

A PHARMACEUTICAL COMPOSITION FOR EYE DROP OIL DOSAGE FORM

REFERENCE TO RELATED APPLICATIONS

[0001] The present invention is the National Stage Application of International Patent Application Serial No. PCT/CN2023/119935, filed on Sep. 20, 2023, which claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 63/442,153, filed on Jan. 31, 2023, the contents of all which are hereby incorporated herein fully by reference into the present disclosure for all purposes.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] The present invention relates to an ophthalmic drug, particularly refers to an eye drop oil dosage form that is preservative-free and non-eye-irritating.

DESCRIPTION OF THE PRIOR ART

[0003] The surface of the normal eyeball is covered by a layer of tears, which provides lubrication and protection for the eyes, called the "tear film". The tear film structure can be divided into three layers: the mucinous layer, the aqueous layer and the lipid layer from inside to outside (FIG. 1). The mucin layer can increase the viscosity of the tears and help the water stay on the surface of the eye. The aqueous layer provides a smooth optical refractive surface for vision and maintains ocular hydration. The outermost lipid layer can prevent excessive evaporation of tears, help lubricate the eyes, and maintain the integrity of the tear film. If deficiency in any layer, the tear film will be unstable, causing dry eye syndromes.

[0004] In 1995, the National Eye Institute (NEI) of the United States divided dry eye into two major types: deficient aqueous production (i.e., aqueous deficient dry eye) and over evaporation (i.e., lipid deficient dry eye). According to a study published in Cornea. 2012 May; 31(5):472-8., most dry eye syndromes are not caused by insufficient tear secretion. Up to 86% of dry eye syndrome patients suffer from over evaporation (evaporative dry eye) caused by

meibomian gland dysfunction, while only 14% suffer from simple deficient aqueous production (aqueous deficiency dry eye). According to the statistics from the GlobalData database, artificial tears are currently still the main drugs for treating dry eye syndromes in most countries in the world, and there is a lack of drugs for patients with evaporative dry eye on the market.

[0005] Common dosage forms of ophthalmic drugs include eye drops, eye suspensions, and eye ointments and the like. Eye drops are aqueous formula, which are easy to microbial contamination. Generally, multi-dose packaging almost is always added preservatives. Preservative-free eye drops can only be made into single-use disposable packaging, but their high price is not conducive to popularization. Long-term and high-frequency use of preservative-containing eye drops may aggravate chronic inflammation of the eyes and increase the degree of corneal cell damage. In addition, eye drops may also wash away the lipid layer of the tear film and destroy the integrity of the tear film, thus causing the development or deterioration of dry eye syndromes. Although some eye drops contain trace amounts of oil, claiming to simulate the composition of tear film, such formulations require the addition of surfactants to dissolve the oil in water, which in turn causes a burden on the eyes.

[0006] Furthermore, some active pharmaceutical ingredients for eye use are insoluble in water and can only be formulated as eye suspensions or eye ointments. In addition to sharing the same problems as eye drops, eye suspensions must be shaken before use. If they are not shaken adequately, the content of active pharmaceutical ingredients may be unevenly distributed, resulting in the risk of inadequate efficacy at times and excessive dosage at others. Eye ointments are packaged in flexible tubes, and the ointment needs to be squeezed into the lower eyelid during application, which can be challenging for elderly patients to use independently. Moreover, they may cause blurred vision and a foreign body sensation, impacting daily life.

[0007] Since eye drops may affect the stability of the tear film and it is necessary to pay attention to preservatives are harmful to the eyes, eye suspensions not only share the same problems as eye drops but also have the risk of inconsistent drug distribution. Eye ointments are difficult to apply and may cause blurred vision or discomfort such as foreign body sensation after use. These commonly available ophthalmic dosage forms exhibit significant drawbacks in practical use. Therefore, there is an urgent need to develop a new ophthalmic dosage form that can not only relieve dry eye syndrome, but also serve as an ophthalmic drug platform for

incorporating of active pharmaceutical ingredients that are poorly water-soluble. Solving this challenge is a key aim of the present invention.

SUMMARY OF THE INVENTION

[0008] In view of the shortcomings of related technologies, the present invention provides a pharmaceutical composition for eye drop oil dosage form. This composition exhibits low eye irritation, preservative-free, and does not cause blurred vision after use. In addition, it can be filled into a standard multi-dose eye drop bottle for convenient use. The pharmaceutical composition for eye drop oil dosage form in the present invention can effectively prevent the moisture loss from the tear film, relieve dry eye syndrome, and can further add pharmaceutical ingredients that are poorly soluble in water, providing another new option for ophthalmic drug delivery platform.

[0009] The purpose of the present invention is to provide a pharmaceutical composition for eye drop oil dosage form, comprising: a lipid, a white petrolatum, and a liquid paraffin, wherein each gram of the pharmaceutical composition contains 3-500 mg of lipid, 100-250 mg of white petrolatum, and 1-797 mg of liquid paraffin.

[0010] To achieve the aforementioned purpose of the present invention, the lipid comprises medium-chain triglyceride (MCT), soybean oil, corn oil, olive oil, canola oil, sunflower oil, isopropyl myristate (IPM), and lanolin oil.

[0011] To achieve the aforementioned purpose of the present invention, the lipid is medium-chain triglyceride.

[0012] To achieve the aforementioned purpose of the present invention, each gram of the pharmaceutical composition comprises 3-500 mg of lipid, 100-250 mg of white petrolatum, and 300-797 mg of liquid paraffin.

[0013] To achieve the aforementioned purpose of the present invention, each gram of the pharmaceutical composition comprises 3-300 mg of lipids, 100-240 mg of white petrolatum, and 500-797 mg of liquid paraffin.

