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(54) Titre : PRODUIT CONTENANT DE LA PROSTAGLANDINE DONT LA MOLECULE COMPORTE UN ATOME DE FLUOR
(54) Title: PRODUCT CONTAINING PROSTAGLANDIN HAVING FLUORINE ATOM IN ITS MOLECULE

(57) **Abrégé/Abstract:**

An object of the present invention is to provide a prostaglandin-containing product, wherein when an aqueous liquid preparation containing a prostaglandin derivative having at least a fluorine atom in its molecule as an active ingredient is stored in a resin container subjected to a sterilization treatment, a decrease in the content of the prostaglandin derivative in the aqueous liquid preparation can be inhibited. The aqueous liquid preparation containing the prostaglandin derivative having at least a fluorine atom in its molecule as an active ingredient is stored in the resin container subjected to a sterilization treatment with ethylene oxide gas. By doing this, a decrease in the content of the prostaglandin derivative in the aqueous liquid preparation can be inhibited.



Abstract

An object of the present invention is to provide a prostaglandin-containing product, wherein when an aqueous liquid preparation containing a prostaglandin derivative having at least a fluorine atom in its molecule as an active ingredient is stored in a resin container subjected to a sterilization treatment, a decrease in the content of the prostaglandin derivative in the aqueous liquid preparation can be inhibited. The aqueous liquid preparation containing the prostaglandin derivative having at least a fluorine atom in its molecule as an active ingredient is stored in the resin container subjected to a sterilization treatment with ethylene oxide gas. By doing this, a decrease in the content of the prostaglandin derivative in the aqueous liquid preparation can be inhibited.

SPECIFICATION

PRODUCT CONTAINING PROSTAGLANDIN HAVING FLUORINE ATOM IN ITS MOLECULE

Technical Field

The present invention relates to a prostaglandin-containing product comprising an aqueous liquid preparation containing a prostaglandin derivative having at least a fluorine atom in its molecule or a salt thereof stored in a resin container subjected to a sterilization treatment, characterized in that a decrease in the content of the prostaglandin derivative in the aqueous liquid preparation is inhibited by performing the sterilization treatment with ethylene oxide gas, and a method for producing the product.

Background Art

In general, as a container for storing an aqueous liquid preparation, a resin container obtained by molding a synthetic resin such as polypropylene, a propylene/ethylene copolymer or polyethylene is used. Here, the aqueous liquid preparation such as an eye drop is administered directly to the eye which is a particularly sensitive organ in the human body, therefore,

it is strictly demanded that a sterile condition should be maintained until it is instilled. In view of this, a container for storing an eye drop has to be in a sterile condition and needs to be subjected to a sterilization treatment. As a sterilization method for such a container, gamma-ray sterilization, electron-ray sterilization, ethylene oxide gas sterilization, hydrogen peroxide solution sterilization, autoclave sterilization and the like are known.

On the other hand, prostaglandin is a physiologically active substance, and a large number of prostaglandin derivatives have been studied and developed. As the prostaglandin useful for ophthalmic applications, a 13,14-dihydro-15-keto-prostaglandin derivative is disclosed in JP-A-2-108, a 13,14-dihydro-17-phenyl-18,19,20-trinor-prostaglandin F2 α derivative is disclosed in JP-T-3-501025, a 15-deoxy-15-monofluoro-prostaglandin F2 α derivative is disclosed in JP-A-10-251225, and a 15-deoxy-15,15-difluoro-prostaglandin F2 α derivative is disclosed in JP-A-11-71344. In terms of the structures of the prostaglandin derivatives, JP-A-2-108 and JP-T-3-501025 are directed to prostaglandin derivatives having no fluorine atom in their molecules, and JP-A-10-251225 and JP-A-11-71344 are directed to prostaglandin derivatives having one or two fluorine atoms in their molecules.

Disclosure of the invention

Problems to be Solved

In terms of the storage stability of such a prostaglandin derivative, when 13,14-dihydro-17-phenyl-18,19,20-trinor-prostaglandin F2 α isopropyl ester (latanoprost), which is a prostaglandin derivative having no fluorine atom in its molecule, is stored in, for example, a resin container subjected to a sterilization treatment with gamma rays or electron rays, the content of latanoprost does not decrease with time. However, a prostaglandin derivative having at least a fluorine atom in its molecule has a specific property that when it is stored in a resin container subjected to a sterilization treatment with gamma rays or electron rays, the content thereof is liable to decrease.

Therefore, in the case where an aqueous liquid preparation containing a prostaglandin derivative having at least a fluorine atom in its molecule is stored in a resin container, it is an important object to find a sterilization method capable of inhibiting the content of the prostaglandin derivative in the aqueous liquid preparation from decreasing.

Means of Solving Problems

The present inventors made intensive studies in order to achieve the above object, and as a result, they found that when an aqueous liquid preparation containing a prostaglandin derivative having at least a fluorine atom in its molecule is stored in a resin container subjected to a sterilization treatment with ethylene oxide, a decrease in the content of the prostaglandin derivative having at least a fluorine atom in its molecule in the aqueous liquid preparation can be significantly inhibited, and thus the present invention has been accomplished.

