

and non-small cell lung cancer), esophageal cancer, salivary gland cancer, gastroesophageal junction adenocarcinoma, bile duct cancer, Paget disease, pancreatic cancer, ovarian cancer, uterine cancer sarcoma, urothelial cancer, prostate cancer, bladder cancer, gastrointestinal stromal tumor, gastrointestinal stromal tumor, cervical cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular carcinoma, colon cancer, rectal cancer, endometrial cancer, uterine cancer, kidney cancer, vulval cancer, thyroid cancer, penile cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, nerve epithelial tissue tumors, nerve sheath tumors, head and neck cancer, skin cancer, throat cancer, gallbladder, bile duct cancer, mesothelioma, and sarcoma. For example, when the antibody-drug conjugates used in the present invention is an anti-HER2 antibody-drug conjugate, the pharmaceutical compositions of the present invention more preferably can be used for the treatment of at least one cancer selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, non-small cell lung cancer, esophageal cancer, salivary gland cancer, esophagogastric junction adenocarcinoma, bile duct cancer, Paget disease, pancreatic cancer, ovarian cancer, and uterine cancer sarcoma; more preferably can be used for the treatment of at least one cancer selected from the group consisting of breast cancer, gastric cancer, colorectal cancer, non-small cell lung cancer,

the first drying, the annealing process and the second drying process were conducted, and based on the results of these studies, the lyophilization method of aqueous solution (1) was set up as shown in Table 14. A feature of this lyophilization method is the annealing parameters, and it has been found that, by annealing at a temperature near the eutectic point, a lyophilized cake having significantly reduced shrinkage can be produced in a short time.

[0205]

[Table 14]

Process	Step No.	Shelf temperature (°C)	Time (min)	Chamber vacuum degree (Pa)
Freezing	1	5	30	Without vacuum
	2	5	120	
	3	-40	60	
	4	-40	120	
	5	-4 to -2	60	
	6	-4 to -2	120	
	7	-40	60	
	8	-40	120	
Primary drying	9	-5	60	7
	10	-5	2400	
Secondary drying	11	45	180	7
	12	45	480	
Unloading	13	5	60	

[0206]

For lyophilized injections produced by the present lyophilization method, storage stabilities at 1 month under 50°C, 3 months under 40°C/75% RH, 3 months under 25°C/60% RH, and 3 months under 5°C were evaluated by employing protein concentration, moisture, insoluble

Claims

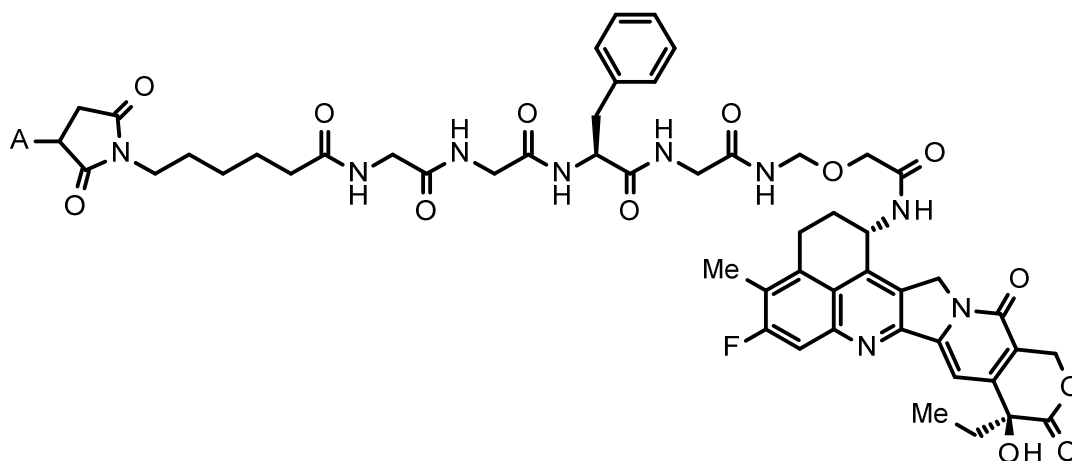
[Claim 1]

A pharmaceutical composition comprising

- (i) an antibody-drug conjugate,
- (ii) a histidine buffer,
- (iii) sucrose or trehalose, and
- (iv) a surfactant,

wherein the antibody-drug conjugate is an antibody-drug conjugate in which a drug-linker represented by the following formula:

[Formula 1]



wherein A represents a connecting position to an antibody, is conjugated to the antibody via a thioether bond.

[Claim 2]

The pharmaceutical composition according to claim 1, wherein the surfactant is polysorbate 80 or polysorbate 20.

[Claim 3]

The pharmaceutical composition according to claim 1 or 2 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 3 to 80 mmol of the histidine buffer,
- (iii) 24 to 320 mg of sucrose or trehalose, and
- (iv) 0.05 to 1.6 mg of polysorbate 80 or polysorbate 20.