[0014] To achieve the aforementioned purpose of the present invention, the pharmaceutical composition may include active pharmaceutical ingredients .

[0015] To achieve the aforementioned purpose of the present invention, the active pharmaceutical ingredients comprise mineral oil, steroids, tetracyclines, macrolide antibiotics, prostaglandins, carbonic anhydrase inhibitors, immunosuppressive agents or other water-insoluble active pharmaceutical ingredients.

[0016] To achieve the aforementioned purpose of the present invention, the steroid comprises loteprednol etabonate, betamethasone, dexamethasone, fluorometholone, prednisolone acetate or hydrocortisone acetate.

[0017] To achieve the aforementioned purpose of the present invention, the tetracycline comprises doxycycline hyclate, tetracycline HCl or minocycline HCl.

[0018] To achieve the aforementioned purpose of the present invention, the macrolide antibiotic comprises erythromycin or azithromycin.

[0019] To achieve the aforementioned purpose of the present invention, the prostaglandin comprises latanoprost, latanoprostene bunod, travoprost, or bimatoprost.

[0020] To achieve the aforementioned purpose of the present invention, the carbonic anhydrase inhibitor comprises brinzolamide.

[0021] To achieve the aforementioned purpose of the present invention, the immunosuppressive agent comprises tacrolimus or sirolimus.

[0022] To achieve the aforementioned purpose of the present invention, the other water-insoluble active pharmaceutical ingredients comprise rebamipide, omega 3, nepafenac, besifloxacin HCl, selenium disulfide, vitamin A or cyclosporin.

[0023] Another purpose of the present invention is to develop an ophthalmic pharmaceutical composition for the preparation of a drug for treating, preventing or improving dry eye syndromes, especially lipid-deficient dry eye caused by meibomian gland dysfunction.

[0024] In summary, the present invention provides an eye drop oil, which is an ophthalmic pharmaceutical composition with a novel dosage form and the ophthalmic pharmaceutical composition has the following advantages compared with the prior art: 1. Without destroying the stability of the tear film like eye drops, the ophthalmic composition is highly safe for long-term use. 2. Compared with eye ointments, the ophthalmic composition of

the present invention is contained in a general eye drop bottle, is convenient to use, has low eye irritation, and will not cause blurred vision after use. 3. The ophthalmic composition can effectively prevent the loss of moisture from the tear film, treat, prevent or improve dry eye syndrome, and meet the treatment needs of patients with tear over evaporation (lipid deficient dry eye). 4. The ophthalmic composition can be added with water-insoluble active pharmaceutical ingredients and can serve as an ophthalmic drug platform. 5. The ophthalmic composition doesn't need to be added with preservatives, thereby reducing preservative-related side effects. 6. The stability of ophthalmic composition is better than that of commercially available products.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] The techniques of present invention would be more understandable from the detailed description given herein below and the accompanying figures are provided for better illustration, and thus description and figures are not limitative for present invention, and wherein:

FIG. 1 is a schematic diagram of the tear film;

FIG. 2 is the change in tear volume one hour after medication.

DETAILED DESCRIPTION OF THE INVENTION

[0026] Example 1 irritation and viscosity detection

[0027] The data of viscosity and biological liquid film (transmittance, %T) were used to confirm and evaluate whether the ophthalmic pharmaceutical composition of the present invention has good viscosity and low eye irritation.

[0028] Viscosity evaluation method: Using a microVISC™ viscometer (in accordance with USP<914> Pressure Driven Methods), the viscosity of water for injection (WFI) was 0.894, and the viscosity of eye ointment (as Control 2) was 2537.7 (as shown in Table 5), which can be used as a reference value for the fluidity of eye medicines. Viscous force is a flow resistance inside a viscous liquid and may be thought of as the friction of fluid itself. Viscous force mainly comes from the mutual attraction between molecules, so substances with lower viscosity are easier to flow. The smaller the viscosity value, the better the fluidity, the vision will not be blurred after dropping into the eyes, the clarity of vision will not be affected, and a

general eye drop bottle can be used, which is more convenient for patients to use than a flexible tube.

[0029] Biological liquid film evaluation method: According to the chemical test Guidelines No. 496: In vitro Macromolecular Test Method for Identifying Chemicals Inducing Serious Eye Damage and Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage published by the Organization for Economic Co-operation and Development (OECD), in vitro tests were conducted on biological liquid films to simulate the irritation of chemicals to the eyes and the level of irritation was determined by using the phenomenon that the solution becomes turbid after the macromolecules react chemically with irritating substances to cause protein denaturation.

[0030] The detection method was that the medicine and the reagent were mixed to denature the protein, which caused the solution to become turbid. Then, the transmittance of each group was measured using a UV spectrophotometer (manufacturer: Hitachi; model: U-2900) in accordance with the United States Pharmacopeia (USP) standards for transmittance. The transmittance of each group at a light wavelength of approximately 405 nanometers is shown in Table 1 below. The level of transmittance can be used to evaluate the degree of irritation to the eyes, and the higher the transmittance, the lower the eye irritation, and the lower the transmittance, the higher the eye irritation. Specifically, when the transmittance is greater than 90%, the eye medicine is considered to have no eye irritation; when the transmittance is greater than 80% and less than or equal to 90%, it is considered to have low eye irritation; when the transmittance is greater than 70% and less than or equal to 80%, it is considered to have moderate eye irritation; and when the transmittance is less than or equal to 70%, it is considered to have high eye irritation.

