

ATROPINE EYE DROPS AND PREPARATION METHOD THEREFOR

TECHNICAL FIELD

[0001] The present application belongs to the field of medicine, and specifically
5 relates to an atropine eye drop and a preparation method therefor.

BACKGROUND

[0002] Atropine is a natural compound that can be extracted from belladonna or
other plants of the Solanaceae family. In clinical medicine, atropine is primarily
10 used to relieve smooth muscle spasms, improve microcirculation, inhibit
glandular secretion, and relieve vagal inhibition on the heart. Atropine sulfate
is a salt form of atropine. Clinical data indicates that ophthalmic preparations of
atropine sulfate have effective pharmacological actions, exhibiting high
selectivity for muscarinic (M) receptors and blocking M cholinergic receptors.
15 This leads to the relaxation of the sphincter pupillae and ciliary muscles, forming
a pupil dilation mechanism and alleviating pain caused by swelling and
inflammation of the eyes.

[0003] Years of research have confirmed that atropine ophthalmic preparations
can relax the tense ciliary muscles of adolescents and children and further restore
20 their regulatory functions during sleep, effectively delaying and treating the
progression of myopia. However, currently commercially available atropine

ophthalmic preparations (such as Myopine, Atropine, Latropine, and USP1%) tend to decompose during storage. The formation of related substances (such as tropic acid, dehydrated atropine, any single unknown related substance, and the total amount of related substances) can affect the efficacy and safety of the drug.

- 5 [0004] Therefore, developing an atropine ophthalmic drug with good storage stability is an urgent technical problem to be solved in this field.

CONTENT OF THE PRESENT INVENTION

[0005] Problem to be Solved by the Invention

- 10 [0006] In view of the deficiencies in the prior art, the present disclosure provides atropine eye drops, which, through the selection of raw materials and optimization of prescription, exhibit good stability and low total impurities.

- [0007] Furthermore, the present disclosure also provides a preparation method for the atropine eye drops. The atropine eye drops prepared by this method
15 demonstrate good stability and low total impurities, making it suitable for long-term storage.

[0008] Solution to the Problem

- [0009] The present disclosure provides an atropine eye drop comprising the following components: by mass concentration, atropine or a pharmaceutically
20 acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, a pH regulator, and water for

injection;

[0010] wherein the pH regulator is a combination of citric acid and borax, or a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, and the amount of the pH regulator used is based on
5 adjusting the pH value to 4.5 to 5.5.

[0011] Preferably, by mass concentration, in the combination of citric acid and borax, citric acid is 0.50 to 2.00 g/L and borax is 1.00 to 2.00 g/L;

[0012] by mass concentration, in the combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, sodium
10 dihydrogen phosphate is 1.49 to 6.00 g/L, disodium hydrogen phosphate is 0.43 to 0.88 g/L, and hydrochloric acid is 0.04 to 0.13 g/L.

[0013] Further preferably, the atropine eye drop of the present disclosure comprises the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at
15 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, citric acid at 0.50 g/L, borax at 1.05 g/L, and water for injection.

[0014] Further preferably, the atropine eye drop of the present disclosure comprises the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at
20 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, sodium dihydrogen phosphate at 1.95 g/L, disodium hydrogen phosphate at 0.56 g/L,

hydrochloric acid at 0.076 g/L, and water for injection.

[0015] Preferably, in the atropine eye drop of the present disclosure, the pharmaceutically acceptable salt is sulfate.

[0016] Preferably, in the atropine eye drop of the present disclosure, the
5 chelating agent comprises one or a combination of two or more of disodium edetate, sodium calcium edetate, and edetic acid.

[0017] Further preferably, in the atropine eye drop of the present disclosure, the chelating agent is disodium edetate.

[0018] Preferably, in the atropine eye drop of the present disclosure, the osmotic
10 pressure regulator comprises one or a combination of two or more of sodium chloride, mannitol, and glycerol;

[0019] further preferably, in the atropine eye drop of the present disclosure, the osmotic pressure regulator is sodium chloride.

[0020] The present disclosure provides a preparation method for the atropine
15 eye drop as described herein, comprising the following steps:

[0021] dissolving a prescribed amount of the chelating agent, osmotic pressure regulator, and pH regulator in the water for injection to obtain solution A;

[0022] adding a prescribed amount of the atropine or the pharmaceutically acceptable salt thereof to the solution A to obtain solution B;

20 [0023] filtering the solution B and filling it into a bottle to obtain the atropine eye drop.

[0024] Preferably, in the preparation method of the present disclosure, the water for injection is at a temperature of 40°C or less.

[0025] Further preferably, in the preparation method of the present disclosure, the water for injection is at a temperature of 21.4 to 24.4°C.

5 **[0026]** Preferably, in the preparation method of the present disclosure, the solution B is filtered through a microfiltration membrane with a pore size of 0.22 µm, and the microfiltration membrane is a PVDF membrane.

[0027] Effect of the Invention

[0028] The atropine eye drops provided by the present disclosure, through the
10 selection of specific chelating agents and osmotic pressure regulators, combined with pH regulators, achieve the beneficial effects of product stability and reduced impurities, making it suitable for long-term storage. Surprisingly, compared to commercially available atropine eye drops, the atropine eye drops provided by the present disclosure have undergone stability tests such as 30-day influencing
15 factor test and 6-month accelerated test, showing significantly lower total impurity content compared to commercial products like Myopine, Atropine, and Latropine. The prescription of the present disclosure demonstrates an unexpected technical effect in terms of stability.

[0029] Further, the atropine eye drops provided by the present disclosure do not
20 contain thickening agents or preservatives, resulting in low toxicity; the pH value is closer to neutral, causing no irritation to the eyes.

[0030] Further, the atropine eye drops provided by the present disclosure use a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid as pH regulators, enhancing safety and suitability for long-term use in children.

- 5 **[0031]** Further, the preparation method for the atropine eye drops provided by the present disclosure results in a product with good stability and low total impurities, making it suitable for long-term storage.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

- 10 **[0032]** The various exemplary embodiments, features, and aspects of the present disclosure will be described in detail below. The term "exemplary" used herein means "serving as an example, embodiment, or illustrative". Any embodiment described herein as "exemplary" should not necessarily be construed as superior to or better than other embodiments.

- 15 **[0033]** Additionally, in order to better illustrate the present disclosure, numerous specific details are provided in the following specific embodiments. It should be understood by those skilled in the art that the present disclosure can be implemented without some of these specific details. In other examples, detailed descriptions of methods, means, equipment, and steps well known to those skilled
20 in the art are not described in detail to emphasize the essence of the present disclosure.

[0034] Unless otherwise specified, the units used in this specification are international standard units, and the numerical values and ranges appearing in the present disclosure should be understood to include the systemic errors inevitable in industrial production.

5 **[0035]** In this specification, a numerical range denoted as "numerical value A to numerical value B" refers to a range that includes the endpoint values A and B.

[0036] In this specification, "optional" or "optionally" indicates that the subsequent described event or situation may or may not occur, and this description includes both the situations where the event occurs and where the event does not
10 occur.

[0037] In this specification, the use of "may" encompasses both the meaning of conducting a certain process and not conducting a certain process.

[0038] In this specification, the terms "some specific/preferred embodiments", "other specific/preferred embodiments", and "embodiments" refer to the
15 particular elements (for example, features, structures, properties, and/or characteristics) related to the described embodiment being included in at least one embodiment described herein, and they may or may not be present in other embodiments. Furthermore, it should be understood that the described elements can be combined in various embodiments in any suitable manner.

20 **[0039]** [Atropine eye drops]

[0040] The present disclosure provides atropine eye drops comprising the

following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, a pH regulator, and water for injection;

- 5 **[0041]** wherein the pH regulator is a combination of citric acid and borax, or a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, and the amount of the pH regulator used is based on adjusting the pH value to 4.5 to 5.5.

