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(54) Titre : FORMULATION PHARMACEUTIQUE DE PROTEINE DE FUSION TACI-FC
(54) Title: PHARMACEUTICAL TACI-FC FUSION PROTEIN FORMULATION

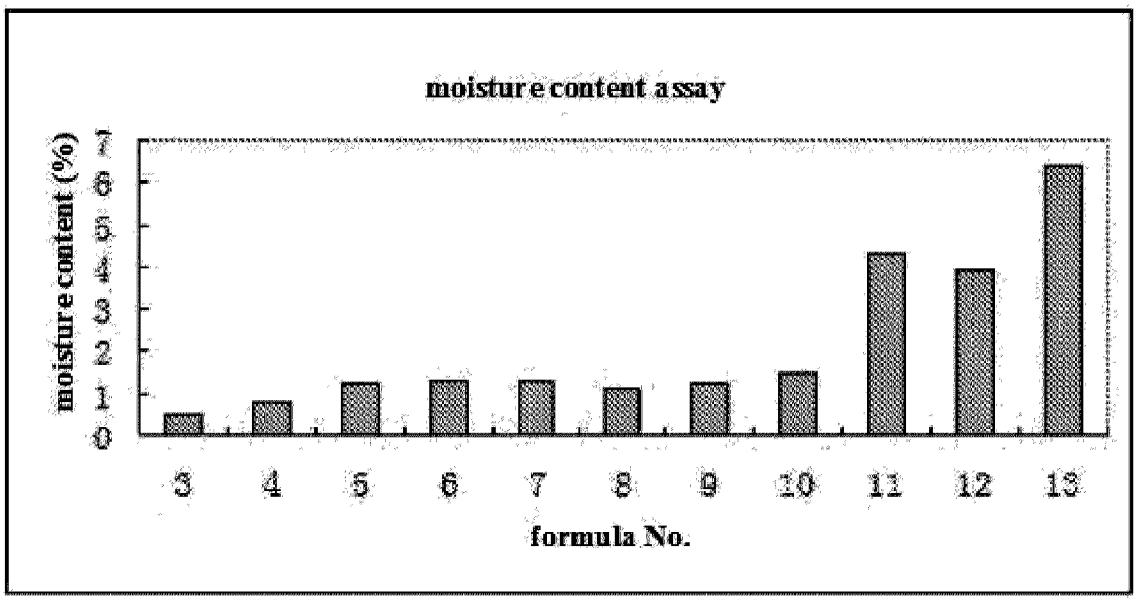

FIG. 1

(57) Abrégé/Abstract:
Disclosed is a pharmaceutical formulation containing a mixture of a non-reducing sugar, a TACI-Fc fusion protein and at least one amino acid. The pharmaceutical formulation has the characteristics of reducing particulate matter, reducing aggregate formation, improving the stability, improving the appearance of a freeze-dried powder, etc.

ABSTRACT

Disclosed is a pharmaceutical formulation containing a mixture of a non-reducing sugar, a TACI-Fc fusion protein and at least one amino acid. The pharmaceutical formulation has the characteristics of reducing particulate matter, reducing aggregate formation, improving the stability, improving the appearance of a freeze-dried powder, etc.

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PHARMACEUTICAL TACI-FC FUSION PROTEIN FORMULATION

FIELD

[0001] The present disclosure relates to a fusion protein pharmaceutical formulation that regulates lymphocytopoiesis and lymphocyte differentiation, and belongs to the field of anti-autoimmune disease drugs.

BACKGROUND

[0002] Lymphocytopoiesis and lymphocyte differentiation are regulated by cytokines. B lymphocyte stimulator (Blys, also known as B cell activating factor, BAFF) and a proliferation-inducing ligand (APRIL) are cytokines with an important regulatory effect on human immune response. They can promote the development and proliferation of B lymphocytes and increase the expression of immunoglobulin in the blood. BlyS and APRIL also have a key regulatory effect on the maturation of T lymphocytes, so they also have an important impact on cellular immunity.

[0003] Blys and APRIL regulate the immune response of lymphocytes through receptors on the surface of lymphocytes. They bind to cell membrane receptors, TACI (Transmenbrane Activator and CAML-interactor) and BCMA (B Cell Maturation Antigen). In addition, BLyS can also bind to another receptor, BAFF-R. B lymphocytes express TACI, BCMA and BAFF-R, and mature T lymphocytes express TACI. BlyS and APRIL regulate the activation, proliferation and development of lymphocytes through the signaling of these receptors, and produce an immune response. Furthermore, for lymphocyte tumors, BlyS and APRIL also have effects of promoting tumor cell division and inhibiting tumor cell apoptosis, thus accelerating the progress of tumors.