[0031] The present invention is an ophthalmic pharmaceutical composition, comprising a medium-chain triglyceride, a white petrolatum, and a liquid paraffin. According to the data viscosity and biological liquid film irritation (transmittance, %T) of the compositions with different proportions of ingredients in Tables 1-3, it is confirmed that the compositions with proportions of ingredients have good fluidity and low eye irritation.

[0032] The content of white petrolatum in the ophthalmic pharmaceutical composition is fixed, and the contents of MCT and liquid paraffin therein are changed. According to the results in Table 1, the MCT content in the ophthalmic pharmaceutical composition is changed.

The ophthalmic pharmaceutical compositions with an MCT content of 3-500 mg/g have a transmittance greater than 90%, and thus considered to be non-irritating to the eyes. Although the viscosities of the ophthalmic pharmaceutical compositions of Formulations T10 and T11 are acceptable, it is considered that a high content of MCT (greater than 500 mg/g) may affect the clarity of vision, and it is not easy to drip out when contained in an eye drop bottle.

Table 1 Ophthalmic Pharmaceutical Compositions with Different Proportions of MCT

Formulation No. Ingredient (mg/g)	T07	T08	T09	T03	T10	T11
MCT	3	30	50	100	300	500
White petrolatum	200	200	200	200	200	200
Liquid paraffin	797	770	750	700	500	300
Viscosity (cp)	37.0	40.7	47.3	40.4	106.6	154.1
Transmittance (%T)	95.1	100.0	97.7	97.6	100.0	100.0

[0033] In order to confirm whether MCT and liquid paraffin can be replaced by other lipids, the contents of white petrolatum and liquid paraffin in the ophthalmic pharmaceutical composition were fixed, and the lipids selected from soybean oil, corn oil, olive oil, canola oil, sunflower oil, isopropyl myristate (IPM) and lanolin oil were added. According to the results in Table 2, when the types of lipids are changed, the ophthalmic pharmaceutical compositions have a transmittance greater than 90% and are considered to have no eye irritation, exhibit a good fluidity, cause no blurred vision, and have no impact on the clarity of vision.

Table 2 Ophthalmic Pharmaceutical Compositions with Different Lipids

Formulation No. Ingredient (mg/g)	T12	T13	T14	T15	T16	T17	T18
Lipid	Soybean oil 100	Corn oil 100	Olive oil 100	Canola oil 100	Sunflower oil 100	IPM 100	Lanolin oil 100
Liquid paraffin	700	700	700	700	700	700	700
White petrolatum	200	200	200	200	200	200	200
Viscosity (cp)	78.9	73.7	72.8	81.9	68.6	38.5	88.2
Transmittance (%T)	100.0	95.1	93.7	94.2	97.5	98.7	98.6

[0034] The content of MCT in the ophthalmic pharmaceutical composition was fixed, and the contents of white petrolatum and liquid paraffin were changed. According to the results in Table 3, the ophthalmic pharmaceutical compositions with a white petrolatum content of 100-250 mg/g have a transmittance greater than 85%, and are considered almost non-irritating to the eyes. Although the viscosity of the ophthalmic pharmaceutical composition of

Formulation T23 is acceptable, it is considered that a high content of white petrolatum (greater than 250 mg/g) will blur vision, affecting the clarity of vision.

Table 3 Ophthalmic Pharmaceutical Compositions with Different Proportions of White Petrolatum

Formulation No. Ingredient (mg/g)	T19	T20	T21	T03	T22	T23
MCT	100	100	100	100	100	100
White petrolatum	100	150	180	200	220	250
Liquid paraffin	800	750	720	700	680	650
Viscosity (cp)	22.4	29.0	41.4	40.4	86.7	104.6
Transmittance (%T)	91.3	89.3	89.7	97.6	87.7	90.0

[0035] The ophthalmic pharmaceutical composition of the present invention is an eye drop oil dosage form, which exhibits good comfort when the proportions of ingredients are in the ranges of 3-300 mg/g lipid, 100-250 mg/g white petrolatum, and 1-797 mg/g liquid paraffin. The subsequent examples are based on Formulation T03: 100 mg/g MCT, 200 mg/g white petrolatum, and 700 mg/g liquid paraffin.

[0036] Table 4 shows the dosage forms and ingredients labeled on the package insert of commercially available ophthalmic products frequently used by patients with dry eye syndromes. Control 1 is an artificial tear commonly used on the market, and Control 2 is an eye ointment for eyeball lubrication. Table 5 shows the comparison of the viscosity and transmittance of the ophthalmic pharmaceutical composition of the present invention with those of commercially available products. The ophthalmic pharmaceutical composition of Formulation T03 of the present invention, water for injection, Control 1, and Control 2 all have a transmittance greater than 90%, and therefore are considered to be non-irritating to the eyes. Control 2 has a high viscosity, and it is considered that it will seriously blur vision and affect the clarity of vision when used, and it can only be contained in a flexible tube, which is inconvenient to use.

Table 4 Dosage Forms and Ingredients of Commercially Available Products (as Labeled on the Package Insert)

Product Name	Control 1	Control 2
Dosage form	Eye drop	Eye ointment
Active ingredient	Sodium chloride Potassium chloride Sodium biphosphate Boric acid	Mineral oil

	Borax Benzalkonium chloride	
Excipient	Hydroxypropyl methylcellulose 606 Purified water	White petrolatum Anhydrous liquid lanolin

Table 5 Comparison of the Ophthalmic Pharmaceutical Composition of the Present Invention with Water for Injection and Commercially Available Products

Product Name	Water for Injection	Control 1	Control 2	T03
Viscosity (cp)	0.894	1.04	2537.7	40.4
Transmittance (%T)	100.0	100.0	100.0	97.6

[0037] Example 2 Stability analysis

[0038] In order to evaluate the stability of the ophthalmic pharmaceutical composition of the present invention, changes in stability were observed using parameters such as moisture, appearance, specific gravity, viscosity, and acid value.

