SUMMARY

This disclosure provides an ophthalmic pharmaceutical composition, its methods of preparation, and its applications in preparing ophthalmic preparations for ameliorating the symptoms of DED and/or the improvement and/or the treatment of DED. The ophthalmic pharmaceutical composition of the disclosure has the advantages of causing minimal irritation, with high stability and a good safety profile.

This disclosure is achieved by the following technical scheme:

Firstly, the disclosure provides an ophthalmic pharmaceutical composition, which comprises of L-Alanyl-L-Glutamine suspended or dissolved in an acceptable isoosmotic ophthalmic solution. In one aspect, the present disclosure provides an ophthalmic pharmaceutical composition, which contains L-Alanyl-L-Glutamine.

Preferably, the concentration of L-Alanyl-L-Glutamine is in the range of 0.1-10% (w/v), preferably 1-10% (w/v), more preferably 1-5% (w/v), and most preferably 1% (w/v).

Preferably, the isoosmotic solution is prepared with an osmotic agent;

Preferably, the osmotic agent is selected from one or more of the following: sodium chloride, potassium chloride, boric acid, borax, sodium sulfate, potassium sulfate, sodium nitrate, potassium nitrate, sodium acetate, mannitol, glycerin, propylene glycol, 2-(4-octylphenylethyl)-2-amino-propylene glycol hydrochloride and glucose;

Preferably, the osmotic agent is selected from either or both sodium chloride and potassium chloride;

Preferably, the osmotic agent is sodium chloride;

Preferably, the concentration of the osmotic agent is 0.01-3% (w/v), preferably 0.1-1% (w/v), more preferably 0.4-0.8% (w/v), and most preferably 0.5%(w/v).

Preferably, the pharmaceutical composition optionally contains a bacteriostatic or antimicrobial agent;

Preferably, the bacteriostatic or antimicrobial agent is selected from one or more of the following: benzalkonium chloride, benzalkonium bromide, chlorhexidine acetate, chlorhexidine gluconate, chlorobutanol, phenoxyethyl alcohol, methyl hydroxybenzoate, ethyl hydroxybenzoate, propyl hydroxybenzoate;

Preferably, the bacteriostatic or antimicrobial agent is selected from one or more of the following: benzalkonium chloride, benzalkonium chloride benzalkonium bromide and ethyl hydroxybenzoate.

Preferably, the bacteriostatic or antimicrobial agent is ethyl hydroxybenzoate;

Preferably, the concentration of the bacteriostatic or antimicrobial agent is 0.003-0.5% (w/v), preferably 0.01-0.05% (w/v), more preferably 0.02-0.035% (w/v), most preferably 0.03%(w/v).

Preferably, the pharmaceutical composition optionally includes a viscosity modifying agent;

Preferably, the viscosity modifying agent is selected from one or more of the following:

sodium hyaluronate, sodium carboxymethyl cellulose, methyl cellulose, polyethylene glycol, polyvinyl alcohol and povidone;

Preferably, the viscosity modifying agent is selected from either or both sodium hyaluronate and sodium carboxymethyl cellulose;

Preferably, the viscosity modifying agent is sodium hyaluronate.

Preferably, the concentration of the viscosity modifying agent is 0.01-0.5% (w/v), preferably 0.05-0.2% (w/v), more preferably 0.1-0.15% (w/v), most preferably 0.1%(w/v).

Preferably, the pharmaceutical composition also includes one or more pH regulators selected from the following: sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, boric acid, borax, acetic acid, sodium acetate, citric acid, sodium citrate, tartaric acid, sodium tartrate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, hydrochloric acid and phosphoric acid. The pH regulator adjusts the pH value to 5.0-9.0, preferably to 6.0-8.0, more preferably to 6.5-7.5, and most preferably to 7.0;

Preferably, the pH adjusting agent is selected from one or more of the following: sodium carbonate, sodium bicarbonate and sodium hydroxide.