10 **[0042]** In some specific embodiments of the present disclosure, in the combination of citric acid and borax, by mass concentration, citric acid is 0.50 to 2.00 g/L, and borax is 1.00 to 2.00 g/L; in the combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, by mass concentration, sodium dihydrogen phosphate is 1.49 to 6.00 g/L, disodium hydrogen phosphate is 0.43 to 0.88 g/L, and hydrochloric acid is 0.04 to 0.13 g/L.

- 15 **[0043]** The atropine eye drops provided by the present disclosure, through the selection of raw materials and optimization of prescription, have good stability, low total impurities, and are suitable for long-term storage; moreover, the pH value is 4.5 to 5.5, which is closer to neutral, causing no irritation to the eyes.

20 **[0044]** In some preferred embodiments of the present disclosure, the atropine eye drops comprise the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent

at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, a pH regulator, and water for injection;

[0045] wherein the pH regulator is a combination of citric acid and borax, or a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid; by mass concentration, citric acid is 0.50 to 2.00 g/L, borax is 1.00 to 2.00 g/L, sodium dihydrogen phosphate is 1.49 to 6.00 g/L, disodium hydrogen phosphate is 0.43 to 0.88 g/L, and hydrochloric acid is 0.04 to 0.13 g/L.

[0046] The present disclosure further optimizes the above prescription so that it does not contain thickening agents (such as hydroxypropyl methylcellulose (60SH)), which can avoid the impact of thickening agents on product stability; and it also does not contain preservatives (such as benzalkonium chloride), thereby enhancing safety and reducing toxicity.

[0047] Atropine or pharmaceutically acceptable salt thereof

[0048] Atropine drugs are currently the most effective in preventing myopia in adolescents and children, which can relax the tense ciliary muscles and further restore their regulatory functions during sleep.

[0049] In some specific embodiments of the present disclosure, by mass concentration, atropine or a pharmaceutically acceptable salt thereof ranges from 0.10 to 0.20 g/L. Exemplarily, the mass concentration can be 0.10 g/L, 0.12 g/L, 0.14 g/L, 0.15 g/L, 0.16 g/L, 0.18 g/L, 0.20 g/L, etc. Clinical research has found that within a certain range, the higher the concentration of atropine or the

pharmaceutically acceptable salt thereof, the better its effectiveness in preventing and/or treating myopia. However, excessively high concentrations (such as 1% concentration, 0.5% concentration, and 0.1% concentration, with mass concentrations of 10 g/L, 5 g/L, and 1 g/L, respectively) are accompanied by numerous adverse reactions, such as strong mydriasis and increased intraocular pressure. In contrast, low-concentration eye drops ensure a good effect in preventing and/or treating myopia while minimizing adverse reactions. Studies have shown that 0.01% concentration (mass concentration of 0.1 g/L) of atropine eye drops are suitable for the correction of progressive myopia in children and adolescents; a 0.02% concentration (mass concentration of 0.2 g/L) represents the highest concentration that does not produce noticeable adverse clinical symptoms.

[0050] In some preferred embodiments of the present disclosure, atropine or the pharmaceutically acceptable salt thereof has a mass concentration of 0.10 g/L or 0.20 g/L.

[0051] In some preferred embodiments of the present disclosure, the pharmaceutically acceptable salt is sulfate (i.e., atropine sulfate).

[0052] Chelating agent

[0053] Considering that the packaging material for atropine eye drops may be made of low-density polyethylene, whose raw material contains metal elements harmful to the human body, and during actual production, the mixing tanks and production pipelines are made of stainless steel, which may introduce metal ions,

and trace heavy metals can catalyze the decomposition of the active ingredients in atropine eye drops through oxidation or other mechanisms, adding a chelating agent can form a stable complex with various metal ions and prevent the decomposition of the active ingredients, so that the atropine eye drops can have
5 good stability and low total impurities.

[0054] In some specific embodiments of the present disclosure, the chelating agent comprises one or a combination of two or more of disodium edetate, sodium calcium edetate, and edetic acid.

[0055] In some preferred embodiments of the present disclosure, the chelating
10 agent is disodium edetate.

[0056] In some specific embodiments of the present disclosure, the chelating agent has a mass concentration of 0 to 1.00 g/L. Exemplarily, the mass concentration can be 0, 0.10 g/L, 0.20 g/L, 0.40 g/L, 0.50 g/L, 0.60 g/L, 0.80 g/L, 1.00 g/L, etc.

15 **[0057]** Osmotic pressure regulator

[0058] Osmotic pressure regulators are used to control the osmotic pressure of atropine eye drops within an appropriate range.

[0059] In some specific embodiments of the present disclosure, the osmotic pressure regulator comprises one or a combination of two or more of sodium
20 chloride, mannitol, and glycerol.

[0060] In some preferred embodiments of the present disclosure, the osmotic

pressure regulator is sodium chloride. The stability of atropine eye drops using sodium chloride as an osmotic pressure regulator is superior to those using mannitol or glycerol.

- [0061]** The human eye can tolerate a wide range of osmotic pressures, equivalent to the osmotic molar concentration of a 0.5 to 1.5% w/v sodium chloride solution. Ideally, eye drops should be isotonic with tears, equivalent to a 0.09% w/v sodium chloride solution. Considering that other salt components in atropine eye drops also affect the osmotic pressure, the amount of the osmotic pressure regulator used should be comprehensively examined. In some specific embodiments of the present disclosure, the osmotic pressure regulator has a mass concentration of 7.80 to 9.00 g/L. Exemplarily, the mass concentration can be 7.80 g/L, 8.00 g/L, 8.20 g/L, 8.40 g/L, 8.60 g/L, 8.80 g/L, 9.00 g/L, etc. When the mass concentration is below 7.80 g/L or above 9.00 g/L, it can lead to osmotic pressure exceeding the tolerable range of the human eye, causing discomfort.
- [0062]** In some preferred embodiments of the present disclosure, the osmotic pressure regulator has a mass concentration of 8.30 g/L and 8.70 g/L.

[0063] pH regulator

- [0064]** pH regulators are used to regulate the pH value of atropine eye drops to 4.5 to 5.5, making it close to neutral and non-irritating to the eyes. The molecular structure of atropine or atropine sulfate contains an ester group, which is prone to hydrolysis at high pH values, with tropic acid and tropine as its

hydrolysis products, leading to quality issues in the eye drops.

[0065] In some specific embodiments of the present disclosure, the pH regulator is a combination of citric acid and borax.

[0066] In other specific embodiments of the present disclosure, the pH regulator
5 is a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid.

[0067] Specifically:

[0068] When the pH regulator is a combination of citric acid and borax, in some specific embodiments of the present disclosure, the atropine eye drops comprise
10 the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, citric acid at 0.50 to 2.00 g/L, borax at 1.00 to 2.00 g/L, and water for injection.

[0069] In some preferred embodiments of the present disclosure, the atropine
15 eye drops comprise the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, citric acid at 0.50 g/L, borax at 1.05 g/L, and water for injection.

[0070] In some more preferred embodiments of the present disclosure, the
20 atropine eye drops comprise the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 g/L, a chelating

agent at 1.00 g/L, an osmotic pressure regulator at 8.70 g/L, anhydrous citric acid at 0.50 g/L, borax at 1.05 g/L, and water for injection.

[0071] In other more preferred embodiments of the present disclosure, the atropine eye drops comprise the following components: by mass concentration,
5 atropine or a pharmaceutically acceptable salt thereof at 0.20 g/L, a chelating agent at 1.00 g/L, an osmotic pressure regulator at 8.70 g/L, anhydrous citric acid at 0.50 g/L, borax at 1.05 g/L, and water for injection.