[0039] The formulation of the ophthalmic pharmaceutical composition of the present invention comprises a mineral oil, a lipid, and a white petrolatum, wherein the lipid is an oil but not a mineral oil and includes, but is not limited to, medium-chain triglycerides, soybean oil, corn oil, olive oil, canola oil, sunflower oil, isopropyl myristate (IPM), lanolin oil, peanut oil, and castor oil. The lipids in the formulation of the following ophthalmic pharmaceutical composition are mainly medium-chain triglycerides.

[0040] The formulation of the ophthalmic pharmaceutical composition of the present invention comprises 3-500 mg/g lipid, 100-250 mg/g white petrolatum, and 1-797 mg/g liquid paraffin.

[0041] The preferred formulation of the ophthalmic pharmaceutical composition of the present invention comprises 3-300 mg/g lipids, 100-250 mg/g white petrolatum, and 300-797 mg/g liquid paraffin.

[0042] The most preferred formulation of the ophthalmic pharmaceutical composition of the present invention comprises 3-300 mg/g lipids, 100-240 mg/g white petrolatum, and 500-797 mg/g liquid paraffin.

[0043] The following experiments were conducted based on the formulation T03: 100 mg/g MCT, 200 mg/g white petrolatum, and 700 mg/g liquid paraffin.

[0044] Detection methods:

Appearance: Slightly white, flowable eye drop oil

Water content: The solvent is 20.0 mL of a mixture of toluene and methanol (7:3). The water content should not exceed 0.5% (using Karl Fischer Moisture Titrator)

Specific gravity: 0.806-0.870 (by weighing conversion)

Acid value: (refer to USP <401> ACID VALUE)

[0045] Take about 20 g of the test sample, accurately weigh in a flask, and add 50 mL of a neutral mixture of ethanol: diethyl ether (1:1) (neutralized with phenolphthalein and 0.1 N potassium hydroxide solution or 0.1 N sodium hydroxide solution, unless otherwise specified). If the test sample is insoluble in the cold solution, the flask can be connected to a reflux condenser and slowly heated, and shaken frequently, until the test sample is dissolved. Add 1 mL of phenolphthalein test solution and titrate with 0.05 N potassium hydroxide solution until the solution remains light red after shaking for 30 seconds.

[0046] The results in Table 6 show that, based on three-month accelerated stability data, the ophthalmic pharmaceutical composition of the present invention is stable in composition and the acid value has not changed significantly. It can be stored for a long time and will not deteriorate during storage and sales.

Table 6 Accelerated Stability Data

Accelerated Stability Test		Appearance	Water Content	Specific Gravity	Acid Value
Time Point	Temperature & Humidity				
Specification		Slightly white eye drop oil	Not more than 0.5%	0.806-0.870	0-1
Initial test		Complies	0.21%, 0.28%	0.852, 0.846	0.01, 0.01
1 st month	40°C + 2°C / < 75% RH	Complies	0.07%, 0.09%	0.837, 0.839	0.04, 0.06
2 st month		Complies	0.44%, 0.14%	0.843, 0.834	0.04, 0.04
3 st month		Complies	0.07%, 0.09%	0.838, 0.836	0.04, 0.04

[0047] Example 3 Water content test (refer to USP <922>, <1112>)

[0048] The moisture content is divided into water content and water activity (a_w). The moisture detected by the water content includes free water and bound water (also known as fixed water or hydrated water). Only free water has water activity because free water is ordinary water that can be used by microorganisms; while bound water has no solvent function and cannot be used by microorganisms.

[0049] Reducing water activity (a_w) helps prevent the proliferation of microorganisms in drugs. The water content test can prove that the formulations of the present invention have a low water activity. Since the ophthalmic pharmaceutical composition of the present invention is prepared aseptically, it can be maintained in a sterile state without the addition of preservatives.

[0050] According to the description of water activity in the United States Pharmacopeia <1112>, drugs with a water activity far lower than 0.75% are the standard for evaluating stability of product. Therefore, this can be used to evaluate whether the present invention can be free of added preservatives and still have no microbial growth.

Table 7 Water Content Test

Ophthalmic Pharmaceutical Composition of the Present invention	Water Content %
T07	0.24
T08	0.14
T09	0.08
T10	0.24
T11	0.28
T12	0.17
T13	0.28
T14	0.47
T15	0.25
T16	0.29
T17	0.10
T18	0.13
T19	0.05
T20	0.14
T21	0.22
T22	0.19
T23	0.3
Control 1	99.47
Control 2	0.16

[0051] From the results of water content test in Table 7, it can be seen that the water content of the ophthalmic pharmaceutical composition with different proportions of ingredients

of the present invention is all lower than 0.5. The water content includes free water and bound water, that is, the free water (water activity) in the ophthalmic pharmaceutical composition of the present invention is far lower than 0.75 which can be utilized by microorganisms. Therefore, the ophthalmic pharmaceutical composition of the present invention can effectively prevent the proliferation of microorganisms in drugs, so it is not necessary to add preservatives. It can also be seen from Tables 4 and 7 that since the artificial tear of Control 1 is an aqueous preparation, preservatives must be added for long-term storage.

[0052] Example 4 The present invention improves tear secretion

[0053] Fifteen participants were administered with artificial tear (Control 1), eye ointment (Control 2), and the ophthalmic pharmaceutical composition of the present invention as test products.