That is, the present invention relates to:

(1) a prostaglandin-containing product comprising an aqueous liquid preparation containing a prostaglandin derivative having at least a fluorine atom in its molecule or a salt thereof stored in a resin container subjected to a sterilization treatment, characterized in that a decrease in the content of the prostaglandin derivative or a salt thereof in the aqueous liquid preparation is inhibited by performing the sterilization treatment of the container with ethylene oxide gas;

(2) the prostaglandin-containing product according to the above (1), wherein the aqueous liquid preparation is an eye drop;

(3) the prostaglandin-containing product according

to the above (1) or (2), wherein the prostaglandin derivative having at least a fluorine atom in its molecule is a prostaglandin F2 α derivative having at least a fluorine atom in its molecule or a salt thereof;

(4) the prostaglandin-containing product according to the above (3), wherein the prostaglandin F2 α derivative having at least a fluorine atom in its molecule is a prostaglandin F2 α derivative having at least a fluorine atom at its 15-position;

(5) the prostaglandin-containing product according to the above (4), wherein the prostaglandin F2 α derivative having at least a fluorine atom at its 15-position is a 15-deoxy-15,15-difluoro-prostaglandin F2 α derivative;

(6) The prostaglandin-containing product according to the above (5), wherein the 15-deoxy-15,15-difluoro-prostaglandin F2 α derivative is 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α , 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α , 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranor-prostaglandin F2 α , or an alkyl ester thereof;

(7) the prostaglandin-containing product according to the above (1) or (2), wherein a material of the resin container is polypropylene, a propylene/ethylene copolymer, polyethylene or polyethylene terephthalate;

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(8) the prostaglandin-containing product according to the above (1) or (2), wherein the prostaglandin derivative having at least a fluorine atom in its molecule is 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α , 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α , 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranor-prostaglandin F2 α , or an alkyl ester thereof, and a material of the resin container is polypropylene, a propylene/ethylene copolymer, polyethylene or polyethylene terephthalate;

(9) a method for producing a prostaglandin-containing product comprising an aqueous liquid preparation containing a prostaglandin derivative having at least a fluorine atom in its molecule or a salt thereof stored in a resin container subjected to a sterilization treatment, characterized by performing the sterilization treatment of the container with ethylene oxide gas to inhibit the content of the prostaglandin derivative or a salt thereof in the aqueous liquid preparation from decreasing;

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(10) the method according to the above (9), wherein the aqueous liquid preparation is an eye drop;

(11) a prostaglandin-containing product comprising an aqueous liquid preparation containing 16-phenoxy-15-deoxy-
5 15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α or an alkyl ester thereof or a salt thereof stored in a resin container made of propylene/ethylene copolymer and subjected to a sterilization treatment, wherein a decrease in the content of the 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-
10 prostaglandin F2 α or the alkyl ester thereof or the salt thereof in the aqueous liquid preparation is inhibited by performing the sterilization treatment of the container with ethylene oxide gas; and

(12) a method for producing a prostaglandin-
15 containing product comprising an aqueous liquid preparation containing 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α or an alkyl ester thereof or a salt thereof stored in a resin container made of propylene/ethylene copolymer and subjected to a sterilization treatment,
20 comprising performing the sterilization treatment of the container with ethylene oxide gas to inhibit the content of the 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α or the alkyl ester thereof or the salt thereof in the aqueous liquid preparation from decreasing.

25 The prostaglandin derivative having at least a fluorine atom in its molecule (hereinafter referred to as

the present prostaglandin derivative), which is an active ingredient of the prostaglandin-containing product according to the present invention, is not particularly limited as long as it contains at least a fluorine atom in its molecule, however, it is preferably a prostaglandin F2 α derivative having at least a fluorine atom in its molecule, more preferably a prostaglandin F2 α derivative having at least a fluorine atom at its 15-position, further more preferably a 15-deoxy-15,15- difluoro-prostaglandin F2 α derivative. Particularly preferred examples thereof include 16-phenoxy-15-deoxy- 15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α , 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α , 16-phenoxy-15-deoxy- 15,15-difluoro-13,14-dihydro-17,18,19,20-tetranor-prostaglandin F2 α , alkyl esters thereof and salts thereof. Specific examples of the alkyl ester include lower alkyl esters such as methyl esters, ethyl esters, propyl esters, isopropyl esters, tert-butyl esters, pentyl esters and hexyl esters.

The resin container subjected to a sterilization treatment with ethylene oxide gas is not particularly limited as long as it is a resin container subjected to a sterilization treatment with ethylene oxide gas.