[0072] When the pH regulator is a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, in some specific
10 embodiments of the present disclosure, the atropine eye drops comprise the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, sodium dihydrogen phosphate at 1.49 to 6.00 g/L, disodium hydrogen phosphate at 0.43 to 0.88 g/L, hydrochloric
15 acid at 0.04 to 0.13 g/L, and water for injection.

[0073] When the concentrations of sodium dihydrogen phosphate and disodium hydrogen phosphate exceed 6.00 g/L and 0.88 g/L respectively, they can cause an increase in the impurity content in the eye drops. Moreover, these two phosphates themselves exert a certain osmotic pressure. If used in large amounts,
20 in order to achieve isotonicity, the amount of the osmotic pressure regulator used needs to be adjusted. The osmotic pressure regulator (especially sodium

chloride) has a certain stabilizing effect on atropine or atropine sulfate and can inhibit the growth of tropic acid. Therefore, in order to ensure the stability of atropine eye drops, it is necessary to collaboratively adjust the amounts of both phosphates and the osmotic pressure regulator. In the eye drops of the present disclosure, the mass concentrations of sodium dihydrogen phosphate, disodium hydrogen phosphate, and the osmotic pressure regulator are 1.49 to 6.00 g/L, 0.43 to 0.88 g/L, and 7.80 to 9.00 g/L, respectively.

[0074] In some preferred embodiments of the present disclosure, the atropine eye drops comprise the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, sodium dihydrogen phosphate at 1.95 g/L, disodium hydrogen phosphate at 0.56 g/L, hydrochloric acid at 0.076 g/L, and water for injection.

[0075] In some more preferred embodiments of the present disclosure, the atropine eye drops comprise the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 g/L, a chelating agent at 1.00 g/L, an osmotic pressure regulator at 8.30 g/L, sodium dihydrogen phosphate at 1.95 g/L, disodium hydrogen phosphate at 0.56 g/L, hydrochloric acid at 0.076 g/L, and water for injection.

[0076] In other more preferred embodiments of the present disclosure, the atropine eye drops comprise the following components: by mass concentration,

atropine or a pharmaceutically acceptable salt thereof at 0.20 g/L, a chelating agent at 1.00 g/L, an osmotic pressure regulator at 8.30 g/L, sodium dihydrogen phosphate at 1.95 g/L, disodium hydrogen phosphate at 0.56 g/L, hydrochloric acid at 0.076 g/L, and water for injection.

- 5 **[0077]** In some preferred embodiments of the present disclosure, the dosage specification of the atropine eye drops is 0.5 mL per bottle, which is suitable for single-dose administration to one eye for users, eliminating the issue of drug contamination and enhancing safety and reliability.

[0078] [Preparation method]

- 10 **[0079]** The present disclosure provides a preparation method for the atropine eye drops, comprising the following steps:

[0080] dissolving a prescribed amount of chelating agent, osmotic pressure regulator, and pH regulator in water for injection to obtain solution A;

- [0081]** adding a prescribed amount of atropine or a pharmaceutically acceptable salt thereof to solution A to obtain solution B;
- 15

[0082] filtering solution B and filling it into a bottle to obtain the atropine eye drops.

[0083] The atropine eye drops prepared by this method exhibit good stability, low total impurities, and are suitable for long-term storage.

- 20 **[0084]** The mixing temperature affects the stability of the atropine eye drops. In some specific embodiments of the present disclosure, the water for injection

(i.e., the mixing temperature) is controlled at a temperature of 40°C or less, preferably 21.4 to 24.4°C. Exemplarily, the temperature can be 21.4°C, 22.5°C, 24.4°C, etc.

[0085] In some specific embodiments of the present disclosure, solution A has a
5 pH value of 4.99 to 5.01. Exemplarily, the pH value can be 4.99, 5.00, 5.01, etc.

[0086] In some specific embodiments of the present disclosure, solution B has a pH value of 4.98 to 5.01. Exemplarily, the pH value can be 4.98, 5.00, 5.01, etc.

[0087] In some specific embodiments of the present disclosure, solution B is
10 filtered through a microfiltration membrane with a pore size of 0.22 µm. The purpose of filtering through a microfiltration membrane is to sterilize, ensuring that the product meets the standards, as atropine eye drops are sterile preparations. In some specific embodiments of the present disclosure, at least two microfiltration membranes are used for enhanced sterilization effectiveness.

15 **[0088]** In some specific embodiments of the present disclosure, the microfiltration membrane is a PVDF membrane. If a microfiltration membrane made of other materials is used, it might introduce impurities.

[0089] The pH regulator is a combination of citric acid and borax, or a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate,
20 and hydrochloric acid.

[0090] Specifically, when the pH regulator is a combination of citric acid and

borax, the term "combination of citric acid and borax" refers to the solute form of the pH regulator in the atropine eye drops. In the actual preparation process, the raw materials added can be a mixture of anhydrous citric acid or a hydrate thereof and borax or a hydrate thereof. Specifically, it can be a mixture of anhydrous citric acid and borax, or a mixture of citric acid monohydrate and borax decahydrate, with the amount added based on the mass concentration of the solute.

5 [0091] In some more specific embodiments of the present disclosure, the preparation method for atropine eye drops comprises the following steps:

[0092] measuring an appropriate amount of water for injection, and controlling
10 the temperature to 21.4 to 22.5°C;

[0093] adding a prescribed amount of stabilizer, osmotic pressure regulator, anhydrous citric acid, and borax; stirring to dissolve, with a stirring speed of 50 to 300 rpm for 10 to 30 minutes; then adding an appropriate amount of water for injection to the preset volume to obtain solution A, at which time the pH value of
15 the system is 4.99 to 5.01;

[0094] adding a prescribed amount of atropine or the pharmaceutically acceptable salt thereof to solution A with a stirring speed of 50 to 300 rpm for 10 to 30 minutes to obtain solution B, at which time the pH value of the system is 4.7 to 5.3;

20 [0095] filtering solution B through a microfiltration membrane; after passing quality inspection, filling the solution into a bottle, sealing the bottle, and thereby

obtaining the atropine eye drops.

[0096] When the pH regulator is a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, similarly, the term "combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid" refers to the solute form of the pH regulator in the atropine eye drops. In the actual preparation process, the raw materials added can be a mixture of sodium dihydrogen phosphate or a hydrate thereof, disodium hydrogen phosphate or a hydrate thereof, and hydrochloric acid, such as a mixture of sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dihydrate, and hydrochloric acid; wherein the hydrochloric acid can be commercially available concentrated hydrochloric acid or diluted hydrochloric acid of other concentrations prepared in-house.

[0097] In some more specific embodiments of the present disclosure, the preparation method for atropine eye drops comprises the following steps:

[0098] preparing 0.1 to 1 mol/L hydrochloric acid for later use;

[0099] measuring an appropriate amount of water for injection, and controlling the temperature to 24.4°C;

[0100] adding a prescribed amount of stabilizer, osmotic pressure regulator, sodium dihydrogen phosphate dihydrate, and disodium hydrogen phosphate dihydrate; stirring to dissolve, with a stirring speed of 50 to 300 rpm for 10 to 30 minutes, at which time the pH value of the system is 5.86 to 5.87; adding the

prepared hydrochloric acid to adjust the pH value to 5.00; then adding an appropriate amount of water for injection to the preset volume to obtain solution A, at which time the pH value of the system is 5.00 to 5.01;

[0101] adding a prescribed amount of atropine or the pharmaceutically acceptable salt thereof to solution A with a stirring speed of 50 to 300 rpm for 10 to 30 minutes to obtain solution B, at which time the pH value of the system is 5.01;

[0102] filtering solution B through a microfiltration membrane; after passing quality inspection, filling the solution into a bottle, sealing the bottle, and thereby obtaining the atropine eye drops.