[0004] A number of studies have shown that the overexpression of BlyS and APRIL is one of the reasons for a variety of autoimmune diseases. These diseases include systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome and the like. Clinical studies have demonstrated that the concentration of BlyS is often positively correlated with the severity of autoimmune diseases. Therefore, inhibiting the production of BlyS and APRIL or reducing their concentration in the body

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becomes an effective way to treat autoimmune diseases. Meanwhile, since BlyS and APRIL can accelerate the process of B lymphocyte tumors, inhibition of BlyS and APRIL can also be used to treat B lymphocyte tumors, such as chronic lymphocytic leukemia, multiple myeloma, and B lymphocyte lymphoma.

[0005] Since TACI has a high affinity for BlyS and APRIL, soluble TACI (the extracellular part of TACI) is used to prevent the interaction between BlyS or APRIL and cell membrane receptors (TACI, BCMA and BAFF-R), so as to achieve the purpose of blocking the biological activity of BlyS and APRIL and treating autoimmune diseases or tumors. Multiple studies have shown that the fusion protein (TACI-Fc) with the extracellular part of TACI binding to IgG Fc fragment can effectively inhibit diseases related to BlyS and APRIL. For example, the clinical results of the TACI fusion protein Atacicept developed by ZymoGenetics and Merck Serono reveal that it has a therapeutic effect on SLE, rheumatoid arthritis, lymphoma and other diseases.

[0006] In addition, the patent CN101323643B discloses a fusion protein consisting of truncated TACI and immunoglobulin Fc. The TACI portion of the fusion protein comprises the amino terminal region sequence starting from amino acid residue 13 in the extracellular region of TACI, the entire cysteine-rich region, and a partial sequence of the stalk region. The immunoglobulin Fc portion of the fusion protein comprises a hinge region, CH2 region and CH3 region. The TACI sequence and the Fc sequence are fused directly or via a linker sequence. Further, the TACI portion thereof is selected from positions 13-108 or 13-118 of the amino acid sequence of TACI, the linker sequence is 9Gly, and the immunoglobulin Fc fragment is selected from human or animal immunoglobulin Fc, which is selected from IgG, IgM, IgD, and IgA, with each immunoglobulin type including each subtype, such as IgG1. Patent CN102085368B discloses the aforementioned TACI-Fc fusion protein useful in the treatment of autoimmune diseases, such as systemic lupus erythematosus. Patent application CN201810512508.8 proved the use of TACI-Fc fusion protein for the treatment of neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS). The NMOSD includes neuromyelitis optica, recurrent optic neuritis, longitudinally extending transverse myelitis, optic-spinal form of multiple sclerosis, long-term transverse myelitis, unilateral or bilateral optic neuritis, optic neuritis or myelitis accompanying with autoimmune disease, optic neuritis or myelitis accompanying with symptomatic or asymptomatic intracranial lesions.

[0007] Part of the formulations of other antibody drugs and fusion proteins that have been on the market are as follows:

Trade name	Common name	Adjuvant ingredient
Humira	adalimumab	mannitol, polysorbate 80
Taltz	ixekizumab	anhydrous citric acid, polysorbate 80, sodium chloride, sodium citrate dihydrate
Trulicity	dulaglutide	anhydrous citric acid, mannitol, polysorbate 80, trisodium citrate dihydrate
Erelzi	etanercept-szzs	citric acid, sodium citrate, sodium chloride, sucrose, lysine
Amevive	alefacept	citric acid monohydrate, glycine, sodium citrate, sucrose
Nulojix	belatacept	sodium dihydrogen phosphate, sodium chloride, sucrose
Tanzeum	albiglutide	mannitol, polysorbate 80, sodium phosphate, trehalose dihydrate
Benlysta	Belimumab	sodium chloride, L-arginine hydrochloride, L-histidine hydrochloride, L-histidine, polysorbate 80

[0008] It can also be seen from the compositions of the adjuvant ingredients of the above antibody preparation and fusion protein that the composition of the fusion protein and antibody preparation has its own uniqueness. On the one hand, due to the low stability and complicated structure of monoclonal antibody drugs, it is extremely challenging to manufacture and store such drugs. On account of the heterogeneous structure of antibodies, especially the complementarity determining regions (CDRs) and Fc glycosylation, the development of different monoclonal antibody formulations needs to be carried out individually based on case. In the development of antibody formulations, there are challenges in antibody conformation, colloid or chemical structure, such as oxidation, isomerization, deamidation, aggregation, denaturation and fragmentation. When exposed to different temperature, humidity, pH and stress conditions, the stereostructure of mAb