Preferably, the pH adjusting agent is sodium hydroxide;

Preferably, the concentration of sodium hydroxide is 0.25 mol/L.

Secondly, the disclosure also provides a method for preparing the pharmaceutical composition. In one aspect, the disclosure provides a method for preparing the pharmaceutical composition as described herein, which contains suspending or dissolving L-Alanyl-L-Glutamine in an iso-osmotic solution and adjusting the pH to 5.0-9.0, preferably 6.0 -8.0, more preferably to 6.5-7.5, most preferably to 7.0; the resulting solution is filtered through a microporous membrane and sterilized:

Preferably, the method includes adding the osmotic agent to water for injection and stirring and dissolving it, preferably at 80-90°C, most preferably at 85°C; and then adding gamma dipeptide, stirring and dissolving before adding water for injection; then adding pH adjusting agent to adjust the pH value to 5.0-9.0, preferably 6.0-8.0, more preferably 6.5-7.5, most preferably 7.0; after boiling and sterilizing at 100°C, it is filtered by a microporous membrane and sterilized, and then packed into sterilized eye drops vials in a sterile environment;

Preferably, the method includes successively dissolving the osmotic agent, the bacteriostatic agent and the water for injection in such order for stirring and dissolution, preferably at 80-90°C, most preferably at 85°C, and after it dissolves, we can optionally add viscosity increasing agent, continue to stir until it dissolves, then add L-Alanyl-L-Glutamine, stir to let it dissolve, add water for injection, add pH adjusting agent to adjust the final pH to 5.0-9.0, preferably 6.0-8.0, more preferably 6.5-7.5, most preferably to

7.0; boil disinfect it to 100°, then filter it through a microporous membrane, sterilize it, and pack it into sterilized eye drops vials in a sterile environment;

Preferably, the microporous filter membrane is a 0.22 μm microporous filter membrane. The method comprises of the following steps: suspending or dissolving the propionic dipeptide in an isoosmotic solution; adjusting the pH value to 5.0-9.0, preferably to 6.0-8.0, more preferably to 6.5-7.5, and most preferably to 7.0; and filtering to sterilize the solution with a microporous filter membrane;

Preferably, the method comprises of the following steps: stirring and dissolving the osmotic agent with water for injection, preferably at 80-90°C, most preferably at 85°C; adding L-Alanyl-L-Glutamine and stirring to dissolve; adding water for injection; adjusting the pH value to 5.0-9.0 with pH adjusting agent, preferably to 6.0-8.0, more preferably to 6.5-7.5, most preferably to 7.0; heating to sterilize at 100°C; filtering to sterilize with a microporous filter membrane; and filling into sterilized eye drops bottles in a aseptic manufacturing environment;

Preferably, the method comprises of the following steps: stirring and dissolving osmotic agents and bacteriostatic or antimicrobial agents with water for injection, preferably at 80-90°C, most preferably at 85°C; after dissolving, optionally adding a viscosity modifying agent while stirring and continuing to stir until dissolved; adding L-Alanyl-L-Glutamine and stirring to dissolve; adding water for injection; adjusting the final pH value to 5.0-9.0 with pH adjusting agent, preferably to 6.0-8.0, more preferably to 6.5-7.5, most preferably to 7.0; heating to sterilize at 100°C; filtering to sterilize with a microporous filter membrane; and filling into sterilized eye drops bottles under aseptic

manufacturing environment;

Thirdly, the present disclosure also provides applications of the above pharmaceutical composition in preparing ophthalmic preparations for ameliorating the symptoms of DED and/or improving DED and/or treating DED. In one aspect, the disclosure provides use of the pharmaceutical composition as described herein in the preparation of an ophthalmic preparation for alleviating and/or improving dry eye conditions and/or treating dry eye. In another aspect, the disclosure provides use of the pharmaceutical composition as described herein in the manufacture of a medicament for relieving and /or ameliorating dry eye conditions and / or treating dry eyes of a patient in need.