[0103] Examples

[0104] The embodiments of the present disclosure will be described in detail below with reference to examples, but it should be understood by those skilled in the art that these examples are only used to illustrate the present disclosure and should not be considered as limiting the scope of the present disclosure. The methods without indication of specific conditions in the examples are conducted in accordance with conventional conditions or the conditions recommended by the manufacturer. All reagents or instruments used, where the manufacturer is not specified, are conventional products that are commercially available.

20 [0105] Example 1

[0106] The present example provides atropine eye drops, with the prescription

detailed in Table 1:

[0107] Table 1: Prescription for atropine eye drops

Ingredient name	Specification: 0.01%	
	Mass (mg) per bottle (calculated as solute)	Mass (g) per 1 L (calculated as solute)
Atropine sulfate	0.05	0.10
Anhydrous citric acid	0.25	0.50
Borax	0.53	1.05
Disodium edetate	0.50	1.00
Sodium chloride	4.35	8.70
Water for injection	Add until a total volume of 0.5 mL	Add until a total volume of 1 L

[0108] The present example provides a preparation method for the atropine eye drops comprising the following steps:

5 **[0109]** (1) measuring 90% of the prescribed amount of water for injection (900 mL) at a temperature of 22.5°C;

[0110] (2) adding the prescribed amount of disodium edetate, sodium chloride, borax, and anhydrous citric acid; stirring to dissolve at a speed of 200 rpm for 10 minutes; adding water for injection to bring the total volume to 1000 mL to obtain

10 solution A; measuring the pH value of the system, which should be 5.01;

[0111] (3) adding the prescribed amount of atropine sulfate to solution A and stirring at a speed of 200 rpm for 10 minutes to obtain solution B; measuring the pH value of the system, which should be 4.98;

[0112] (4) filtering solution B using a 0.22 μm PVDF membrane and sending
5 the resulting solution for analysis to detect the atropine sulfate content;

[0113] (5) filling 0.5 mL of the solution into 1 mL eye drop bottles (a total of 162 bottles) using a glass syringe, and sealing the bottles with thermal melting; after cooling the bottle mouths to room temperature, performing leak detection; sealing the remaining solution in glass bottles and storing at room temperature.

10 **[0114]** Example 2

[0115] The present example provides atropine eye drops, with the prescription detailed in Table 2:

[0116] Table 2: Prescription for atropine eye drops

Ingredient name	Specification: 0.02%	
	Mass (mg) per bottle (calculated as solute)	Mass (g) per 1 L (calculated as solute)
Atropine sulfate	0.10	0.20
Anhydrous citric acid	0.25	0.50
Borax	0.53	1.05
Disodium edetate	0.50	1.00

Sodium chloride	4.35	8.70
Water for injection	Add until a total volume of 0.5 mL	Add until a total volume of 1 L

[0117] The present example provides a preparation method for the atropine eye drops comprising the following steps:

[0118] (1) measuring 90% of the prescribed amount of water for injection (900 mL) at a temperature of 21.4°C;

5 **[0119]** (2) adding the prescribed amount of disodium edetate, sodium chloride, borax, and anhydrous citric acid; stirring to dissolve at a speed of 200 rpm for 10 minutes; adding water for injection to bring the total volume to 1000 mL to obtain solution A; measuring the pH value of the system, which should be 4.99;

[0120] (3) adding the prescribed amount of atropine sulfate to solution A and
10 stirring at a speed of 200 rpm for 10 minutes to obtain solution B; measuring the pH value of the system, which should be 4.98;

[0121] (4) filtering solution B using a 0.22 µm PVDF membrane and sending the resulting solution for analysis to detect the atropine sulfate content;

[0122] (5) filling 0.5 mL of the filtrate into 1 mL eye drop bottles (a total of 150
15 bottles) using a glass syringe, and sealing the bottles with thermal melting; after cooling the bottle mouths to room temperature, performing leak detection; sealing the remaining solution in glass bottles and storing at room temperature.

[0123] Example 3

[0124] The present example provides atropine eye drops, with the prescription detailed in Table 3:

[0125] Table 3: Prescription for atropine eye drops

Ingredient name	Specification: 0.01%	
	Mass (mg) per bottle (calculated as solute)	Mass (g) per 1 L (calculated as solute)
Atropine sulfate	0.05	0.10
Sodium dihydrogen phosphate dihydrate	0.98	1.95
Disodium hydrogen phosphate dihydrate	0.28	0.56
Disodium edetate	0.50	1.00
Sodium chloride	4.15	8.30
Hydrochloric acid	0.038	0.076
Water for injection	Add until a total volume of 0.5 mL	Add until a total volume of 1 L

[0126] The present example provides a preparation method for the atropine eye drops comprising the following steps:

[0127] (1) precisely measuring 0.9 mL of 36% hydrochloric acid and adding it to 100 mL of water for injection to prepare 0.1 mol/L hydrochloric acid for later use;

[0128] (2) measuring 90% of the prescribed amount of water for injection (900 mL) at a temperature of 24.4°C;

[0129] (3) adding the prescribed amount of disodium edetate, sodium chloride, sodium dihydrogen phosphate dihydrate, and disodium hydrogen phosphate
5 dihydrate; stirring to dissolve at a speed of 200 rpm for 10 minutes; measuring the pH value of the system, which should be 5.87;

[0130] adjusting the pH value to 5.00 with 0.1 mol/L hydrochloric acid and adding water for injection to bring the total volume up to 1000 mL to obtain solution A; measuring the pH value of the system, which should be 5.00;

10 [0131] (4) adding the prescribed amount of atropine sulfate to solution A and stirring at a speed of 200 rpm for 10 minutes to obtain solution B; measuring the pH value of the system, which should be 5.01;

[0132] (5) filtering solution B using a 0.22 µm PVDF membrane and sending the resulting solution for analysis to detect the atropine sulfate content;

15 [0133] (6) filling 0.5 mL of the solution into 1 mL eye drop bottles (a total of 156 bottles) using a glass syringe, and sealing the bottles with thermal melting; after cooling the bottle mouths to room temperature, performing leak detection; sealing the remaining solution in glass bottles and storing at room temperature.

[0134] Example 4

20 [0135] The present example provides atropine eye drops, with the prescription detailed in Table 4:

[0136] Table 4: Prescription for atropine eye drops

Ingredient name	Specification: 0.02%	
	Mass (mg) per bottle (calculated as solute)	Mass (g) per 1 L (calculated as solute)
Atropine sulfate	0.10	0.20
Sodium dihydrogen phosphate dihydrate	0.98	1.95
Disodium hydrogen phosphate dihydrate	0.28	0.56
Disodium edetate	0.50	1.00
Sodium chloride	4.15	8.30
Hydrochloric acid	0.038	0.076
Water for injection	Add until a total volume of 0.5 mL	Add until a total volume of 1 L

[0137] The present example provides a preparation method for the atropine eye drops comprising the following steps:

[0138] (1) precisely measuring 0.9 mL of 36% hydrochloric acid and adding it
5 to 100 mL of water for injection to prepare 0.1 mol/L hydrochloric acid for later use;

[0139] (2) measuring 90% of the prescribed amount of water for injection (900 mL) at a temperature of 24.4°C;

[0140] (3) adding the prescribed amount of disodium edetate, sodium chloride, sodium dihydrogen phosphate dihydrate, and disodium hydrogen phosphate dihydrate; stirring to dissolve at a speed of 200 rpm for 10 minutes; measuring the pH value of the system, which should be 5.86;

- 5 **[0141]** adjusting the pH value to 5.00 with 0.1 mol/L hydrochloric acid and adding water for injection to bring the total volume up to 1000 mL to obtain solution A; measuring the pH value of the system, which should be 5.01;

[0142] (4) adding the prescribed amount of atropine sulfate to solution A and stirring at a speed of 200 rpm for 10 minutes to obtain solution B; measuring the

- 10 pH value of the system, which should be 5.01;

[0143] (5) filtering solution B using a 0.22 μm PVDF membrane and sending the resulting solution for analysis to detect the atropine sulfate content;

[0144] (6) filling 0.5 mL of the filtrate into 1 mL eye drop bottles (a total of 104 bottles) using a glass syringe, and sealing the bottles with thermal melting; after

- 15 cooling the bottle mouths to room temperature, performing leak detection; sealing the remaining solution in glass bottles and storing at room temperature.