may change, especially in the hypervariable regions (HVRs). Poor products may exhibit reduced activity, and more importantly, increased immunogenicity can endanger the patient. Therefore, it is of vital importance to choose the best adjuvants to protect the antibody (Reference 1: Monoclonal antibodies: formulations of marketed products and recent advances in novel delivery system, Yanan Cui et al., Drug Development and Industrial Pharmacy, Volume 43, Issue 4, Pages 519-530, 2017). On the other hand, the easy aggregation and poor stability of fusion protein products cause adverse immune responses or interfere with the purification process, which has always been a problem to be solved in this field. Moreover, the factors that affect the aggregation of fusion proteins are also complicated, which can be divided into external factors and internal factors. The external factors mainly include temperature, physical pressure and solvent factors (pH, ionic strength, concentration, metal ions, etc.); and the internal factors mainly include the structural characteristics of the fusion protein, sensitive residues and unpaired cysteine, etc.. These factors will affect the aggregation of the fusion protein, thereby affecting its stability and storage time. Therefore, the selection of adjuvants for fusion proteins requires a lot of experimental exploration (Reference 2: Production Challenges for Complex Biologics: Fusion Proteins, Stefan R. Schmidt, American Pharmaceutical Review, pages 1-5, 2017).

[0009] Therefore, the purpose of the present disclosure is to obtain a formulation combination of TACI-Fc fusion protein through a wide range of screening and concentration range research on the available adjuvants for biological formulations to achieve the following technical effects: the TACI-Fc fusion protein can dissolve well before and after lyophilization, with the insoluble microparticles and visible foreign matters meeting the standards of injection for human use, and yet remain stable for a long time during the lyophilization and storage process, which is not prone to polymerization or degradation after redissolution, maintaining a good biological activity.

SUMMARY

[0010] The present disclosure relates to an aqueous liquid pharmaceutical formulation of TACI-Fc fusion protein, comprising the TACI-Fc fusion protein, a non-reducing sugar, and an amino acid; wherein the non-reducing sugar is selected from mannitol, sucrose, trehalose and a combination

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thereof; and the amino acid is selected from histidine, alanine, arginine, glycine, glutamic acid and a combination thereof.

[0011] In some embodiments, wherein the histidine is histidine hydrochloride at a concentration of 1-100 mmol/L, preferably 5-50 mmol/L, 5-20 mmol/L, 8-12 mmol/L, or about 10 mmol/L; and the arginine is arginine hydrochloride at a concentration of 10-160 mmol/L, preferably 20-120 mmol/L, 50-100 mmol/L, 70-95 mmol/L, 75-90 mmol/L, or about 90 mmol/L, or about 75 mmol/L.

[0012] In some embodiments, wherein the concentration of sucrose is 1-300 mmol/L, preferably 5-200 mmol/L, 10-100 mmol/L, 35-45 mmol/L, or about 40 mmol/L.

[0013] In some embodiments, wherein the concentration of mannitol is 10-300 mmol/L, preferably 10-200 mmol/L, 60-150 mmol/L, 85-125 mmol/L L, 90-120mmol/L, or about 120 mmol/L, or about 90 mmol/L.

[0014] In some embodiments, the TACI-Fc fusion protein has an amino acid sequence as shown in SEQ ID NO. 1. The protein comprises amino acids 13-118 of TACI and an optimized Fc fragment that reduces ADCC and CDC effects.

[0015] In the TACI-Fc fusion protein shown in SEQ ID NO. 1, in order to avoid antibody-dependent cell-mediated toxicity (ADCC) effect generated by membrane-bound BLyS or a proliferation-inducing ligand (APRIL), the Fc fragment derived from IgG1 was sequenced optimized, wherein amino acids 120-123 in the CH2 region of the Fc fragment were mutated from leucine (L)-leucine (L)-glycine (G)-glycine (G) to alanine (A)-glutamic acid (E)-glycine (G)-alanine (A), to reduce the affinity of Fcγ receptors. In addition, the CH2 region of the Fc sequence was also mutated (amino acid residues 216~217 were mutated from alanine (A)-proline (P) to serine (S)-serine (S)) to reduce complement binding or fixation, thereby reducing complement-dependent cytotoxicity (CDC) effects.

[0016] The sequence of SEQ ID NO:1 is as follows:

001 SRVDQEERFP QGLWTGVAMR SCPEEQYWDP LLGTCMSCKT ICNHQSQRTC

051 AAFCRSLSCR KEQGKFYDHL LRDCISCASI CGQHPKQCAY FCENKLRSPV

101 NLPPELDKTH TCPPCPAPEA EGAPSVFLFP PKPKDTLMIS RTPEVTCVVV

151 DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL

201 NGKEYKCKVS NKALPSSIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS

251 LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK

301 SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK

[0017] In the liquid formulation, two TACI-Fc fusion protein monomers may form a double-stranded structure due to the formation of an interchain disulfide bond in Fc hinge region.

