DM1, or DM4~~, or a derivative thereof~~.

~~6. The aqueous liquid pharmaceutical formulation according to claim 5, wherein the antibody-drug conjugate is an anti-HER2 monoclonal antibody-vc-MMAE, wherein the anti-HER2 monoclonal antibody is connected to MMAE via a linker vc, and the structure of the linker and MMAE after connection is:~~



~~7~~24. The aqueous liquid pharmaceutical formulation according to claim ~~5 or 6~~23, wherein ~~the anti-HER2 monoclonal antibody comprises a heavy chain and a light chain,~~

~~(i) the heavy chain comprises CDRs 1-3 having amino acid sequences as shown in SEQ ID NO: 1, 2 and 3, respectively; and/or~~

~~(ii) the light chain comprises CDRs 1-3 having amino acid sequences as shown in SEQ ID NO: 4, 5 and 6, respectively; and~~

the monoclonal antibody is ~~preferably~~ a chimeric antibody or a humanized antibody.

~~8~~25. The aqueous liquid pharmaceutical formulation according to ~~any one of claims 1-7~~claim 1, wherein the concentration of the anti-HER2 monoclonal antibody-vc-MMAE is 5-30 mg/ml.

~~9~~26. The aqueous liquid pharmaceutical formulation according to claim 25~~8~~, wherein the non-reducing sugar is 240-260 mmol/L of mannitol and/or 40-60 mmol/L of sucrose, the amino

acid is 8-12 mmol/L of histidine hydrochloride, and the solubilizer is 0-0.02% (w/v) of polysorbate~~Tween~~ 80.

27. The aqueous liquid pharmaceutical formulation according to claim 25, wherein the non-reducing sugar is 240-260 mmol/L of mannitol and/or 40-60 mmol/L of sucrose, the amino acid is 8-12 mmol/L of histidine, and the solubilizer is 0-0.02% (w/v) of polysorbate 80.

28. The aqueous liquid pharmaceutical formulation according to claim 25, wherein the non-reducing sugar is 240-260 mmol/L of mannitol and/or 40-60 mmol/L of sucrose, the amino acid is 8-12 mmol/L of histidine and histidine hydrochloride, and the solubilizer is 0-0.02% (w/v) of polysorbate 80.

~~10~~29. The aqueous liquid pharmaceutical formulation according to claim ~~9~~26, wherein the non-reducing sugar is about 260 mmol/L of mannitol and about 40 mmol/L of sucrose, the amino acid is about 10 mmol/L of histidine hydrochloride, the concentration of the antibody-drug conjugate is about 10 mg/ml, and the solubilizer is 0.02% (w/v) of polysorbate~~Tween~~ 80.

30. The aqueous liquid pharmaceutical formulation according to claim 27, wherein the non-reducing sugar is about 260 mmol/L of mannitol and about 40 mmol/L of sucrose, the amino acid is about 10 mmol/L of histidine, the concentration of the antibody-drug conjugate is about 10 mg/ml, and the solubilizer is 0.02% (w/v) of polysorbate 80.

31. The aqueous liquid pharmaceutical formulation according to claim 28, wherein the non-reducing sugar is about 260 mmol/L of mannitol and about 40 mmol/L of sucrose, the amino acid is about 10 mmol/L of histidine and histidine hydrochloride, the concentration of the antibody-drug conjugate is about 10 mg/ml, and the solubilizer is 0.02% (w/v) of polysorbate 80.

~~11~~32. The aqueous liquid pharmaceutical formulation according to claim 26~~10~~, wherein the non-reducing sugar is about 240 mmol/L of mannitol and about 60 mmol/L of sucrose, the amino acid is about 10 mmol/L of histidine hydrochloride, the concentration of the antibody-drug conjugate is about 10 mg/ml, and the solubilizer is about 0.02% (w/v) of polysorbate~~Tween~~ 80.

33. The aqueous liquid pharmaceutical formulation according to claim 27, wherein the non-reducing sugar is about 240 mmol/L of mannitol and about 60 mmol/L of sucrose, the amino acid is about 10 mmol/L of histidine, the concentration of the antibody-drug conjugate is about 10 mg/ml, and the solubilizer is about 0.02% (w/v) of polysorbate 80.

34. The aqueous liquid pharmaceutical formulation according to claim 28, wherein the non-reducing sugar is about 240 mmol/L of mannitol and about 60 mmol/L of sucrose, the amino acid is about 10 mmol/L of histidine and histidine hydrochloride, the concentration of the antibody-drug conjugate is about 10 mg/ml, and the solubilizer is about 0.02% (w/v) of polysorbate 80.

~~12~~35. The aqueous liquid pharmaceutical formulation according to any one of claims 1-34~~11~~, wherein the formulation has a pH of 4.5-7~~, preferably 5.6-6.8, more preferably 5.6-6.5, 5.6-6.4, 5.6-6.3, 6.1-6.4, or 6.1-6.3~~.