[0145] Test examples

[0146] 1. Testing of influencing factors of atropine eye drops

[0147] 1.1 Testing of atropine eye drops prepared in examples 1 and 2

- 20 **[0148]** In examples 1 and 2, the pH regulator used is a combination of citric acid and borax. For the atropine eye drops, the influencing factor tests investigated

high temperature (40°C and 50°C) and strong light exposure (5000lx) conditions. Considering potential transportation conditions, tests were also conducted under low temperature (4°C) and freeze-thaw (-18°C) conditions. The investigation results are shown in Tables 5 and 6, respectively:

5 **[0149]** Table 5: Test results of influencing factors of atropine eye drops
prepared in example 1

Specification: 0.01%				Example 1			
Time	pH value	Osmotic pressure mOsmol/kg	Atropine sulfate content%	Related substances			
				Tropic acid%	Dehydrated atropine%	Maximum unknown single impurity%	Total impurities%
0 days	4.98	299	101.46	ND	ND	ND	ND
40°C - 5 days	4.99	301	101.78	0.043	ND	ND	0.043
40°C - 10 days	5.01	305	103.20	0.087	ND	0.037	0.151
40°C - 30 days	4.97	309	104.71	0.263	0.030	0.061	0.463
50°C - 5 days	4.99	305	102.67	0.133	0.016	0.127	0.394

50°C - 10 days	5.03	314	104.58	0.282	0.038	0.131	0.715
50°C - 30 days	4.98	331	110.14	0.841	0.121	0.168	1.950
Light exposure - 5 days	5.00	302	101.14	ND	ND	0.028	0.141
Light exposure - 10 days	5.03	304	101.81	0.018	ND	0.220	0.616
Light exposure - 30 days	4.97	301	96.74	0.094	ND	1.718	4.71
Low temperature	5.01	299	101.19	0.058	ND	ND	0.058
Freeze- thaw conditions	5.02	302	101.01	0.054	ND	ND	0.054

[0150] Note: The impurity dehydrated atropine in the related substances is obtained by dehydration of atropine. It has an antispasmodic effect and is highly toxic.

[0151] Table 6: Test results of influencing factors of atropine eye drops

prepared in example 2

Specification: 0.02%				Example 2			
Time	pH value	Osmotic pressure mOsmol/kg	Atropine sulfate content%	Related substances			
				Tropic acid%	Dehydrated atropine%	Maximum unknown single impurity%	Total impurities%
0 days	4.98	301	100.33	ND	ND	ND	ND
40°C - 5 days	4.99	302	100.93	0.044	ND	ND	0.044
40°C - 10 days	5.00	306	101.90	0.084	ND	0.01	0.094
40°C - 30 days	4.96	315	103.27	0.264	0.030	0.027	0.321
50°C - 5 days	4.99	307	101.91	0.139	0.018	0.068	0.291
50°C - 10 days	5.01	312	103.20	0.282	0.039	0.066	0.472
50°C - 30 days	4.98	328	108.27	0.819	0.115	0.087	1.371

Light exposure - 5 days	4.99	301	100.40	ND	ND	0.027	0.027
Light exposure - 10 days	5.00	304	100.85	0.013	ND	0.188	0.315
Light exposure - 30 days	4.96	305	98.45	0.061	ND	1.264	2.728
Low temperature	5.00	302	100.10	0.053	ND	ND	0.053
Freeze-thaw conditions	4.97	302	100.36	0.052	ND	0.040	0.092

[0152] Based on the test results of Tables 5 and 6, it is evident that with the passage of time, the atropine eye drops provided by the present disclosure exhibit an increasing trend in the content of atropine sulfate at high temperatures of 40°C and 50°C, and the increase is more pronounced at 50°C than at 40°C. This is

5 due to the use of semi-permeable containers as inner packaging materials in the atropine eye drops provided by the present disclosure, which have a dehydrating effect, leading to an increase in the content of atropine sulfate in the eye drops.

Under the conditions of high temperature (50°C) and strong light exposure, there is a significant increase in the levels of tropic acid and dehydrated atropine in the eye drops provided by the present disclosure. Therefore, it is advisable to avoid high temperatures and strong light exposure during the storage and transportation of the atropine eye drops provided by the present disclosure.

[0153] 1.2 Testing of atropine eye drops prepared in examples 3 and 4

[0154] In examples 3 and 4, the pH regulator used is a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid.

For the atropine eye drops, the influencing factor tests investigated high temperature (40°C and 50°C) and strong light exposure (5000lx) conditions. Considering potential transportation conditions, tests were also conducted under low temperature (4°C) and freeze-thaw (-18°C) conditions. The investigation results are shown in Tables 7 and 8, respectively:

[0155] Table 7: Test results of influencing factors of atropine eye drops prepared in example 3

Specification: 0.01%				Example 3			
Time	pH value	Osmotic pressure mOsmol/kg	Atropine sulfate content%	Related substances			
				Tropic acid%	Dehydrated atropine%	Maximum unknown single impurity%	Total impurities%

0 days	5.01	304	101.41	ND	ND	ND	ND
40°C - 5 days	5.04	308	101.84	0.044	ND	ND	0.044
40°C - 10 days	5.08	310	103.21	0.094	ND	0.033	0.172
40°C - 30 days	5.01	319	106.44	0.284	0.030	0.051	0.506
50°C - 5 days	5.05	314	102.42	0.135	0.018	0.108	0.451
50°C - 10 days	5.05	319	105.04	0.305	0.043	0.144	1.056
50°C - 30 days	5.02	338	111.79	0.874	0.130	0.158	1.965
Light exposure - 5 days	5.04	308	101.42	ND	ND	ND	ND
Light exposure - 10 days	5.08	309	102.41	0.014	ND	0.064	0.415
Light exposure -	5.00	308	100.29	0.074	ND	1.868	3.966

30 days							
Low temperature	5.02	304	102.76	0.062	ND	ND	0.062
Freeze- thaw conditions	5.00	304	103.55	0.058	ND	ND	0.058

[0156] Table 8: Test results of influencing factors of atropine eye drops

prepared in example 4

Specification: 0.02%				Example 4			
Time	pH value	Osmotic pressure mOsmol/kg	Atropine sulfate content%	Related substances			
				Tropic acid%	Dehydrated atropine%	Maximum unknown single impurity%	Total impurities%
0 days	5.01	301	99.62	ND	ND	ND	ND
40°C - 5 days	5.02	308	100.90	0.039	ND	ND	0.039
40°C - 10 days	5.05	312	101.43	0.089	0.011	ND	0.100
40°C - 30 days	5.00	313	103.77	0.266	0.032	0.025	0.352
50°C - 5 days	5.00	308	100.32	0.113	0.033	0.049	0.227
50°C - 10 days	5.06	314	102.55	0.239	0.036	0.079	0.523
50°C - 30 days	4.98	338	108.88	0.794	0.121	0.076	1.273

Light exposure - 5 days	5.01	307	100.53	ND	ND	ND	ND
Light exposure - 10 days	5.05	306	100.62	0.011	ND	0.093	0.124
Light exposure - 30 days	4.98	305	100.21	0.095	ND	0.733	1.754
Low temperature	5.00	302	101.15	0.060	ND	ND	0.056
Freeze-thaw conditions	5.00	302	101.23	0.064	ND	ND	0.064

[0157] Based on the test results of Tables 7 and 8, it is evident that with the passage of time, the atropine eye drops provided by the present disclosure exhibit an increasing trend in the content of atropine sulfate at high temperatures of 40°C and 50°C, and the increase is more pronounced at 50°C than at 40°C. This is

5 due to the use of semi-permeable containers as inner packaging materials in the atropine eye drops provided by the present disclosure, which have a dehydrating effect, leading to an increase in the content of atropine sulfate in the eye drops.