[Claim 4]

The pharmaceutical composition according to any one of claims 1 to 3 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 10 to 40 mmol of the histidine buffer,
- (iii) 90 mg of sucrose or 100 mg of trehalose hydrate, and
- (iv) 0.2 to 0.4 mg of polysorbate 80 or polysorbate 20.

[Claim 5]

The pharmaceutical composition according to any one of claims 1 to 4 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 10 or 25 mmol of the histidine buffer,
- (iii) 90 mg of sucrose, and
- (iv) 0.2 or 0.3 mg of polysorbate 80 or polysorbate 20.

[Claim 6]

The pharmaceutical composition according to any one of claims 1 to 5, wherein the pH of the composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 4.0 to 7.0.

[Claim 7]

The pharmaceutical composition according to any one of claims 1 to 6, wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody, an anti-HER3 antibody, an anti-TROP2 antibody, an anti-B7-H3 antibody, or an anti-GPR20 antibody.

[Claim 8]

The pharmaceutical composition according to claim 7, wherein the antibody in the antibody-drug conjugate is an anti-HER2 antibody.

[Claim 9]

The pharmaceutical composition according to claim 8, wherein the anti-HER2 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 1 to 449 of SEQ ID NO: 1 and a light chain consisting of an amino acid sequence consisting of amino acid residues 1 to 214 of SEQ ID NO: 2, or an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 1 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 2.

[Claim 10]

The pharmaceutical composition according to claim 8 or 9, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[Claim 11]

The pharmaceutical composition according to any one of claims 8 to 10 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 25 mmol of the histidine buffer,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 80,

wherein the pH of the composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 5.5.

[Claim 12]

The pharmaceutical composition according to any one of claims 8 to 10 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.89 mg of L-histidine and 4.04 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 80.

[Claim 13]

The pharmaceutical composition according to any one of claims 8 to 10 comprising

- (i) 100 mg of the antibody-drug conjugate,

- (ii) 4.45 mg of L-histidine and 20.2 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and
- (iv) 1.5 mg of polysorbate 80.

[Claim 14]

The pharmaceutical composition according to claim 7, wherein the antibody in the antibody-drug conjugate is an anti-HER3 antibody.

[Claim 15]

The pharmaceutical composition according to claim 14, wherein the anti-HER3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a light chain consisting of an amino acid sequence represented by SEQ ID NO: 4, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[Claim 16]

The pharmaceutical composition according to claim 14 or 15, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[Claim 17]

The pharmaceutical composition according to any one of claims 14 to 16 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 25 mmol of the histidine buffer,
- (iii) 90 mg of sucrose, and

(iv) 0.3 mg of polysorbate 20,
wherein the pH of the composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 5.4.

[Claim 18]

The pharmaceutical composition according to any one of claims 14 to 16 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.81 mg of L-histidine and 4.14 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 20.

[Claim 19]

The pharmaceutical composition according to any one of claims 14 to 16 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 4.06 mg of L-histidine and 20.7 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and
- (iv) 1.5 mg of polysorbate 20.

[Claim 20]

The pharmaceutical composition according to claim 7, wherein the antibody in the antibody-drug conjugate is an anti-TROP2 antibody.

[Claim 21]

The pharmaceutical composition according to claim 20, wherein the anti-TROP2 antibody is an antibody comprising

a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 470 of SEQ ID NO: 5 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 6, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[Claim 22]

The pharmaceutical composition according to claim 20 or 21, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3 to 5.

[Claim 23]

The pharmaceutical composition according to any one of claims 20 to 22 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 10 mmol of the histidine buffer,
- (iii) 90 mg of sucrose, and
- (iv) 0.2 or 0.3 mg of polysorbate 80,

wherein the pH of the composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 6.0.

[Claim 24]

The pharmaceutical composition according to any one of claims 20 to 22 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.78 mg of L-histidine and 1.05 mg of L-histidine hydrochloride hydrate,

(iii) 90 mg of sucrose, and

(iv) 0.2 or 0.3 mg of polysorbate 80.

[Claim 25]

The pharmaceutical composition according to any one of claims 20 to 22 comprising

(i) 100 mg of the antibody-drug conjugate,

(ii) 3.88 mg of L-histidine and 5.26 mg of L-histidine hydrochloride hydrate,

(iii) 450 mg of sucrose, and

(iv) 1.0 or 1.5 mg of polysorbate 80.

[Claim 26]

The pharmaceutical composition according to claim 7, wherein the antibody in the antibody-drug conjugate is an anti-B7-H3 antibody.

[Claim 27]

The pharmaceutical composition according to claim 26, wherein the anti-B7-H3 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 471 of SEQ ID NO: 7 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 233 of SEQ ID NO: 8, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[Claim 28]

The pharmaceutical composition according to claim 26 or 27, wherein the average number of units of the drug-

linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 3 to 5.

[Claim 29]

The pharmaceutical composition according to any one of claims 26 to 28 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 10 mmol of the histidine buffer,
- (iii) 90 mg of sucrose, and
- (iv) 0.2 or 0.3 mg of polysorbate 20,

wherein the pH of the composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 5.9.