[0018] In some embodiments, wherein the concentration of the TACI-Fc fusion protein is 5-240 mg/ml, preferably about 50 mg/ml to about 100 mg/ml, and most preferably about 80 mg/ml to about 100 mg/ml.

[0019] In some embodiments, the non-reducing sugar is 90-120 mmol/L of mannitol and/or 35-45 mmol/L of sucrose, the amino acid is 75-125 mmol/L of arginine hydrochloride and/or 8-12 mmol/L of histidine hydrochloride, and the concentration of the TACI-Fc fusion protein is 80-100 mg/ml; and the concentration of the histidine hydrochloride is more preferably about 10 mmol/L.

[0020] In some embodiments, it comprises about 1% to about 10% (w/v, g/100 ml) of the TACI-Fc fusion protein, preferably about 6-10% (w/v, g/100 ml) of the TACI-Fc fusion protein.

[0021] In some embodiments, the non-reducing sugar is about 90 mmol/L of mannitol and about 40 mmol/L of sucrose, the amino acid is about 90 mmol/L of arginine hydrochloride and about 10 mmol/L of histidine hydrochloride, and the concentration of the TACI-Fc fusion protein is about 80 mg/ml.

[0022] In some embodiments, the non-reducing sugar is about 120 mmol/L of mannitol and about 40 mmol/L of sucrose, the amino acid is about 75 mmol/L of arginine hydrochloride and about 10 mmol/L of histidine hydrochloride, and the concentration of the TACI-Fc fusion protein is about 80 mg/ml.

[0023] In some embodiments, the formulation has a pH of 4.0 to 8.0, preferably 4.5 to 7.0, 5.0 to 6.0, or about 5.5. The pH value of the solution is adjusted by NaOH or hydrochloric acid.

[0024] In another aspect, the present disclosure relates to a lyophilized pharmaceutical formulation obtained by lyophilization of the aqueous liquid pharmaceutical formulation.

[0025] In some embodiments of the lyophilized pharmaceutical formulation, the aqueous liquid pharmaceutical formulation comprises about 90 mmol/L of mannitol, about 40 mmol/L of sucrose, about 90 mmol/L of arginine hydrochloride, about 10 mmol/L of histidine hydrochloride, and about 80 mg/ml of the TACI-Fc fusion protein, and the aqueous liquid pharmaceutical formulation has a pH of 5.0 to 6.0.

[0026] In some embodiments of the lyophilized pharmaceutical formulation, the aqueous liquid pharmaceutical formulation comprises about 120 mmol/L of mannitol, about 40 mmol/L of sucrose, about 75 mmol/L of arginine hydrochloride, about 10 mmol/L of histidine hydrochloride, and about 80 mg/ml of the TACI-Fc fusion protein, and the aqueous liquid pharmaceutical formulation has a pH of 5.0 to 6.0.

[0027] In some embodiments of the lyophilized pharmaceutical formulation, the non-reducing sugars in the aqueous liquid pharmaceutical formulation are mannitol and sucrose at concentrations of about 16.4 mg/ml and about 13.7 mg/ml, respectively; and the amino acids in the aqueous liquid pharmaceutical formulation are arginine hydrochloride and histidine hydrochloride at concentrations of about 19.0 mg/ml and about 2.1 mg/ml, respectively.

[0028] In some embodiments of the lyophilized pharmaceutical formulation, the non-reducing sugars in the aqueous liquid pharmaceutical formulation are mannitol and sucrose at concentrations of about 21.9 mg/ml and about 13.7 mg/ml, respectively; and the amino acids in the aqueous liquid pharmaceutical formulation are arginine hydrochloride and histidine hydrochloride at concentrations of about 15.8 mg/ml and about 2.1 mg/ml, respectively.

[0029] The present disclosure further relates to use of the pharmaceutical formulation in the manufacture of a medicament for the treatment of an autoimmune disease, and the autoimmune disease includes systemic lupus erythematosus, rheumatoid arthritis, neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS) and Sjogren's syndrome, wherein the neuromyelitis

optica spectrum disorder comprises neuromyelitis optica, recurrent optic neuritis, longitudinally extending transverse myelitis, optic-spinal form of multiple sclerosis, long-term transverse myelitis, unilateral or bilateral optic neuritis, optic neuritis or myelitis accompanying with autoimmune disease, optic neuritis or myelitis accompanying with symptomatic or asymptomatic intracranial lesions, and the lymphoma includes chronic lymphocytic leukemia, multiple myeloma and B lymphocyte lymphoma.