Under the conditions of high temperature (50°C) and strong light exposure, there is a significant increase in the levels of tropic acid and dehydrated atropine in the eye drops provided by the present disclosure. Therefore, it is advisable to avoid high temperatures and strong light exposure during the storage and transportation of the atropine eye drops provided by the present disclosure.

[0158] 2. Comparison of stability data between homemade and commercially available eye drops

[0159] Table 9: Comparison of influencing factor data at high temperature between homemade and commercially available eye drops

Sample		Time	Related substances (area normalized)			
			Tropic acid%	Dehydrated atropine%	Maximum unknown single impurity%	Total impurities%
Homemade eye drops	Homemade sample 1	0 days	ND	ND	ND	ND
		40°C - 5 days	0.082	ND	0.029	0.111
		40°C - 10 days	0.165	ND	0.036	0.236
		40°C - 30 days	0.468	0.057	0.076	0.795
	Homemade	0 days	ND	ND	ND	ND

	sample 2	40°C - 5 days	0.085	ND	ND	0.085
		40°C - 10 days	0.168	ND	0.036	0.230
		40°C - 30 days	0.499	0.059	0.060	0.725
	Homemade sample 3	0 days	ND	ND	ND	ND
		40°C - 5 days	0.087	0.022	0.026	0.136
		40°C - 10 days	0.159	ND	0.024	0.183
		40°C - 30 days	0.490	0.063	0.082	0.837
	Homemade sample 4	0 days	ND	ND	ND	ND
		40°C - 5 days	0.086	ND	ND	0.086
		40°C - 10 days	0.181	ND	0.032	0.256
		40°C - 30 days	0.536	0.059	0.078	0.781
	Homemade sample 5	0 days	ND	ND	ND	ND
		40°C - 5 days	0.078	ND	ND	0.078
		40°C - 10 days	0.148	0.031	ND	0.179

		40°C - 30 days	0.439	0.055	0.036	0.593
Commercially available eye drops	Myopine	0 days	0.061	0.117	0.241	1.132
		40°C - 30 days	0.505	0.170	0.240	1.676
	Atropine	0 days	0.238	0.072	10.05	12.634
		40°C - 5 days	0.305	0.057	6.158	8.698
		40°C - 10 days	0.331	0.061	3.742	6.246
		40°C - 30 days	0.464	0.084	0.506	2.974
	Latropine	0 days	1.341	0.089	0.264	2.073
		40°C - 5 days	1.585	0.086	0.231	2.321
		40°C - 10 days	1.766	0.090	0.206	2.376
		40°C - 30 days	2.495	0.135	0.193	3.437

[0160] Note: In this table, homemade sample 1 follows the prescription of example 1 with a batch size of 100 mL; homemade sample 2 is the atropine eye drops prepared according to example 1; homemade sample 3 follows the prescription of example 3 with a batch size of 100 mL; homemade sample 4 is the

atropine eye drops prepared according to example 3; homemade sample 5 follows the prescription of example 3 with a batch size of 500 mL.

[0161] According to the test results, for homemade eye drops, regardless of the specific prescription provided by the present disclosure, there is no significant difference in stability after long-term storage at high temperature (40°C for 30 days). The total impurity content (0.593% to 0.837%) is significantly less than that of commercially available products such as Myopine (1.676%), Atropine (2.974%), and Latropine (3.437%), indicating that the homemade preparations have lower impurity levels compared to commercially available preparations.

10 **[0162]** Table 10: Comparison of influencing factor data under strong light exposure between homemade and commercially available eye drops

Sample		Time	Related substances (area normalized)			
			Tropic acid%	Dehydrated atropine %	Maximum unknown single impurity%	Total impurities %
Homemade eye drops	Homemade sample 1	0 days	ND	ND	ND	ND
		Light exposure - 5 days	ND	ND	0.027	0.139
		Light exposure - 10 days	0.034	ND	0.214	0.618

		Light exposure - 30 days	0.185	ND	1.687	4.767
	Homemade sample 2	0 days	ND	ND	ND	ND
		Light exposure - 5 days	ND	ND	ND	ND
		Light exposure - 10 days	0.027	ND	0.193	0.417
		Light exposure - 30 days	0.146	ND	1.424	3.556
	Homemade sample 3	0 days	ND	ND	ND	ND
		Light exposure - 5 days	ND	ND	0.067	0.067
		Light exposure - 10 days	ND	ND	0.153	0.394
		Light exposure - 30 days	0.153	ND	1.121	3.505
	Commercially available eye drops	Myopine	0 days	0.061	0.117	0.241
			Light exposure - 30 days	0.115	0.103	13.217
		Atropine	0 days	0.238	0.072	10.05
			Light exposure - 5	0.242	0.049	9.582

		days				
		Light exposure - 10 days	0.239	0.048	9.108	17.314
		Light exposure - 30 days	0.236	0.059	7.222	17.866
	Latropine	0 days	1.341	0.089	0.264	2.073
		Light exposure - 5 days	1.354	0.067	4.691	7.199
		Light exposure - 10 days	1.346	0.069	6.335	9.085
		Light exposure - 30 days	1.435	0.070	7.699	11.638

[0163] Note: In this table, homemade sample 1 is the atropine eye drops prepared according to example 1; homemade sample 2 is the atropine eye drops prepared according to example 3; homemade sample 3 follows the prescription of example 3 with a batch size of 500 mL.

- 5 **[0164]** According to the test results, compared to commercially available eye drops, the homemade eye drops of the present disclosure produce fewer unknown impurities. Furthermore, the unknown impurities are due to the complex sample retention environment in the light stability box used, and the total impurity content of the homemade eye drops is still less than that of commercially available

preparations. The homemade eye drops of the present disclosure should be stored away from light.

[0165] Table 11: Comparison of accelerated test (40°C, 25% RH) data between homemade and commercially available eye drops

Sample		Time	Related substances (area normalized)			
			Tropic acid%	Dehydrated atropine%	Maximum unknown single impurity%	Total impurities %
Homemade eye drops	Homemade sample 1	0 days	ND	ND	ND	ND
		1 month of acceleration	0.428	0.045	0.025	0.498
		2 months of acceleration	0.870	0.081	0.024	0.997
		3 months of acceleration	1.361	0.163	0.037	1.611
		6 months of acceleration	1.726	0.199	0.079	2.120
	Homemade sample 2	0 days	ND	ND	ND	ND
		1 month of acceleration	0.494	0.055	0.039	0.613

		2 months of acceleration	0.963	0.094	0.040	1.144
		3 months of acceleration	1.495	0.190	0.073	1.805
		6 months of acceleration	1.808	0.220	0.112	2.261
Commercially available eye drops	Myopine	0 days	0.061	0.117	0.241	1.132
		1 month of acceleration	0.480	0.167	0.291	2.061
		2 months of acceleration	0.869	0.244	0.245	2.603
		3 months of acceleration	1.283	0.262	0.641	3.917
		6 months of acceleration	2.411	0.413	0.173	5.000
	Latropine	0 days	1.341	0.089	0.264	2.073
		1 month of acceleration	2.475	0.125	0.372	3.461
		2 months of acceleration	3.606	0.186	0.271	4.477
		3 months of	4.587	0.229	0.215	5.354

		acceleration				
		6 months of acceleration	8.753	0.473	0.513	9.953

[0166] Note 1: In this table, the data for tropic acid and dehydrated atropine have not been processed with correction factors.