[Claim 30]

The pharmaceutical composition according to any one of claims 26 to 28 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.65 mg of L-histidine and 1.22 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.2 or 0.3 mg of polysorbate 20.

[Claim 31]

The pharmaceutical composition according to any one of claims 26 to 28 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 3.23 mg of L-histidine and 6.12 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and

(iv) 1.0 or 1.5 mg of polysorbate 20.

[Claim 32]

The pharmaceutical composition according to claim 7, wherein the antibody in the antibody-drug conjugate is an anti-GPR20 antibody.

[Claim 33]

The pharmaceutical composition according to claim 32, wherein the anti-GPR20 antibody is an antibody comprising a heavy chain consisting of an amino acid sequence consisting of amino acid residues 20 to 472 of SEQ ID NO: 9 and a light chain consisting of an amino acid sequence consisting of amino acid residues 21 to 234 of SEQ ID NO: 10, or a variant of the antibody in which a lysine residue at the carboxyl terminus of the heavy chain is deleted.

[Claim 34]

The pharmaceutical composition according to claim 32 or 33, wherein the average number of units of the drug-linker conjugated per antibody molecule in the antibody-drug conjugate is in the range of from 7 to 8.

[Claim 35]

The pharmaceutical composition according to any one of claims 32 to 34 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 10 mmol of the histidine buffer,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 80,

wherein the pH of the composition when the antibody-drug conjugate is dissolved in water at a concentration of 20 mg/mL is 5.4.

[Claim 36]

The pharmaceutical composition according to any one of claims 32 to 34 comprising,

- (i) per 20 mg of the antibody-drug conjugate,
- (ii) 0.32 mg of L-histidine and 1.66 mg of L-histidine hydrochloride hydrate,
- (iii) 90 mg of sucrose, and
- (iv) 0.3 mg of polysorbate 80.

[Claim 37]

The pharmaceutical composition according to any one of claims 32 to 34 comprising

- (i) 100 mg of the antibody-drug conjugate,
- (ii) 1.62 mg of L-histidine and 8.29 mg of L-histidine hydrochloride hydrate,
- (iii) 450 mg of sucrose, and
- (iv) 1.5 mg of polysorbate 80.

[Claim 38]

The pharmaceutical composition according to any one of claims 1 to 37, wherein the composition is in the form of an injection.

[Claim 39]

The pharmaceutical composition according to claim 38, wherein the composition is in the form of an aqueous injection.

[Claim 40]

The pharmaceutical composition according to claim 39, wherein the concentration of the antibody-drug conjugate is 20 mg/mL.

[Claim 41]

The pharmaceutical composition according to claim 39 or 40, wherein the composition is frozen.

[Claim 42]

The pharmaceutical composition according to claim 38, wherein the composition is in the form of a lyophilized injection.

[Claim 43]

The pharmaceutical composition according to claim 42, wherein the composition is stored in a brown vial.

[Claim 44]

The pharmaceutical composition according to any one of claims 1 to 43, for use in therapy.

[Claim 45]

Use of the pharmaceutical composition according to any one of claims 1 to 43, for the preparation of a medicament for treating cancer.

[Claim 46]

A method for producing a pharmaceutical composition according to claim 42, comprising the steps of:

(1) preparing an aqueous solution comprising predetermined amounts of

(i) an antibody-drug conjugate,

- (ii) a histidine buffer,
- (iii) sucrose or trehalose, and
- (iv) a surfactant,
- (2) if necessary, adjusting the pH of the aqueous solution to a predetermined value, and then
- (3) lyophilizing the aqueous solution.

[Claim 47]

The production method according to claim 46, wherein the step of lyophilizing the aqueous solution comprises a process of annealing at a shelf temperature which is near the eutectic point of the aqueous solution, wherein near the eutectic point indicates the range of from a temperature which is 1.5°C lower than the eutectic point to a temperature which is 1.5°C higher than the eutectic point.

[Claim 48]

The production method according to claim 47, characterized in that the time for a process of primary drying is shortened compared with that when annealing at a shelf temperature which is 5°C lower than the eutectic point is performed.

[Claim 49]

The production method according to claim 47 or 48, characterized in that a lyophilized cake having less shrinkage is obtained compared with that when annealing at a shelf temperature which is 5°C lower than the eutectic point is performed.

[Claim 50]

The production method according to claim 46, wherein the step of lyophilizing the aqueous solution comprises a process of performing annealing at a shelf temperature of -4 to -1°C.

[Claim 51]

The production method according to claim 50, wherein the step of lyophilizing the aqueous solution further comprises a process of primary drying at a shelf temperature of -5 to 5°C under a vacuum of 5 to 15 Pa.

[Claim 52]

The production method according to claim 51, wherein the step of lyophilizing the aqueous solution further comprises a process of secondary drying at a shelf temperature of 40 to 50°C under a vacuum of 5 to 15 Pa.