[0030] The present disclosure also relates to a method for preparing a TACI-Fc fusion protein pharmaceutical formulation, comprising: (1) preparing the formulation as described above; and (2) evaluating the stability of the TACI-Fc fusion protein in the formulation.

[0031] In another aspect, the present disclosure also relates to a method for preparing the pharmaceutical formulation as described above, comprising the following steps: obtaining the protein stock solution, pre-freezing, primary drying, secondary drying, and subpackaging.

[0032] In certain embodiments, the step of obtaining the protein stock solution includes:

[0033] 1. Culturing genetically recombinant CHO cells capable of expressing the TACI-Fc fusion protein, and when the cell viability reaches an acceptable lower limit, separating the cells by centrifugation or filtration, and collecting the supernatant;

2. Performing a first step of purification using Protein A affinity chromatography column, and eluting the obtained target protein for ultrafiltration and concentration. Then performing a second step of purification on a composite packing chromatography column, and collecting the target protein peak. Finally, performing a third step of purification on the third column in a target protein penetration mode.

[0034] In certain embodiments, the step of obtaining the protein stock solution further includes: upon passing the test, the purified protein is mixed with "5× formulation buffer" for ultrafiltration and concentration to obtain the protein stock solution.

[0035] In certain embodiments, the obtained protein stock solution needs to be accurately diluted to the required protein concentration with a protein-free formulation buffer to obtain a semi-finished protein solution, which is then divided into vials for vacuum lyophilization. The main

technical effect achieved by the present disclosure is that, the TACI-Fc protein after highly purified has a purity of more than 99% of non-reducing SDS-PAGE, and the CHO cell host protein, CHO cell host DNA, bacterial endotoxin and other indicators meet the requirements of "Chinese Pharmacopoeia" (2005 Edition) standard. The pharmaceutical formulation comprising the TACI-Fc fusion protein obtained in the present disclosure has reached excellent standards in terms of moisture content, number of particles, number of visible foreign matters and insoluble microparticles, and the pharmaceutical formulation has long-term storage stability.

BRIEF DESCRIPTION OF DRAWINGS

[0036] FIG. 1: Determination of moisture content. The results show that the lyophilized powders of formulas 11, 12, and 13 are very easy to absorb water, and the moisture content does not meet the requirements. Formulas 3 to 9 meet the requirements of moisture content test.

[0037] FIG. 2: Visible foreign matters inspection assay. The results show that formulas 3 and 4 do not meet the requirements of visible foreign matters test.

[0038] FIG. 3: Insoluble microparticles inspection assay. The results show that formulas 3 and 4 do not meet the requirements of insoluble microparticles inspection.

DETAILED DESCRIPTION

[0039] Example 1: Acquisition and purification of TACI-Fc fusion protein

[0040] Total RNA was extracted from human peripheral blood mononuclear cells with Qiagen's RNA extraction kit. Then cDNA was synthesized from RNA by reverse transcriptase, before polymerase chain reaction was performed with the primers (Forward: **AGCCGTGTGGACCAGGAGG** ; Reverse: **GAGCTCTGGTGGAAGGTTCACTG**) to amplify the desired TACI fragments. The immunoglobulin Fc fragment was obtained by PCR amplification from a cloned sequence-optimized IgG1 Fc plasmid with reduced ADCC and CDC effects. Finally, the TACI and Fc sequences were fused by PCR to construct a DNA sequence of the TACI-Fc fusion protein (its amino acid sequence is shown in SEQ ID NO. 1). Later, by using TA cloning kit, the

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CLAIMS

1. An aqueous liquid pharmaceutical formulation of TACI-Fc fusion protein, comprising TACI-Fc fusion protein, a non-reducing sugar, and an amino acid; wherein the non-reducing sugar is selected from mannitol, sucrose, trehalose and a combination thereof; and the amino acid is selected from histidine, alanine, arginine, glycine, glutamic acid and a combination thereof.

2. The aqueous liquid pharmaceutical formulation according to claim 1, wherein the histidine is histidine hydrochloride at a concentration of 1-100 mmol/L, preferably 5-50 mmol/L, 5-20 mmol/L, 8-12 mmol/L, or about 10 mmol/L; and the arginine is arginine hydrochloride at a concentration of 10-160 mmol/L, preferably 20-120 mmol/L, 50-100 mmol/L, 70-95 mmol/L, 75-90 mmol/L, or about 90 mmol/L, or about 75 mmol/L.

