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(54) **AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION CONTAINING AS MAIN COMPONENT BENZOPYRAN DERIVATIVE**

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(58) **Field of Search** 514/382

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,976,760 * 3/1999 Sasatani et al. 424/494

FOREIGN PATENT DOCUMENTS

0641569 3/1995 (EP) .
96/41628 12/1996 (WO) .

OTHER PUBLICATIONS

Database WPI, Section Ch, Week 9621, Derwent Publications Ltd., London, GB; Class A96, AN 96–205438, XP002081469 & JP 08 073353 A (Ono Pharmaceutical) Mar. 19, 1996.

* cited by examiner

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(57) **ABSTRACT**

In order to promote solubilization or suspension of 4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran or its hydrate (pranlukast) in water, at least one component selected from surfactants, water-soluble cellulose derivatives and water-soluble vinyl polymers is formulated together with pranlukast. Thus, it is possible to provide an aqueous liquid pharmaceutical composition containing higher concentration of pranlukast and having good properties.

37 Claims, 2 Drawing Sheets

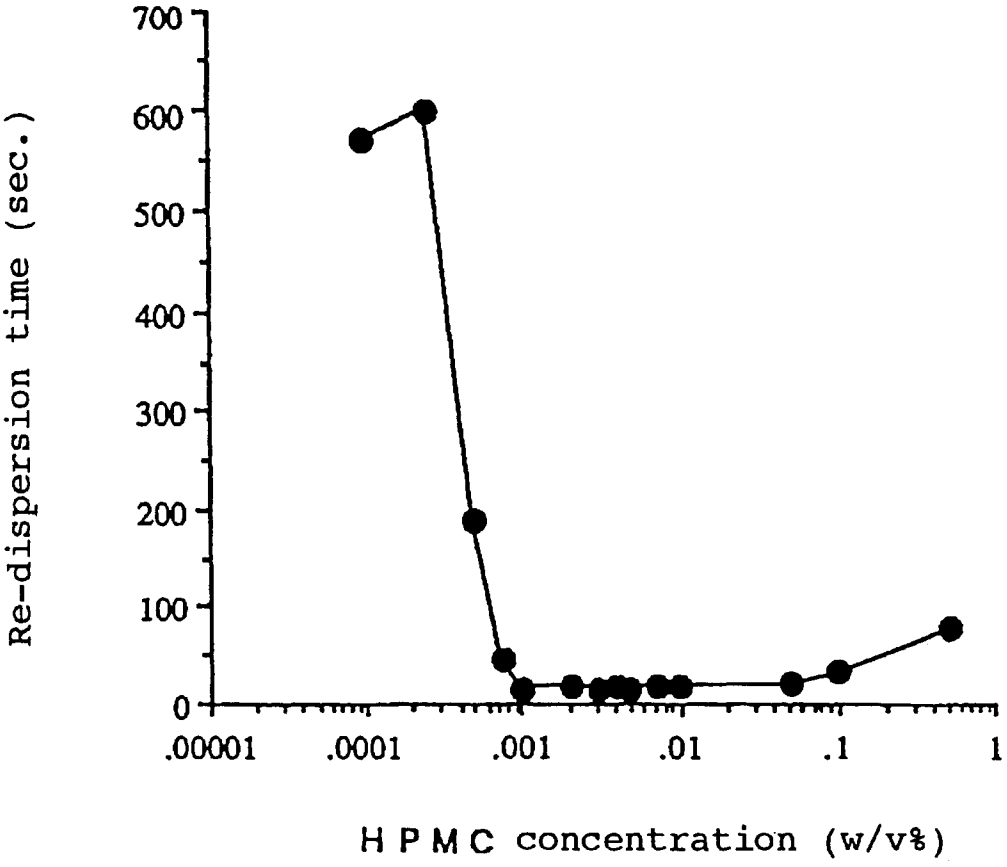

Fig. 1

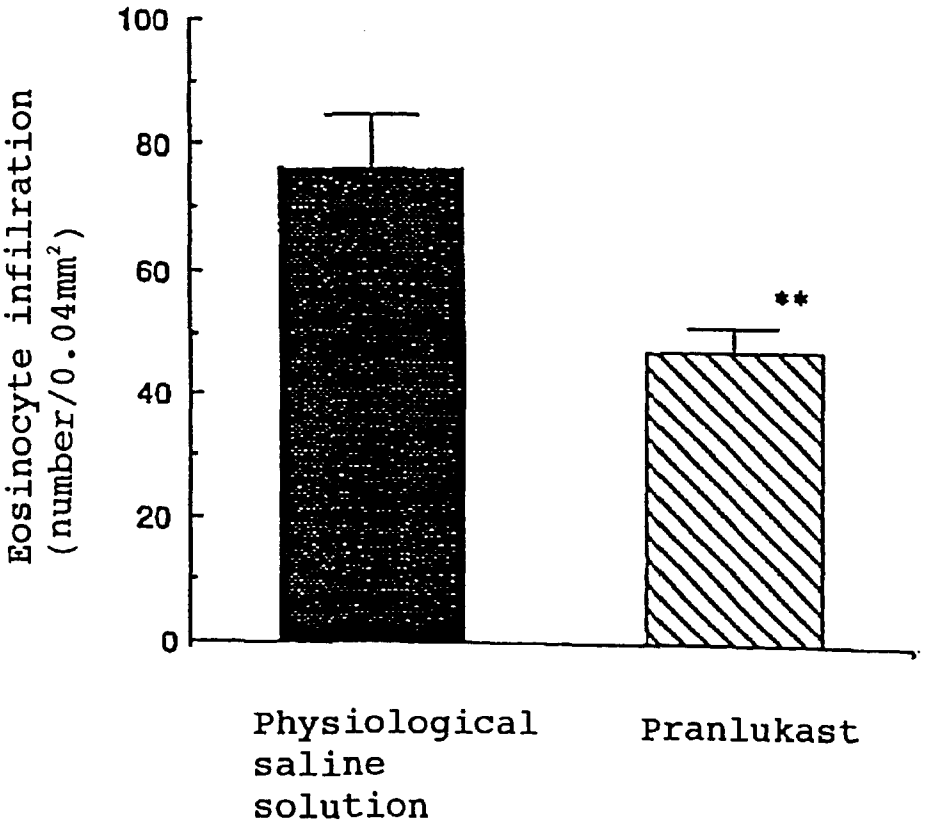

Fig. 2

AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION CONTAINING AS MAIN COMPONENT BENZOPYRAN DERIVATIVE

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising as a main component 4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran or its hydrate. In particular, it relates to an aqueous liquid pharmaceutical composition containing the benzopyran derivative or its hydrate in higher concentration and having good properties.

BACKGROUND OF THE INVENTION

4-Oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran is an antagonist toward leukotrienes (LTC4, LTD4, LTE4) and is known to be a medicine having excellent pharmacological activities on various allergic diseases including asthma (JP-A 61-50977). Its ½ hydrate is called as "pranlukast" and is utilized as an anti-allergic medicine. Then, in the field of ophthalmology, it has been proposed to apply such a medicine to allergic eye diseases such as vernal keratoconjunctivitis, etc.