[0167] Note 2: In this table, homemade sample 1 follows the prescription of example 1 with a batch size of 100 mL; homemade sample 2 follows the
5 prescription of example 3 with a batch size of 100 mL.

[0168] According to the accelerated test data in Table 11, after 3 months of acceleration, the content of tropic acid in the homemade eye drops is slightly higher than that in the commercially available eye drops Myopine. The reason for this is that the pH of Myopine is 4.7, whereas the pH of the homemade eye
10 drops is closer to 5.0. Since tropic acid is greatly affected by the pH value, the content of tropic acid in the homemade eye drops is slightly higher. Tropic acid is a hydrolysis product of atropine and a metabolite in the body. In the quality standards for 1% atropine sulfate eye drops as per the United States Pharmacopeia, the limit for tropic acid is set at 7.0%. Therefore, the presence of tropic acid in
15 the homemade eye drops has no impact on safety. However, after 6 months of acceleration, the content of tropine acid is significantly increased in commercially available eye drops compared to homemade ones. Throughout the entire investigation period, the contents of tropic acid, dehydrated atropine, and the

maximum unknown single impurity in the homemade eye drops remain at a low level. This indicates that the homemade eye drops produce fewer impurities and have lower total impurity levels compared to commercially available eye drops, demonstrating better stability.

5 **[0169]** 3. Impact of thickening agents on product impurities

[0170] The addition of thickening agents to the prescription is investigated to assess their impact on product stability. Considering that the generation of impurities in the product might be a result of the combined action of the pH regulator and thickening agent, the present disclosure further comprehensively
10 investigates the impact of the thickening agent on product stability by varying the amount of the pH regulator. The sample prescription composition and experimental results are shown in Tables 12 to 13.

[0171] Table 12: Prescription of atropine eye drops with added thickening agent hydroxypropyl methylcellulose

Prescription composition	Prescription 1 Mass (g)/1 L (calculated as solute)	Prescription 2 Mass (g)/1 L (calculated as solute)	Prescription 3 Mass (g)/1 L (calculated as solute)	Prescription 4 Mass (g)/1 L (calculated as solute)
Atropine sulfate (Minsheng Pharmaceutical)	0.10	0.10	0.10	0.10
Sodium dihydrogen phosphate dihydrate	9.60	2.70	/	/
Disodium hydrogen phosphate dihydrate	1.50	0.40	/	/
Boric acid	/	/	14.70	4.30
Disodium edetate	1.00	1.00	1.00	1.00
Sodium chloride	9.00	9.00	9.00	9.00
Hydroxypropyl methylcellulose	5.00	5.00	5.00	5.00

(60SH)				
Water for injection	Add until a total volume of 100 mL	Add until a total volume of 100 mL	Add until a total volume of 100 mL	Add until a total volume of 100 mL
pH value	5.0	5.0	5.0	5.0

[0172] The preparation method for the above prescription can follow the preparation methods described in examples 1 to 2. Specifically, the corresponding products can be prepared according to the preparation method in example 1.

[0173] Table 13: Impact of adding thickening agent on product stability

Product (identified by prescription number)	Time	Related substances (area normalized)			
		Tropic acid (%)	Dehydrated atropine (%)	Maximum unknown single impurity (%)	Total impurities (%)
Prescription 1	0 days	0.077	0.129	0.021	0.227
Prescription 2		0.074	0.073	0.020	0.165
Prescription 3		0.074	0.068	/	0.142
Prescription 4		0.074	0.115	0.062	0.211
Prescription 1	40°C - 5 days	0.126	0.086	0.104	0.573
Prescription 2		0.160	0.093	0.287	0.890
Prescription 3		0.178	0.106	0.316	0.973
Prescription 4		0.161	0.144	0.232	1.008
Prescription 1	40°C - 10 days	0.334	0.199	0.139	1.139
Prescription 2		0.214	0.168	2.541	5.397
Prescription 3		0.441	0.196	2.789	6.101
Prescription 4		0.226	0.172	2.966	6.153
Prescription 1	40°C - 30 days	0.817	0.252	1.261	3.521
Prescription 2		0.539	0.152	0.522	2.222
Prescription 3		0.932	0.148	0.542	2.729
Prescription 4		0.498	0.196	1.612	3.849

[0174] After integrating the data from Tables 12 and 13, it is evident that prescriptions 1 to 4, which include a thickening agent, exhibit reduced stability of the corresponding products after long-term storage at high temperature (40°C for 30 days). In prescriptions 1 and 2, both phosphates and thickening agents were added, and in prescriptions 3 and 4, both boric acid and thickening agents were added. There is no significant difference in product stability, indicating that the decreased product stability is not due to the addition of phosphates or boric acid. Furthermore, there is no significant difference in product stability between prescription 1 and prescription 2, which have different phosphate concentrations, indicating that the decreased product stability is not due to different phosphate concentrations; there is no significant difference in product stability between prescription 3 and prescription 4, which have different boric acid concentrations, indicating that the decreased product stability is not due to different boric acid concentrations.

[0175] In conclusion, the addition of the thickening agent hydroxypropyl methylcellulose leads to decreased stability and an increase in impurities in the products. The atropine eye drops provided by the present disclosure, through the selection of raw materials and optimization of prescription, do not contain thickening agents and have good stability, low total impurities, and are suitable for long-term storage.

[0176] 4. Examination of phosphate concentration

[0177] The phosphate concentration was halved to examine its impact on sample stability. The sample prescription composition and experimental results are shown in Tables 14 to 15.

[0178] Table 14: Prescription of atropine eye drops with different phosphate concentrations

Prescription composition	Specification: 0.01%	
	Prescription 1 Mass (g)/1 L (calculated as solute)	Prescription 2 Mass (g)/1 L (calculated as solute)
Atropine sulfate	0.10	0.10
Sodium dihydrogen phosphate dihydrate	7.80	3.90
Disodium hydrogen phosphate dihydrate	2.20	1.10
Sodium chloride	9.00	9.00
Hydrochloric acid	Appropriate amount	Appropriate amount
Water for injection	Add until a total volume of 100 mL	Add until a total volume of 100 mL
pH value	5.0	5.0

[0179] Table 15: Examination results of different phosphate concentrations - influencing factor test (40°C)

Product (identified by prescription number)	Time	Related substances (area normalized)			
		Tropic acid (%)	Dehydrated atropine (%)	Maximum unknown single impurity (%)	Total impurities (%)
Prescription 1	0 days	0.106	0.127	ND	0.233
Prescription 2		0.106	0.115	0.025	0.247
Prescription 1	40°C - 5 days	0.192	0.137	0.04	0.465
Prescription 2		0.171	0.127	0.077	0.475
Prescription 1	40°C - 10 days	0.319	0.168	0.089	0.837
Prescription 2		0.272	0.15	0.134	0.857
Prescription 1	40°C - 30 days	0.718	0.236	0.238	1.356
Prescription 2		0.589	0.206	0.245	1.268

[0180] According to the experimental results shown in Table 15, the increase in tropic acid is affected by the phosphate concentration. With a low phosphate concentration, the increase in tropic acid is relatively slow, which is an unexpected outcome. At the same time, the increase in the maximum unknown single impurity is relatively fast, and there is also an increase in total impurities.

Therefore, it appears that the phosphate concentration in atropine eye drops should be controlled at a slightly high level. However, considering that phosphate itself has a certain osmotic pressure, if a large amount of phosphate is used, it is necessary to adjust the amount of sodium chloride to achieve isotonicity;

and sodium chloride also has a certain impact on the stability of atropine sulfate. Therefore, from the perspective of ensuring the stability and osmotic pressure of atropine eye drops, it is necessary to collaboratively adjust the amounts of both phosphates and sodium chloride.