36. The aqueous liquid pharmaceutical formulation according to claim 35, wherein the formulation has a pH of 5.6-6.8.

37. The aqueous liquid pharmaceutical formulation according to claim 35, wherein the formulation has a pH of 5.6-6.5, 5.6-6.4, 5.6-6.3, 6.1-6.4, or 6.1-6.3.

38. The aqueous liquid pharmaceutical formulation according to claim 1, wherein the non-reducing sugar is mannitol at a concentration of 240 mmol/L and sucrose at a concentration of 60 mmol/L, wherein the amino acid is about 10 mmol/L of histidine and histidine hydrochloride, wherein the concentration of polysorbate 80 is 0.02% (w/v), wherein the concentration of the anti-HER2 monoclonal antibody-vc-MMAE is 5-30 mg/ml, and wherein the formulation has a pH of 6.1-6.3.

39. The aqueous liquid pharmaceutical formulation according to claim 1, wherein the non-reducing sugar is mannitol at a concentration of 240 mmol/L and sucrose at a concentration

of 60 mmol/L, wherein the amino acid is about 10 mmol/L of histidine hydrochloride, wherein the concentration of polysorbate 80 is 0.02% (w/v), wherein the concentration of the anti-HER2 monoclonal antibody-vc-MMAE is 5-30 mg/ml, and wherein the formulation has a pH of 6.1-6.3.

~~13~~40. A lyophilized pharmaceutical formulation of an antibody-drug conjugate, wherein the lyophilized pharmaceutical formulation is obtained by lyophilization of the aqueous liquid pharmaceutical formulation according to any one of claims 1-39~~12~~.

~~14. The lyophilized pharmaceutical formulation according to claim 13, wherein the aqueous liquid pharmaceutical formulation comprises about 260 mmol/L of mannitol, about 40 mmol/L of sucrose, about 10 mmol/L of histidine hydrochloride, about 0.02% (w/v) of Tween 80, and about 10 mg/ml of anti-HER2 monoclonal antibody-vc-MMAE, and the aqueous liquid pharmaceutical formulation has a pH of 5.6-6.8.~~

~~15. The lyophilized pharmaceutical formulation according to claim 13, wherein the aqueous liquid pharmaceutical formulation comprises about 240 mmol/L of mannitol, about 60 mmol/L of sucrose, about 10 mmol/L of histidine hydrochloride, about 0.02% of Tween 80, and about 10 mg/ml of anti-HER2 monoclonal antibody-vc-MMAE, and the aqueous liquid pharmaceutical formulation has a pH of 5.6-6.8.~~

~~16. The lyophilized pharmaceutical formulation according to claim 13, wherein the non-reducing sugars in the aqueous liquid pharmaceutical formulation are mannitol and sucrose at concentrations of about 47.36 mg/ml and about 13.69 mg/ml, respectively, and the amino acid is histidine hydrochloride at a concentration of about 2.10 mg/ml, and the solubilizer is Tween 80 at a content of about 0.02% (w/v).~~

~~17. The lyophilized pharmaceutical formulation according to claim 13, wherein the non-reducing sugars in the aqueous liquid pharmaceutical formulation are mannitol and sucrose at concentrations of about 43.72 mg/ml and about 20.54 mg/ml, respectively, and the amino acid is histidine hydrochloride at a concentration of about 2.10 mg/ml, and the solubilizer is Tween 80 at a content of about 0.02% (w/v).~~

~~18~~41. Use of the pharmaceutical formulation according to any one of claims 1-~~40~~17 in the manufacture of a medicament for treating a disease caused by abnormal expression of Her2~~, preferably cancer, further preferably Her2 positive cancer, and most preferably breast cancer, ovarian cancer, gastric cancer, urothelial cancer, gastroesophageal cancer, oesophageal cancer, endometrial cancer, lung cancer, or bladder cancer~~.

42. The use of claim 41, wherein the disease caused by abnormal expression is cancer.

43. The use of claim 42, wherein the cancer is Her2 positive cancer.

44. The use of claim 43, wherein the Her2 positive cancer is breast cancer, ovarian cancer, urothelial cancer, gastroesophageal cancer, endometrial cancer, lung cancer, or bladder cancer.

45. A pharmaceutical formulation according to any one of claims 1-40, for use in therapy.

~~19~~46. A method for preparing a pharmaceutical formulation of an antibody-drug conjugate, comprising:

(1) preparing the formulation of any one of claims 1-~~40~~17; and

(2) evaluating the stability of the antibody-drug conjugate in the formulation.

ANTI-HER2 ANTIBODY DRUG CONJUGATE PHARMACEUTICAL PREPARATION

ABSTRACT

A pharmaceutical preparation comprising a mixture of a nonreducing sugar, a recombinant humanized anti-Her2 monoclonal antibody-MMAE conjugate, and a surfactant. The pharmaceutical preparation has the characteristics of reducing particulate matters, reducing aggregate formation, improving the stability of a conjugate, improving the appearance of freeze-dried powder, etc.

[Fig. 1]