[0054] The formulation of the ophthalmic pharmaceutical composition of the present invention comprises 3-500 mg/g lipids, 100-250 mg/g white petrolatum, and 1-797 mg/g liquid paraffin.

[0055] The preferred formulation of the ophthalmic pharmaceutical composition of the present invention comprises 3-300 mg/g lipids, 100-250 mg/g white petrolatum, and 300-797 mg/g liquid paraffin.

[0056] The most preferred formulation of the ophthalmic pharmaceutical composition of the present invention comprises 3-300 mg/g lipids, 100-240 mg/g white petrolatum, and 500-797 mg/g liquid paraffin.

[0057] The following test was conducted based on Formulation T03: 100 mg/g MCT, 200 mg/g white petrolatum, and 700 mg/g liquid paraffin.

[0058] Fifteen participants were subjected to repeated medication in three groups, as shown in Table 8. The Schirmer's test was performed for tear secretion detection before and one hour after medication. The purpose of the test was to confirm whether the ophthalmic pharmaceutical composition of the present invention has a better effect on tear secretion than that of the commercially available products.

Table 8 Test Group

Group	Left Eye	Right Eye
Group 1	One drop of artificial tear of Control 1	One drop of the ophthalmic pharmaceutical composition of the present invention
Group 2	First, apply one drop of artificial tear of Control 1, and then immediately apply one drop of the ophthalmic pharmaceutical composition of the present invention	One drop of the ophthalmic pharmaceutical composition of the present invention
Group 3	Squeeze 1 cm of eye ointment of Control 2 into the lower eyelid	One drop of the ophthalmic pharmaceutical composition of the present invention

[0059] Evaluation method: Tear secretion test (Schirmer's Test)

Baseline (Before medication)

One hour after medication: Calculate the results by subtracting the baseline after measurement

[0060] Test steps:

Baseline value: Before medication, Schirmer's test was performed on both eyes of each participant using tear test strips.

[0061] The left and right eyes of each participant were medicated according to the groups in Table 8, and then the following steps were followed.

[0062] Schirmer's test was performed on both eyes of each participant 1 hour after medication.

[0063] After each group was medicated, it was necessary to wait for a 1-day drug clearance period before the next group was medicated.

[0064] Tear secretion test (Schirmer's test) results

[0065] A total of 15 participants' trial results were included for statistics, and the measured data was averaged. As shown in Table 9, the baseline was subtracted from the measured data 1 hour after medication to obtain the results that show whether the tear secretion increased or decreased after medication, and the changes in the measured data before and after medication were converted into percentages to further show the ratio of tear increase or

decrease. The results showed that, for the right eye of Group 1 using the ophthalmic pharmaceutical composition of the present invention, its tear secretion after 1 hour of medication was significantly greater than that of the left eye using the artificial tear of Control 1 ($p=0.013$). There was no significant difference in tear secretion between the test results of the left and right eyes in other medication groups. In addition, according to the test results of Group 2, even if the ophthalmic pharmaceutical composition of the present invention was used together with artificial tear of Control 1, the tear secretion was not significantly better than that of the ophthalmic pharmaceutical composition of the present invention alone.

Table 9 Change of Schirmer's Test Tear Secretion One Hour After Medication

Group 1	Left Eye	Right Eye
Change of Tear Secretion (mm)	-1.3	0.9
Change Rate of Tear Secretion (%)	-27.5	20.9
Comparison of Left and Right Eyes	$p=0.013$	
Group 2	Left Eye	Right Eye
Change of Tear Secretion (mm)	0.6	0.3
Change Rate of Tear Secretion (%)	16.1	5.8
Comparison of Left and Right Eyes	$p=0.814$	
Group 3	Left Eye	Right Eye
Change of Tear Secretion (mm)	0.7	0.7
Change Rate of Tear Secretion (%)	24.4	19.2
Comparison of Left and Right Eyes	$p=0.964$	

[0066] The results of Schirmer's Test one hour after medication are presented in a bar graph, which can more intuitively show the tear secretion change, as shown in FIG. 2.

[0067] Compared with other commercially available products, the ophthalmic pharmaceutical composition of the present invention is significantly better than artificial tear of Control 1, according to the tear secretion test results in Table 9. Moreover, even if the ophthalmic pharmaceutical composition of the present invention is used together with artificial tear of Control 1, the efficacy will not be better than that of the ophthalmic pharmaceutical composition of the present invention alone. The ophthalmic pharmaceutical composition of the present invention has similar efficacy to the eye ointment of Control 2. However, according to the fluidity results in Table 5, the ophthalmic pharmaceutical composition of the present invention has better fluidity than that of the eye ointment of Control 2, and can be contained in an eye drop bottle for greater convenience for patients to use, and will not blur vision after use.

[0068] Example 5 Addition of active pharmaceutical ingredients to the ophthalmic pharmaceutical composition of the present invention

[0069] Active pharmaceutical ingredients that are insoluble in water could only be made into eye suspensions or eye ointments in the past because of their poor water solubility. In addition to the need for added preservatives, eye suspensions may also have the risk of inhomogeneous content. Eye ointments are difficult to apply and can easily obstruct vision or cause discomfort such as foreign body sensation after use. The ophthalmic pharmaceutical composition of the present invention is an oil-based preparation, and can serve as an ophthalmic drug platform to which water-insoluble active pharmaceutical ingredients are added and can be used in the eye drop oil dosage form.

[0070] The water-insoluble active pharmaceutical ingredients comprise steroids, tetracyclines, macrolide antibiotics, prostaglandins, carbonic anhydrase inhibitors (CAI), immunosuppressive agents or other water-insoluble active pharmaceutical ingredients.