3. The aqueous liquid pharmaceutical formulation according to claim 1 or 2, wherein the concentration of the sucrose is 1-300 mmol/L, preferably 5-200 mmol/L, 10-100 mmol/L, 35-45 mmol/L, or about 40 mmol/L.

4. The aqueous liquid pharmaceutical formulation according to any one of claims 1-3, wherein the concentration of the mannitol is 10-300 mmol/L, preferably 10-200 mmol/L, 60-150 mmol/L, 85-125 mmol/L L, 90-120mmol/L, or about 120 mmol/L, or about 90 mmol/L.

5. The aqueous liquid pharmaceutical formulation according to any one of claims 1-4, wherein the TACI-Fc fusion protein has an amino acid sequence as shown in SEQ ID NO. 1.

6. The aqueous liquid pharmaceutical formulation according to any one of claims 1-5, wherein the concentration of TACI-Fc fusion protein is 5-240 mg/ml, preferably about 50 mg/ml to about

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100 mg/ml, and most preferably about 80 mg/ml to about 100 mg/ml.

7. The aqueous liquid pharmaceutical formulation according to claim 6, wherein the non-reducing sugar is 90-120 mmol/L of mannitol and/or 35-45 mmol/L of sucrose, the amino acid is 75-125 mmol/L of arginine hydrochloride and/or 8-12 mmol/L of histidine hydrochloride, and the concentration of TACI-Fc fusion protein is 80-100 mg/ml; and the concentration of histidine hydrochloride is more preferably about 10 mmol/L.

8. The aqueous liquid pharmaceutical formulation according to any one of claims 1-7, comprising about 1% to about 10% (w/v, g/100 ml) of TACI-Fc fusion protein, preferably about 6-10% (w/v, g/100 ml) of TACI-Fc fusion protein.

9. The aqueous liquid pharmaceutical formulation according to claim 7 or 8, wherein the non-reducing sugar is about 90 mmol/L of mannitol and about 40 mmol/L of sucrose, the amino acid is about 90 mmol/L of arginine hydrochloride and about 10 mmol/L of histidine hydrochloride, and the concentration of TACI-Fc fusion protein is about 80 mg/ml.

10. The aqueous liquid pharmaceutical formulation according to claim 7 or 8, wherein the non-reducing sugar is about 120 mmol/L of mannitol and about 40 mmol/L of sucrose, the amino acid is about 75 mmol/L of arginine hydrochloride and about 10 mmol/L of histidine hydrochloride, and the concentration of TACI-Fc fusion protein is about 80 mg/ml.

11. The aqueous liquid pharmaceutical formulation according to any one of claims 1-10, wherein the formulation has a pH of 4.0 to 8.0, preferably 4.5 to 7.0, 5.0 to 6.0, or about 5.5.

12. The aqueous liquid pharmaceutical formulation according to any one of claims 1-11,

wherein two of the TACI-Fc fusion proteins in the aqueous liquid pharmaceutical formulation form a double-stranded structure via a linking disulfide bond formed in Fc hinge region.

13. A lyophilized pharmaceutical formulation obtained by lyophilization of the aqueous liquid pharmaceutical formulation according to any one of claims 1-12.

14. The lyophilized pharmaceutical formulation according to claim 13, wherein the aqueous liquid pharmaceutical formulation comprises about 90 mmol/L of mannitol, about 40 mmol/L of sucrose, about 90 mmol/L of arginine hydrochloride, about 10 mmol/L of histidine hydrochloride, and about 80 mg/ml of TACI-Fc fusion protein, and has a pH of 5.0 to 6.0.

15. The lyophilized pharmaceutical formulation according to claim 13, wherein the aqueous liquid pharmaceutical formulation comprises about 120 mmol/L of mannitol, about 40 mmol/L of sucrose, about 75 mmol/L of arginine hydrochloride, about 10 mmol/L of histidine hydrochloride, and about 80 mg/ml of TACI-Fc fusion protein, and has a pH of 5.0 to 6.0.

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 16.4 mg/ml and about 13.7 mg/ml, respectively; and the amino acids in the aqueous liquid pharmaceutical formulation are arginine hydrochloride and histidine hydrochloride at concentrations of about 19.0 mg/ml and about 2.1 mg/ml, respectively.

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 21.9 mg/ml and about 13.7 mg/ml, respectively; and the amino acids in the aqueous liquid pharmaceutical formulation are arginine hydrochloride and histidine hydrochloride

at concentrations of about 15.8 mg/ml and about 2.1 mg/ml, respectively.

18. Use of the pharmaceutical formulation according to any one of claims 1-17 in the manufacture of a medicament for the treatment of an autoimmune disease, wherein the autoimmune disease includes systemic lupus erythematosus, rheumatoid arthritis, neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS) and Sjogren's syndrome.