In general, for preparing an aqueous liquid pharmaceutical composition such as water-soluble eye drops, it is considered that a pharmacologically active component should be present in concentration of about 0.01 to 0.1%. However, 4-oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H -1-benzopyran and its hydrate (hereinafter, they are referred to as "pranlukast" all together, unless otherwise stated) have very low water-solubility, which makes every difficult to prepare a useful aqueous liquid pharmaceutical composition thereof. Then, the use of polyvinyl pyrrolidone and β-cyclodextrin has been proposed to solubilize pranlukast (JP-A 8-73353).

However, even if polyvinyl pyrrolidone, which is a material known to have strongest solubilization power, is used, pranlukast dissolves in water in concentration of, at highest, about 0.01%.

OBJECTS OF THE INVENTION

The main object of the present invention is to promote solubilization or suspension of pranlukast in water, thereby providing an aqueous liquid pharmaceutical composition containing higher concentration of pranlukast and having good properties.

This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph illustrating the relation between hydroxypropylmethyl cellulose (HPMC) concentration and time required for re-dispersion of pranlukast.

FIG. **2** is a graph illustrating the results of the test for inhibitory activity on conjunctival eosinocyte infiltration hereinafter.

SUMMARY OF THE INVENTION

The present inventors have extensively studied to promote solubilization or suspension of pranlukast in water and, consequently, have found that the desired solubilization or suspension can be obtained by using at least one component selected from surfactants and specific high-molecular weight substances. Thus, the present inventors have succeeded in preparing the desired aqueous liquid pharmaceutical composition containing higher concentration of pranlukast and having good properties, and have completed the present invention.

That is, according to the present invention, there is provided an aqueous liquid pharmaceutical composition which comprises 4-oxo-8-[4-(4-phenylbutoxy) benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran or its hydrate and at least one component selected from surfactants, water-soluble cellulose derivatives and water-soluble vinyl polymers.