[0071] The water-insoluble active pharmaceutical ingredient steroids comprise loteprednol etabonate, betamethasone, dexamethasone, fluorometholone, prednisolone acetate, hydrocortisone acetate, etc. Among them, loteprednol etabonate has the worst water solubility and is used as a representative steroid for subsequent experiments.

[0072] The water-insoluble active pharmaceutical ingredient tetracyclines comprise doxycycline hyclate, tetracycline HCl, minocycline HCl, etc. Among them, doxycycline hyclate has the worst water solubility and is used as a representative of tetracyclines for subsequent experiments.

[0073] The water-insoluble active pharmaceutical ingredient macrolide antibiotics comprise erythromycin, azithromycin, etc. Among them, azithromycin has the worst water solubility and is used as a representative macrolide antibiotic for subsequent experiments.

[0074] The water-insoluble active pharmaceutical ingredient prostaglandins comprise latanoprost, latanoprostene bunod, travoprost or bimatoprost and the like.

[0075] The water-insoluble active pharmaceutical ingredient carbonic anhydrase inhibitors comprise brinzolamide and the like.

[0076] The water-insoluble active pharmaceutical ingredient immunosuppressive agents comprise tacrolimus, sirolimus, etc. Among them, sirolimus has the worst water solubility and is used as a representative immunosuppressive agent for subsequent experiments.

[0077] Other water-insoluble active pharmaceutical ingredients comprise rebamipide, omega 3, nepafenac, besifloxacin HCl, selenium disulfide, cyclosporin, vitamin A, etc.

[0078] The aforementioned active pharmaceutical ingredients such as cyclosporin, tacrolimus, sirolimus, rebamipide, omega 3, selenium disulfide, vitamin A, etc. have the efficacy of preventing, treating or improving dry eye syndromes.

[0079] The aforementioned doxycycline hyclate, erythromycin, minocycline HCl, azithromycin, etc. have the efficacy of preventing, treating or improving meibomian gland dysfunction.

[0080] The aforementioned besifloxacin HCl, tetracycline HCl, doxycycline hyclate, erythromycin, minocycline HCl, azithromycin, etc. have the efficacy of treating bacterial infections.

[0081] The aforementioned active pharmaceutical ingredients such as loteprednol etabonate, betamethasone, dexamethasone, fluorometholone, prednisolone acetate, hydrocortisone acetate, etc. can be steroids.

[0082] The aforementioned active pharmaceutical ingredients such as nepafenac etc. are nonsteroidal anti-inflammatory drugs (NSAIDs).

[0083] The aforementioned active pharmaceutical ingredients such as brinzolamide, latanoprost, latanoprostene bunod, travoprost or bimatoprost etc. have the efficacy of a drug for preventing, treating or improving glaucoma.

Table 10 Experimental Results of Transmittance, Viscosity and Water Content of Active Pharmaceutical Ingredients Added to the Ophthalmic Pharmaceutical Composition of the Present Invention

Unit Quantity mg/g	T24	T25	T26	T27	T28	T29	T30	T31	T32	T33
Doxycycline Hyclate	0.1	-	-	-	-	-	-	-	-	-
Latanoprost	-	0.05	-	-	-	-	-	-	-	-

Omega 3	-	-	2	-	-	-	-	-	-	-
Cyclosporin	-	-	-	0.9	-	-	-	-	-	-
Azithromycin	-	-	-	-	15	-	-	-	-	-
Sirolimus	-	-	-	-	-	0.2	-	-	-	-
Tacrolimus	-	-	-	-	-	-	-	0.1	0.1	0.1
Vitamin A	-	-	-	-	-	-	0.005	-	-	-
MCT	799.9	100	100	100	200	100	100	100	50	30
IPM	50	-	-	-	-	-	-	-	-	-
Liquid paraffin	-	749.95	748	749.1	635	749.8	699.995	699.9	699.9	719.9
White petrolatum	150	150	150	150	150	150	200	200	250	250
Transmittance (%T)	88.5	89.7	91.9	92.2	100	91.8	84.6	86.4	89.0	87.0
Viscosity (CP)	99.1	28.0	31.8	35	32.5	32.5	49.4	45.1	93.9	87.7
Water content (%)	0.21	0.11	0.12	0.11	0.14	0.29	0.07	0.14	0.12	0.11

[0084] From the experimental results in the Table 10 of biological liquid membrane irritation (transmittance), viscosity, and water content of the ophthalmic pharmaceutical composition of the present invention with the addition of water-insoluble active pharmaceutical ingredients, it is found that the transmittance of T24 to T33 is higher than 80%, indicating low or no eye irritation after use. T24 to T33 have a viscosity less than 100, showing a good fluidity. They can be used as an eye drop oil dosage form and will not cause blurred vision after use. From the water content results, it can be seen that the water content of T24 to T33 is far lower than 0.75 which can be utilized by microorganisms. Therefore, the ophthalmic pharmaceutical composition of the present invention is not conducive to the growth of microorganisms, so it is not necessary to add preservatives.

[0085] Example 6 Adding active pharmaceutical ingredients to the pharmaceutical composition for eye drop oil dosage form of the present invention, taking the addition of tacrolimus as an example

[0086] Appropriate amounts of tacrolimus, liquid paraffin, lipid, and white petrolatum ingredients were placed in a glass beaker, then heated to about 90°C, and stirred with a magnet,

until the ingredients were completely dissolved to obtain a homogeneously mixed solution. Then, the mixed solution was stirred and cooled to obtain the pharmaceutical composition for eye drop oil dosage form containing tacrolimus with different proportions in Table 12.