DRAWINGS

Figure 1 shows the statistical analysis of tear secretion in mice. NS represented normal group, DS5 represented DED group, DS5+Vehicle represented solvent control group, and DS5+AG represented treatment group; *P<0.05; ** P<0.01; ***P<0.001;

Figure 2 shows the statistics of the number of conjunctival goblet cells in mice. NS represented the normal group, DS5 represented the DED group, DS5+Vehicle represented the solvent control DED group, and DS5+AG represented the DED treatment group treated with ophthalmic preparation; *P<0.05 ; **P<0.01; ***P<0.001;

Figure 3 shows the corneal epithelial defect in mice. Figure 3A was a typical image of mouse corneal OGD staining. Figure 3B was the statistics of the fluorescence intensity of mouse corneal OGD staining. NS represented normal group, DS5 represented DED group, DS5+ Vehicle represented the solvent control group, and DS5+AG represented the DED treatment group; *P<0.05; **P<0.01; ***P<0.001.

DETAILED DESCRIPTION

The technical solutions of this invention will be specified in the form of embodiments below, but the following examples or experimental examples do not limit the scope of the present invention.

Unless otherwise specified, the embodiments in the following examples are conventional methods, and the raw materials and reagent materials used in the following examples are all commercially available products.

Preparation example 1

1. Pharmaceutical composition

Sodium hyaluronate	1.0 g
Ethyl hydroxybenzoate	0.3 g
Sodium chloride	5.0 g
L-Alanyl-L-Glutamine	10.0 g
Water for injection	Add water until total volume reaches 1000mL
pH	Adjust pH to 7.0 with 0.25 mol/L sodium hydroxide

2. Preparation method

Weigh sodium chloride and ethyl hydroxybenzoate, then add 800 mL (85℃) of water and stir to dissolve. After dissolving, add sodium hyaluronate while stirring and continue to stir until dissolved, then add L-Alanyl-L-Glutamine and stir to dissolve.

Claims

1. An ophthalmic pharmaceutical composition, which contains L-Alanyl-L-Glutamine.

2. The pharmaceutical composition as described in Claim 1, which contains L-Alanyl-L-Glutamine suspended or dissolved in an ophthalmically acceptable iso-osmotic solution.

3. The pharmaceutical composition as described in Claim 1 or 2, which is characterized in that the concentration of the L-Alanyl-L-Glutamine is 0.1-10% (w/v), preferably 1-10% (w/v), more preferably 1-5% (w/v), most preferably 1%(w/v).

4. The pharmaceutical composition as described in any one of claims 1 to 3, which is characterized in that the iso-osmotic solution is prepared from an osmotic agent;

Preferably, the osmotic agent is one or more selected from sodium chloride, potassium chloride, boric acid, borax, sodium sulfate, potassium sulfate, sodium nitrate, potassium nitrate, sodium acetate, mannitol, glycerin, propylene glycol, 2-(4-n-octylphenethyl)-2-amino-propylene glycol hydrochloride and glucose;

Preferably, the osmotic agent is one or more selected from sodium chloride and potassium chloride;

Preferably, the osmotic agent is sodium chloride;

Preferably, the concentration of the osmotic agent is 0.01-3% (w/v), preferably 0.1-1% (w/v), more preferably 0.4-0.8% (w/v), most preferably 0.5% (w/v).

5. The pharmaceutical composition as described in any one of claims 1 to 4, which is characterized in that the pharmaceutical composition optionally contains a bacteriostatic agent;

Preferably, the bacteriostatic agent is one or more selected from benzalkonium chloride, benzalkonium bromide, chlorhexidine acetate, chlorhexidine gluconate, chlorobutanol, phenoxyethanol, methyl hydroxybenzoate, ethyl hydroxybenzoate and propyl hydroxybenzoate;

Preferably, the bacteriostatic agent is one or more selected from benzalkonium chloride, benzalkonium bromide and ethyl hydroxybenzoate;

Preferably, the bacteriostatic agent is ethyl hydroxybenzoate;

Preferably, the concentration of the bacteriostatic agent is 0.003-0.5% (w/v), preferably 0.01-0.05%
(w/v), more preferably 0.02-0.035% (w/v), most preferably 0.03% (w/v).