19. The use according to claim 18, wherein the neuromyelitis optica spectrum disorder includes neuromyelitis optica, recurrent optic neuritis, longitudinally extending transverse myelitis, optic-spinal form of multiple sclerosis, long-term transverse myelitis, unilateral or bilateral optic neuritis, optic neuritis or myelitis accompanying with autoimmune disease, optic neuritis or myelitis accompanying with symptomatic or asymptomatic intracranial lesions.

20. Use of the pharmaceutical formulation according to any one of claims 1-17 in the manufacture of a medicament for the treatment of lymphoma, wherein the lymphoma includes chronic lymphocytic leukemia, multiple myeloma and B lymphocyte lymphoma.

21. A method for preparing a TACI-Fc fusion protein pharmaceutical formulation, comprising: (1) preparing the formulation according to any one of claims 1-17; and (2) evaluating the stability of TACI-Fc fusion protein in the formulation.

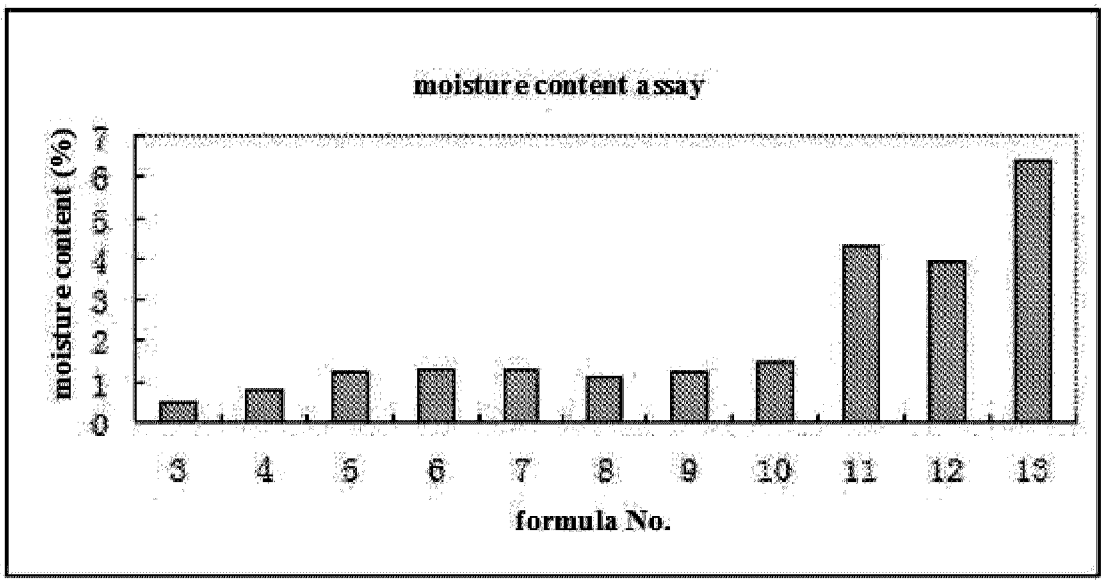

FIG. 1

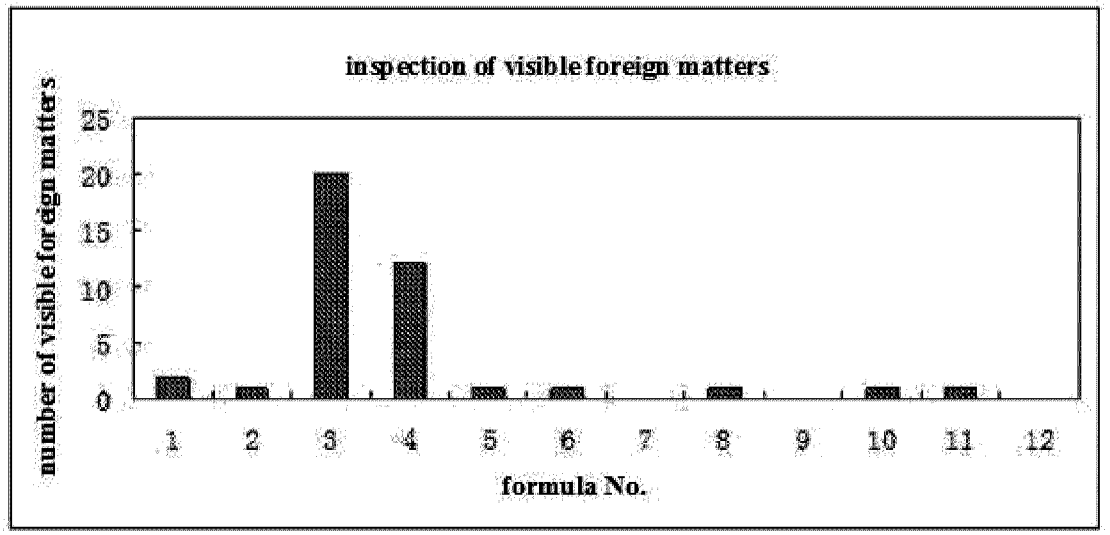

FIG. 2

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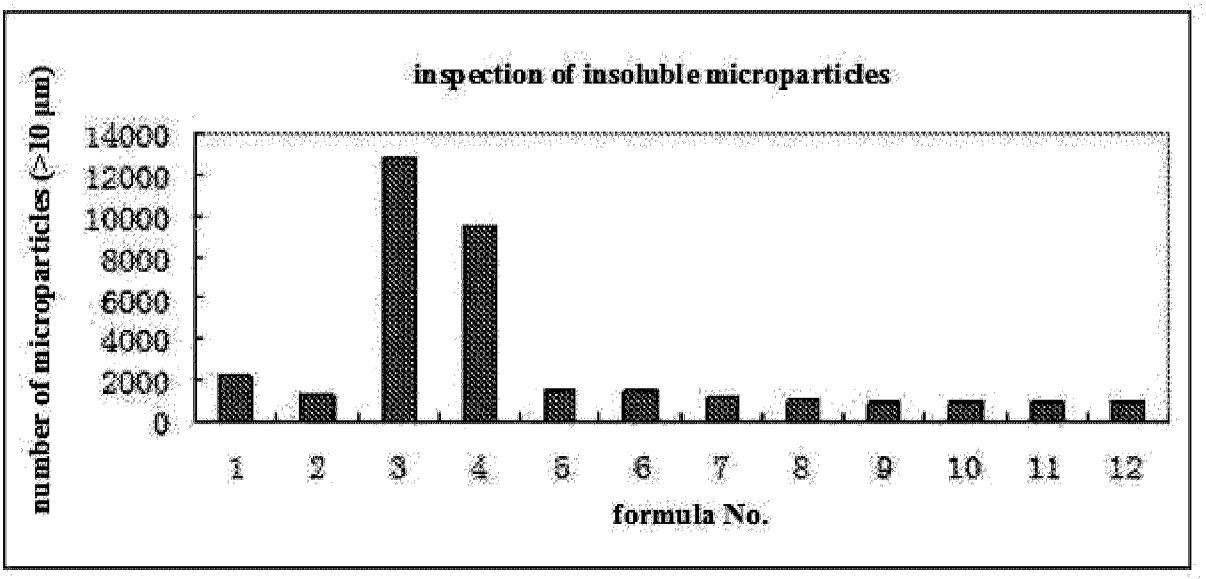
inspection of insoluble microparticles
number of microparticles (>10 μm)
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12000
10000
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5
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7
8
9
10
11
12
formula No.

FIG. 3

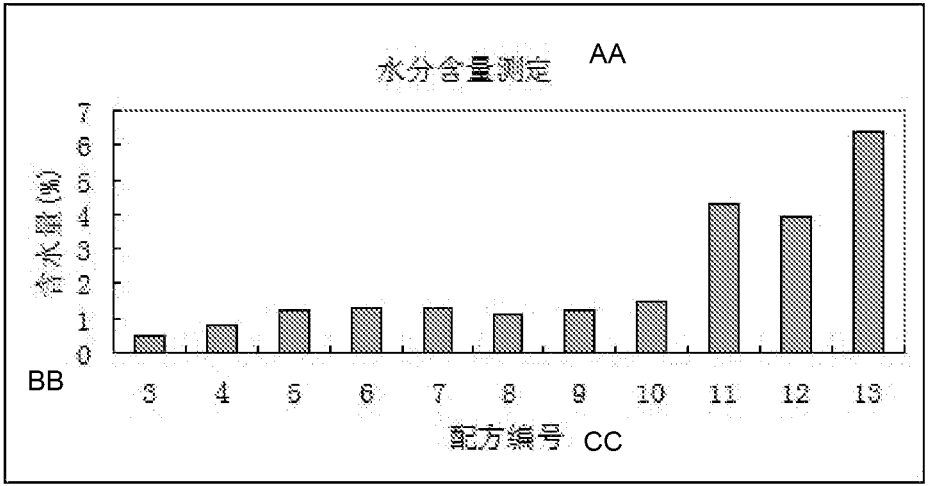

图 1

AA WATER CONTENT DETERMINATION
BB WATER CONTENT
CC FORMULATION NUMBER