5 **[0181]** 5. Examination of sodium chloride concentration

[0182] In the present disclosure, the mass concentrations of sodium dihydrogen phosphate and disodium hydrogen phosphate were initially set at 1.95 g/L and 0.56 g/L, respectively. Under these conditions, the effect of the amount of sodium chloride on osmotic pressure was investigated. Blank excipient solutions with different sodium chloride concentrations were prepared, and the osmotic pressure of the samples was measured. The sample prescription and osmotic pressure results are shown in Table 16.

[0183] Table 16: Prescription of blank excipient solutions with different sodium chloride concentrations and osmotic pressure results

	Prescription	Prescription	Prescription	Prescription	Prescription
	1	2	3	4	5
Prescription composition	Mass (g) per 1 L (calculated as solute)	Mass (g) per 1 L (calculated as solute)	Mass (g) per 1 L (calculated as solute)	Mass (g) per 1 L (calculated as solute)	Mass (g) per 1 L (calculated as solute)
Sodium	1.95	1.95	1.95	1.95	1.95

dihydrogen phosphate dihydrate					
Disodium hydrogen phosphate dihydrate	0.56	0.56	0.56	0.56	0.56
Sodium chloride	7.80	8.10	8.30	8.50	9.00
Disodium edetate	1.00	1.00	1.00	1.00	1.00
Water for injection	100 mL	100 mL	100 mL	100 mL	100 mL
Osmotic pressure (mOsmol/kg)	283	294	298	306	309

[0184] Based on the requirement for eye drops to be isotonic with tears, the present disclosure selected an osmotic pressure range of 280 to 320 mOsmol/kg, corresponding to a sodium chloride concentration of 7.80 to 9.00 g/L. Taking into account the osmotic pressure of existing commercially available preparations,

5 the osmotic pressure of the atropine eye drops of the present disclosure was

initially set at around 300 mOsmol/kg, corresponding to a sodium chloride concentration of 8.30 g/L, which was used as a basis to investigate the impact of sodium chloride concentration on stability.

[0185] Samples were prepared according to the adjusted sodium chloride concentration in the prescription, and the stability of these samples was then examined. The sample prescription composition and experimental results are shown in Tables 17 to 18.

[0186] Table 17: Prescription of atropine eye drops with different sodium chloride concentrations

Prescription composition	Prescription 1 Mass (g) per 1 L (calculated as solute)	Prescription 2 Mass (g) per 1 L (calculated as solute)
Atropine sulfate (homemade)	0.10	0.10
Sodium dihydrogen phosphate dihydrate	1.95	1.95
Disodium hydrogen phosphate dihydrate	0.56	0.56
Sodium chloride	9.00	8.30
Disodium edetate	1.00	1.00
Hydrochloric acid	0.076	0.076
Water for injection	100 mL	100 mL

pH value	5.0	5.0
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[0187] Table 18: Examination results of osmotic pressure regulator amounts -
influencing factor test (40°C)

Product (identified by prescription number)	Time	Related substances (area normalized)			
		Tropic acid (%)	Dehydrated atropine (%)	Maximum unknown single impurity (%)	Total impurities (%)
Prescription 1	0 days	ND	ND	ND	0
Prescription 2		ND	ND	ND	0
Prescription 1	40°C - 5 days	0.093	ND	ND	0.093
Prescription 2		0.087	0.022	0.026	0.136
Prescription 1	40°C - 10 days	0.189	ND	0.029	0.218
Prescription 2		0.159	ND	0.024	0.183
Prescription 1	40°C - 30 days	0.587	0.053	0.066	0.759
Prescription 2		0.490	0.063	0.082	0.837

[0188] According to the results of the influencing factor tests, adjusting the amount of sodium chloride from 9.00 g/L to 8.30 g/L did not affect the stability of the sample. This indicates that further reducing the amount of sodium chloride, while ensuring product stability, can enhance the safety and overall quality of the atropine eye drops.

[0189] In summary, to ensure the stability of the atropine eye drops, it is

necessary to collaboratively adjust the amounts of both phosphate salts and the osmotic pressure regulator. Based on the investigation conducted in the aforementioned manner, it can be concluded that in the eye drops of the present disclosure, the mass concentrations of sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride are 1.49 to 6.00 g/L, 0.43 to 0.88 g/L, and 7.80 to 9.00 g/L, respectively. Furthermore, after further screening by the present disclosure, it is found that when the mass concentrations of sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride are 1.95 g/L, 0.56 g/L, and 8.30 g/L, respectively, the stability of the eye drops is even better.

[0190] The various embodiments of the present disclosure have been described above. The foregoing description is illustrative and not exhaustive, and is not limited to the disclosed embodiments. Numerous modifications and variations are apparent to one of ordinary skill in the art without departing from the scope and spirit of the described embodiments. The terminology used herein is chosen to best explain the principles of the embodiments, practical applications, or improvements to the technology in the market, or to enable others of ordinary skill in the art to understand the disclosed embodiments.

CLAIMS

1. An atropine eye drop, comprising the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80
5 to 9.00 g/L, a pH regulator, and water for injection;

wherein the pH regulator is a combination of citric acid and borax, or a combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, and the amount of the pH regulator used is based on adjusting the pH value to 4.5 to 5.5.

10 2. The atropine eye drop according to claim 1, wherein by mass concentration, in the combination of citric acid and borax, citric acid is 0.50 to 2.00 g/L, and borax is 1.00 to 2.00 g/L;

by mass concentration, in the combination of sodium dihydrogen phosphate, disodium hydrogen phosphate, and hydrochloric acid, sodium dihydrogen
15 phosphate is 1.49 to 6.00 g/L, disodium hydrogen phosphate is 0.43 to 0.88 g/L, and hydrochloric acid is 0.04 to 0.13 g/L.

3. The atropine eye drop according to claim 2, comprising the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic
20 pressure regulator at 7.80 to 9.00 g/L, citric acid at 0.50 g/L, borax at 1.05 g/L, and water for injection.

4. The atropine eye drop according to claim 2, comprising the following components: by mass concentration, atropine or a pharmaceutically acceptable salt thereof at 0.10 to 0.20 g/L, a chelating agent at 0 to 1.00 g/L, an osmotic pressure regulator at 7.80 to 9.00 g/L, sodium dihydrogen phosphate at 1.95 g/L,
5 disodium hydrogen phosphate at 0.56 g/L, hydrochloric acid at 0.076 g/L, and water for injection.

5. The atropine eye drop according to any one of claims 1 to 4, wherein the pharmaceutically acceptable salt is sulfate.

6. The atropine eye drop according to any one of claims 1 to 4, wherein the
10 chelating agent comprises one or a combination of two or more of disodium edetate, sodium calcium edetate, and edetic acid, preferably disodium edetate.

7. The atropine eye drop according to any one of claims 1 to 4, wherein the osmotic pressure regulator comprises one or a combination of two or more of sodium chloride, mannitol, and glycerol, preferably sodium chloride.

15 8. A preparation method for the atropine eye drop according to any one of claims 1 to 7, comprising the following steps:

dissolving a prescribed amount of the chelating agent, osmotic pressure regulator, and pH regulator in the water for injection to obtain solution A;

adding a prescribed amount of the atropine or the pharmaceutically
20 acceptable salt thereof to the solution A to obtain solution B;

filtering the solution B and filling it into a bottle to obtain the atropine eye

drop.

9. The preparation method according to claim 8, wherein the water for injection is controlled at a temperature of 40°C or less, preferably 21.4 to 24.4°C.

10. The preparation method according to claim 8 or 9, wherein the solution
5 B is filtered through a microfiltration membrane with a pore size of 0.22 µm, and the microfiltration membrane is a PVDF membrane.