6. The pharmaceutical composition as described in any one of claims 1 to 5, which is characterized in that the pharmaceutical composition optionally includes a viscosity increasing agent;

Preferably, the viscosity increasing agent is one or more selected from sodium hyaluronate, sodium carboxymethyl cellulose, methyl cellulose, polyethylene glycol, polyvinyl alcohol and povidone;

Preferably, the viscosity increasing agent is one or more selected from one or more of sodium hyaluronate and sodium carboxymethyl cellulose;

Preferably, the viscosity increasing agent is sodium hyaluronate;

Preferably, the concentration of the viscosity increasing agent is 0.01-0.5% (w/v), preferably 0.05-0.2% (w/v), more preferably 0.1-0.15% (w/v), most preferably 0.1% (w/v).

7. The pharmaceutical composition as described in any one of claims 1 to 6, which is characterized in that the pharmaceutical composition contains one or more pH adjusting agents selected from sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, boric acid, borax, acetic acid, sodium acetate, citric acid, sodium citrate, tartaric acid, sodium tartrate, sodium carbonate, potassium carbonate, sodium bicarbonate , Potassium bicarbonate, sodium hydroxide, potassium hydroxide, hydrochloric acid and phosphoric acid, and the said pH adjusting agents adjust the pH value to 5.0-9.0, preferably 6.0-8.0, more preferably 6.5-7.5, most preferably 7.0;

Preferably, the pH adjusting agents are one or more selected from sodium carbonate, sodium bicarbonate, and sodium hydroxide;

Preferably, the pH adjusting agent is sodium hydroxide;

Preferably, the concentration of the sodium hydroxide is 0.25 mol/L.

8. A method for preparing the pharmaceutical composition as described in any one of claims 1 to 7, which contains suspending or dissolving L-Alanyl-L-Glutamine in an iso-osmotic solution and adjusting the pH to 5.0-9.0, preferably 6.0 -8.0, more preferably to 6.5-7.5, most preferably to 7.0; the resulting solution is filtered through a microporous membrane and sterilized:

Preferably, the method includes adding the osmotic agent to water for injection and stirring and dissolving it, preferably at 80-90°C, most preferably at 85°C; and then adding gamma dipeptide, stirring and dissolving before adding water for injection; then adding pH adjusting agent to adjust the pH value to 5.0-9.0, preferably 6.0-8.0, more preferably 6.5-7.5, most preferably 7.0; after boiling and sterilizing at 100°C, it is filtered by a microporous membrane and sterilized, and then packed into sterilized eye drops vials in a sterile environment;

Preferably, the method includes successively dissolving the osmotic agent, the bacteriostatic agent and the water for injection in such order for stirring and dissolution, preferably at 80-90°C, most preferably at 85°C, and after it dissolves, we can optionally add viscosity increasing agent, continue to stir until it dissolves, then add L-Alanyl-L-Glutamine, stir to let it dissolve, add water for injection, add pH adjusting agent to adjust the final pH to 5.0-9.0, preferably 6.0-8.0, more preferably 6.5-7.5, most preferably to 7.0; boil disinfect it to 100°, then filter it through a microporous membrane, sterilize it, and pack it into sterilized eye drops vials in a sterile environment;

Preferably, the microporous filter membrane is a 0.22 μm microporous filter membrane.

9. Use of the pharmaceutical composition as described in any one of claims 1 to 8 in the preparation of an ophthalmic preparation for alleviating and/or improving dry eye conditions and/or treating dry eye.

10. Use of the pharmaceutical composition as described in any one of claims 1 to 7 in the manufacture of a medicament for relieving and /or ameliorating dry eye conditions and / or treating dry eyes of a patient in need.

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