[0087] Comparative Example 1 Commercially available tacrolimus-containing eye drop

[0088] Comparative Example 1 was prepared in accordance with the ingredients labeled in the package insert of the commercially available tacrolimus-containing eye drops. The ingredients were listed in Table 11, and Comparative Example 1 contained 0.1 wt% of tacrolimus. The eye drop was prepared as follows. 20% of water and polyvinyl alcohol were added to a beaker. The mixture was heated to 80°C, stirred until dissolved, and then cooled to 30°C. Next, tacrolimus was added and homogenized at 3000 rpm for 15 minutes to obtain the main ingredient phase. Separately, 60% of water and the remaining ingredients were added to another beaker, and stirred until dissolved. The main ingredient phase was added, and a fixed amount of water was added and stirred evenly.

Table 11 Ingredients Labeled in the Package Insert of Commercially Available Tacrolimus-containing Eye Drop

Ingredient	Content wt%
Tacrolimus	0.1
Polyvinyl Alcohol	1.4
Benzalkonium Chloride	0.01
Sodium Chloride	0.5
Sodium Phosphate Monobasic 2H ₂ O	0.04
Sodium Phosphate Dibasic 12H ₂ O	0.9
Water For Inj. Add To	100%

Table 12 Pharmaceutical Composition for Eye Drop Oil Dosage Form Containing Tacrolimus

Pharmaceutical Composition of the Present Invention	Tacrolimus	Lipid	White Petrolatum	Drug Excipient
T34	0.1 wt%	30 wt%	20 wt%	49.9 wt% of liquid paraffin
T35	0.05 wt%	15 wt%	20 wt%	64.95 wt% of liquid paraffin
T36	0.03 wt%	15 wt%	20 wt%	64.97 wt% of liquid paraffin
T37	0.01 wt%	10 wt%	20 wt%	69.99 wt% of liquid paraffin
T38	0.005 wt%	10 wt%	20 wt%	69.995 wt% of liquid paraffin

T39	0.001 wt%	10 wt%	20 wt%	69.999 wt% of liquid paraffin
T40	0.001 wt%	30 wt%	20 wt%	49.999 wt% of liquid paraffin
T41	0.001 wt%	15 wt%	20 wt%	64.999 wt% of liquid paraffin
T42	0.01 wt%	5 wt%	25 wt%	69.99 wt% of liquid paraffin
T43	0.01 wt%	3 wt%	25 wt%	71.99 wt% of liquid paraffin
T44	0.1 wt%	30 wt%	-	69.9 wt% of canola oil
T45	0.1 wt%	30 wt%	-	Combination of 39.9 wt% of liquid paraffin and 30 wt% of canola oil
T46	0.1 wt%	-	-	Combination of 69.9 wt% of liquid paraffin and 30 wt% of soybean oil
T47	0.1 wt%	-	-	Combination of 69.9 wt% of liquid paraffin and 30 wt% of lanolin oil
T48	0.1 wt%	-	-	Combination of 69.9 wt% of liquid paraffin and 30 wt% of olive oil
T49	0.1 wt%	-	-	Combination of 69.9 wt% of liquid paraffin and 30 wt% of corn oil

[0089] Eye irritation evaluation

Table 13 Transmittance and Corresponding Eye Irritation Measured by In vitro Test of Biological Liquid Film

Group	Transmittance (%)	Eye Irritation
T34	99.1	No eye irritation
T35	98.6	No eye irritation
T36	98.1	No eye irritation
T37	99.8	No eye irritation
T38	98.3	No eye irritation
T39	96.3	No eye irritation
T40	100.0	No eye irritation
T41	100.0	No eye irritation
T42	99.6	No eye irritation
T43	98.8	No eye irritation
T44	82.9	Low eye irritation
T45	91.3	No eye irritation
T46	86.7	Low eye irritation

T47	91.0	No eye irritation
T48	87.8	Low eye irritation
T49	89.2	Low eye irritation
Comparative Example 1	58.2	High eye irritation

[0090] From the results in Table 13, it can be seen that the tacrolimus-containing pharmaceutical compositions for eye drop oil dosage form of the present invention have a transmittance higher than 80%, so they are low-irritating or even non-irritating to the eyes, and the tacrolimus-containing pharmaceutical compositions of eye drop oil dosage form of T34 to T43 have a transmittance higher than 95%. In contrast, the commercially available tacrolimus-containing eye drops in Comparative Example 1 have a transmittance of only 58.2%, so they are obviously highly irritating to the eyes.

[0091] This demonstrates that, compared to the commercially available tacrolimus-containing eye drops with high eye irritation, the tacrolimus-containing pharmaceutical compositions for eye drop oil dosage form of the present invention do have a better effect of avoiding eye irritation.

[0092] Stability evaluation

[0093] In this test, T34 to T43 and Comparative Example 1 were selected for the stability test. Specifically, the tacrolimus-containing pharmaceutical compositions for eye drop oil dosage form of T34 to T43 and the commercially available tacrolimus-containing eye drops of Comparative Example 1 were placed at 25°C for 1 month, and then at 70°C for 3 days. After that, according to the method for testing tacrolimus raw materials specified in USP, the tacrolimus content of each group was detected by high performance liquid chromatography (HPLC-UV; which adopts L1 specification, silica gel particle size of 3 microns, column diameter of 4.6 cm, and length of 15 cm), where the flow rate of the mobile phase of the high performance liquid chromatography is about 1.5 ml/min, the composition formulation of the mobile phase is shown in Table 14 below, and the composition proportion of the mobile phase at different times is shown in Table 15 below. The results of tacrolimus content determination for T34 to T43 and Comparative Example 1 are listed in Table 16 below.