In particular, one aspect of the aqueous liquid pharmaceutical composition of the present invention is an aqueous solution containing pranlukast and a surfactant. Preferably, the composition further contains a stabilizer.

Another aspect of the aqueous liquid pharmaceutical composition of the present invention is an aqueous suspension containing pranlukast and at least one component selected from the group consisting of water-soluble cellulose derivatives and water-soluble vinyl polymers. Optionally, the suspension may further contain a surfactant. Preferably, the suspension contains a relatively small amount of a surfactant together with the water-soluble high-molecular weight substance.

These aqueous liquid pharmaceutical compositions have good re-dispersibility over a long time and are stable. In addition, they can contain higher concentration of pranlukast. Then, they can be useful as eye drops, nasal drops, injectable preparations, internal medicine and the like and can be used as an eosinocyte infiltration inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

4-Oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran or its hydrate to be used in the present invention is not specifically limited but its ½ hydrate available from Ono Pharmaceutical Co., Ltd. as "pranlukast" is suitable for the present invention.

The amount of pranlukast to be formulated in the composition is not specifically limited but, in case of an aqueous solution, it is formulated in an amount of 0.2 w/v % or less, normally, 0.001 to 0.2 w/v %, preferably 0.005 to 0.1 w/v % based on the total weight of the composition and, in case of an aqueous suspension, 0.01 to 5.0 w/v %, preferably 0.1 to 2.0 w/v % based on the total weight of the composition, in terms of its ½ hydrate.

The surfactants to be used are at least one member selected from nonionic surfactants, cationic surfactants and anionic surfactants. As the nonionic surfactants, it is preferred to use those having HLB of 10 to 18. Examples of the nonionic surfactants include polyoxyethylene sorbitan fatty acid ester (e.g., Polysorbate 80, Polysorbate 60, Polysorbate 40, etc.), polyoxyethylene hydrogenated castor oil (e.g., polyoxyethylene hydrogenated castor oil 60, polyoxyethylene hydrogenated castor oil 50, polyoxyethylene castor oil 40, etc.), polyoxyethylene alkylphenyl formaldehyde condensate (e.g., Tyloxapol, etc.), polyoxyethylene polyoxypropylene block copolymer (e.g., Poloxamer 188, Poloxamer 403, etc.) and sucrose ester of fatty acid (e.g., Ryutosugar ester P-1570 and S-1570 manufactured by Mitsubishi Chemical Foods), among others.

Examples of the cationic surfactants include quaternary ammonium salt (e.g., benzalkonium chloride, etc.), among others. Examples of the anionic surfactants include alkyl sulfate (e.g., sodium lauryl sulfate, etc.), among others.

The surfactant can be used alone or in combination of two or more thereof and, normally, in case of an aqueous solution, the surfactant(s) are formulated in an amount of 0.5 to 8 w/v %, preferably 1 to 5 w/v %, more preferably 2 to 4 w/v % based on the total weight of the composition. And, in this case, the proportion of the surfactant(s) to pranlukast is such that 5 to 100 parts, preferably 10 to 60 parts by weight of the surfactant(s) are formulated per 1 part of pranlukast (½ hydrate).

In case that the composition is an aqueous suspension, optionally, the surfactant(s) are formulated in an amount of 0.0001 to 0.2 w/v %, preferably 0.001 to 0.2 w/v %, more preferably 0.01 to 0.2 w/v % based on the total weight of the composition together with the water-soluble high-molecular weight substance as described hereinafter. And, in this case, the proportion of the surfactant(s) to pranlukast is such that 0.0001 to 0.2 part, preferably 0.001 to 0.2 part, more preferably 0.01 to 0.2 part by weight of the surfactant(s) are formulated per 1 part of pranlukast (½ hydrate).

In the present invention, when the composition is in the form of an aqueous solution, normally, pH of the composition is adjusted to 6 or higher, preferably 6 to 9, more preferably 6 to 8. Further, in addition to the surfactants, it is preferred to formulate at least one stabilizer selected from anti-oxidants and chelating agents in an amount of about 0.001 to 0.1 w/v %, thereby improving stability of pranlukast.

As such stabilizers, there are, for example, anti-oxidants such as butylated hydroxytoluene, butylated hydroxyanisole, etc. and chelating agents such as sodium edetate, etc. They can be used alone or in combination of two or more thereof.

The water-soluble cellulose derivatives used in the present invention include at least one member selected from methylcellulose, carboxymethylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, and hydroxypropylmethyl cellulose.

The water-soluble vinyl polymers used in the present invention include at least one member selected from polyvinyl pyrrolidone K25, polyvinyl pyrrolidone K30, polyvinyl pyrrolidone K90, polyvinyl alcohol and carboxyvinyl polymer.

These water-soluble high-molecular weight substances can be used alone or in combination of two or more thereof.

As described above, these water-soluble high-molecular weight substances can be used together with one or more surfactants, thereby further improving re-dispersibility of the aqueous suspension, in particular, after storage.

In the present invention, the water-soluble cellulose derivatives and the water-soluble vinyl polymers function, in particular, as a suspending agent of the aqueous liquid pharmaceutical composition in the form of a suspension. Then, they are formulated in an amount of 0.00001 to 0.1 w/v %, preferably 0.00005 to 0.05 w/v % based on the total weight of the composition. And, the proportion of the water-soluble high-molecular weight substance(s) to pranlukast is such that 0.0001 to 0.1 part by weight, preferably 0.0005 to 0.02 part by weight of the water-soluble high-molecular weight substance(s) are formulated per 1 part by weight of pranlukast (½ hydrate).

In a liquid pharmaceutical composition, such suspending agent is generally used in concentration ranging from 0.1 to 4 w/v % based on the total weight of the composition. In view of this, it is very surprising that the suspending agent functions even in such a small amount as in the present invention.

When the aqueous liquid pharmaceutical composition is in the form of a suspension, pH of the composition may be within, for example, the range normally employed for eye drops (e.g., pH 4 to 9, preferably pH 5 to 8).

If necessary, the aqueous liquid pharmaceutical composition may further contain suitable additives, for example, an isotonic agent such as inorganic salt (e.g., sodium chloride, boric acid, potassium chloride, etc.) and polyhydric alcohol (e.g., glycerin, mannitol, sorbitol, etc.); a buffer solution such as borate buffer solution, phosphate buffer solution, acetate buffer solution, citrate buffer solution, Tris buffer solution, etc. and buffer agent such as amino acid (e.g., glutamic acid, ϵ-aminocapronic acid, etc.); a chelating agent such as sodium edetate, citric acid, etc.; a preservative such as quaternary ammonium salt (e.g., benzalkonium chloridie, benzethonium chloride, etc.), p-hydroxybenzoate (methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate, etc.), sorbic acid, chlorobutanol, sodium edetate, boric acid, etc., and the like. Normally, an isotonic agent can be formulated in an amount of 0.5 to 6.5 w/v % based on the total weight of the composition. Likewise, 0.01 to 1.0 w/v % of a buffer and 0.001 to 0.1 w/v % of a chelating agent can be formulated based on the total weight of the composition.

The aqueous liquid pharmaceutical composition of the present invention can be prepared in the form of an aqueous solution or suspension such as eye drops, nasal drops, injectable preparations, internal medicine and the like according to a per se known method. For example, the composition can be prepared by adding the solubilizing agent and/or suspending agent, a buffer, an isotonic agent and a preservative to sterilized purified water and, if necessary, heating to dissolve them. The desired liquid pharmaceutical composition can be prepared by dissolving or suspending pranlukast in the resultant solution.

The aqueous liquid pharmaceutical composition of the present invention has eosinocyte infiltration inhibitory activity and is useful as an eosinocyte infiltration inhibitor. Then, it can be used for prophylaxis and therapy of seasonal or year-round allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis, giant papillary conjunctivitis, contact blephroconjunctivits, keratitis, scleritis, uveitis, eye itch, allergic rhinitis, sneeze, nasal itching, nasal hypersensitivity, nasofrontal eczema, nasal obstruction and the like. In general, the composition is topically or systemically administered once to six times per day at a daily dosage of 20 to 100 μg/ml of pranlukast.

The present invention will be further illustrated by the following experiments and preparation examples, but the present invention is not limited to these preparation examples. In the following experiments and preparation examples, "pranlukast" used is the ½ hydrate and all the "percents" are by weight unless otherwise stated.

Experiment 1

Study of solubilizing agents of pranlukast

Method

Pranlukast (manufactured by Ono Pharmaceutical Co., Ltd.) was suspended in 0.1% borate buffer (pH 9 or 8) or 0.1% phosphate buffer (pH 8 or 7) at concentration of 0.1 w/v %. Likewise, pranlukast was suspended in each 0.5% solution of surfactants (polysorbate 80, polysorbate 60, polysorbate 40, polyoxyethylene hydrogenated castor oil 60, Tyloxapol, benzalkonium chloride, and sodium lauryl sulfate), water-soluble vinyl polymers (polyvinyl pyrrolidone K30, and polyvinyl alcohol), cyclodextrins (β-cyclodextrin, γ-cyclodextrin, and 2HP-β-cyclodextrin)

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