Table 14 Mobile Phase Formulation for High Performance Liquid Chromatography

Solution A	Solution B	Solution C	Solution D
Phosphoric acid at a	A solution of acetonitrile	A solution of solution	A solution of solution

concentration of 6 mM	and tertiary methyl butyl ether mixed in a volume ratio of 81:19	A and solution B mixed in a volume ratio of 4:1	A and solution B mixed in a volume ratio of 1:4
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Table 15 Composition Proportions of Mobile Phase in High Performance Liquid Chromatography at Different Times

Time (minute)	Composition proportion of mobile phase (%)	
	Solution C	Solution D
0	72	28
30	72	28
53	15	85
54	72	28
60	72	28

Table 16 Results of Tacrolimus Determination for T34 to T43 and Comparative Example 1

Group	Tacrolimus Content (%)
T34	95.4
T35	102.6
T36	98.1
T37	102.3
T38	104.9
T39	103.2
T40	103.7
T41	87.2
T42	96.1
T43	86.4
Comparative Example 1	71.8

[0094] From the results in Table 16 above, it can be seen that after the stability test, the tacrolimus content in the pharmaceutical composition for eye drop oil dosage form of T34 to T43 is still higher than 85%, among which the tacrolimus content in T34 to T40 and T42 is higher than 95%. In contrast, for the commercially available tacrolimus-containing eye drops in Comparative Example 1, after the stability test, the tacrolimus content contained therein is only 71.8%, which is significantly lower than the results of the pharmaceutical composition of the present invention. It can be seen therefrom that the tacrolimus-containing pharmaceutical composition for eye drop oil dosage form of the present invention does have a better stability.

[0095] In summary, the present invention provides an eye drop oil, which is an ophthalmic pharmaceutical composition with a novel dosage form. Compared with the prior arts, the ophthalmic composition has the following advantages: 1. Without destroying the stability of the tear film like eye drops, the ophthalmic composition is highly safe for long-term use. 2. Compared with eye ointments, the ophthalmic composition of the present invention is

contained in a general eye drop bottle, is convenient to use, has low eye irritation, and will not cause blurred vision after use. 3. The ophthalmic composition can effectively prevent the loss of water from the tear film, treat, prevent or improve dry eye syndrome, and meet the treatment needs of patients with tear over evaporation (lipid deficient dry eye). 4. The ophthalmic composition can be added with water-insoluble active pharmaceutical ingredients and can serve as an ophthalmic drug platform. 5. Because of the low water content and low water activity, there is no need to add preservatives, avoiding preservative-related side effects. 6. From the results of ophthalmic pharmaceutical compositions containing tacrolimus, it can be seen that the ophthalmic composition of the present invention has a stability better than that of commercially available products.

CLAIMS

What is claimed is:

1. A pharmaceutical composition for eye drop oil dosage form, comprising: a lipid, and a white petrolatum and a liquid paraffin, wherein each gram of the ophthalmic pharmaceutical composition comprises 3- 500 mg of lipid, 100-250 mg of white petrolatum, and 1-797 mg of liquid paraffin.

2. The pharmaceutical composition according to claim 1, wherein the lipid comprises medium-chain triglycerides, soybean oil, corn oil, olive oil, canola oil, sunflower oil, isopropyl myristate (IPM), lanolin oil, peanut oil, and castor oil.

3. The pharmaceutical composition according to claim 1, wherein the lipid is a medium-chain triglyceride.

4. The pharmaceutical composition according to claim 1, wherein each gram of the pharmaceutical composition comprises 3-300 mg of lipid, 100-250 mg of white petrolatum, and 300-797 mg of liquid paraffin.

5. The pharmaceutical composition according to claim 1, wherein each gram of the pharmaceutical composition comprises 3-300 mg of lipid, 100-240 mg of white petrolatum, and 500-797 mg of liquid paraffin.

6. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition for eye drop oil dosage form can be added with active pharmaceutical ingredients.

7. The pharmaceutical composition according to claim 6, wherein the active pharmaceutical ingredient comprises mineral oil, steroids, tetracyclines, macrolide antibiotics, prostaglandins, carbonic anhydrase inhibitors, immunosuppressive agents or other water-insoluble active pharmaceutical ingredients.

8. The pharmaceutical composition according to claim 7, wherein the steroid comprises loteprednol etabonate, betamethasone, dexamethasone, fluorometholone, prednisolone acetate or hydrocortisone acetate.

9. The pharmaceutical composition according to claim 7, wherein the tetracycline

comprises doxycycline hyclate, tetracycline HCl or minocycline HCl.

10. The pharmaceutical composition according to claim 7, wherein the macrolide antibiotic comprises erythromycin or azithromycin.

11. The pharmaceutical composition according to claim 7, wherein the prostaglandin comprises latanoprost, latanoprostene bunod, travoprost or bimatoprost.

12. The pharmaceutical composition according to claim 7, wherein the carbonic anhydrase inhibitor comprises brinzolamide.

13. The pharmaceutical composition according to claim 7, wherein the immunosuppressive agent comprises tacrolimus or sirolimus.

14. The pharmaceutical composition according to claim 7, wherein the other water-insoluble active pharmaceutical ingredient comprises rebamipide, omega 3, nepafenac, besifloxacin HCl, selenium disulfide, vitamin A or cyclosporin.

15. Use of the pharmaceutical composition according to claim 1 for preparing a drug for treating, preventing or improving dry eye syndromes.

16. The use according to claim 15, wherein the dry eye syndrome is over evaporation.

17. The use according to claim 15, wherein the dry eye syndrome is caused by meibomian gland dysfunction.