The ethylene oxide gas sterilization is not

particularly limited as long as it is a method of performing a sterilization treatment with ethylene oxide gas, however, for example, it is carried out by the following process. Sterilization is carried out by exposing a resin container to ethylene oxide gas under predetermined temperature and humidity conditions for a time sufficient to effect sterilization, and then, aeration may be carried out for removing ethylene oxide gas. The sterilization temperature can be selected appropriately according to the characteristic of the resin container, however, it is preferably in the range of from 30 to 60°C. Further, the relative humidity is in the range of from 20 to 90%, preferably from 30 to 80%.

Examples of the material of the resin container include polypropylene, propylene/ethylene copolymers, polyethylene, polyethylene terephthalate, polyvinyl chloride, acrylic resins, polystyrene and the like. Preferred examples thereof include polypropylene, propylene/ethylene copolymers, polyethylene, polyethylene terephthalate and the like. Particularly preferred examples thereof include polypropylene, propylene/ethylene copolymers and the like. Here, the propylene/ethylene copolymer is not particularly limited as long as it is a propylene polymer containing an ethylene component, however, it is preferably a propylene polymer containing

an ethylene component in an amount of 10 mol% or less.

In the prostaglandin-containing product of the present invention, it is preferred that the present prostaglandin derivative exists in the container in a state of being dissolved in water. The concentration of the present prostaglandin derivative can be selected appropriately in view of the application of the aqueous liquid preparation or the like. For example, in the case of an eye drop, the concentration of the present prostaglandin derivative in the eye drop is preferably in the range of from 0.00005 to 0.05% (w/v), although it can be selected appropriately according to the disease to be treated, symptoms or the like.

The content of the present prostaglandin derivative refers to the ratio (%) of the concentration of the present prostaglandin derivative existing in the aqueous liquid preparation after a predetermined period of time to the original concentration of the present prostaglandin derivative existing in the aqueous liquid preparation when the prostaglandin-containing product is produced throughout the claims and the specification. For example, in the case where the present prostaglandin derivative is dissolved in water, it refers to the ratio (%) of the concentration of the present prostaglandin derivative existing in the aqueous solution after a predetermined

period of time to the concentration of the present prostaglandin derivative dissolved in water.

When the prostaglandin-containing product of the present invention is an eye drop, a surfactant, an antioxidant, a tonicity agent, a buffer, a preservative or the like can be added thereto as needed. Examples of the surfactant include polysorbate 80, polyoxyethylene hydrogenated castor oil 60, polyoxyl 40 stearate and the like. Examples of the antioxidant include ethylenediamine tetraacetic acid, salts thereof, dibutyl hydroxy toluene and the like. Examples of the tonicity agent include sodium chloride, potassium chloride, calcium chloride, glycerin, propylene glycol and the like. Examples of the buffer include boric acid, borax, citric acid, disodium hydrogenphosphate, ϵ -aminocaproic acid and the like. Examples of the preservative include benzalkonium chloride, chlorhexidine gluconate, benzethonium chloride, sorbic acid, sodium sorbate, ethyl parahydroxybenzoate, butyl parahydroxybenzoate and the like. A method for preparing the eye drop containing the present prostaglandin derivative does not require a special method or procedure, and the eye drop can be prepared by a widely used method. The pH of the eye drop is preferably adjusted to 3 to 8, particularly preferably 4 to 7.

Effect of the Invention

As will be explained in detail in the section of storage stability test described later, when the aqueous liquid preparation of the present invention containing the present prostaglandin derivative is stored in the resin container subjected to a sterilization treatment with ethylene oxide, a decrease in the content of the present prostaglandin derivative in the aqueous liquid preparation can be significantly inhibited in comparison with the case where it is stored in the resin container treated by either gamma-ray sterilization or electron-ray sterilization.

Best Mode for Carrying Out the Invention

Hereinafter, the present invention will be described in detail through carrying out a storage stability test. However, such descriptions are disclosed for the purpose of understanding the present invention better and are not meant to limit the scope of the present invention.

1. Preparation of Eye Drop

1-1. Preparation Method for Eye Drop 1

As a typical example of the present prostaglandin derivative, 0.0005% (w/v) of 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α isopropyl ester (hereinafter, referred to as the present compound)

was used. The present compound was dissolved in purified water by using polysorbate 80 at 0.05% (w/v) as a nonionic surfactant, and then, additives, which are commonly used in an eye drop, such as ethylenediamine tetraacetic acid (q.s.), concentrated glycerin (q.s.) and benzalkonium chloride (q.s.), and the like were added thereto, whereby Eye drop 1 with an osmotic pressure of about 1 and a pH of about 6 was obtained.

1-2. Preparation Method for Eye Drop 2

By using latanoprost which is a prostaglandin derivative having no fluorine atom in its molecule instead of the present compound, Eye drop 2 was obtained by the same procedure as that of the preparation method for Eye drop 1 of item 1-1.

2. Production of Resin Container

A 5-ml eye drop resin container was obtained by injection blow molding of a propylene/ethylene random copolymer (containing an ethylene component in an amount of 3%).

3. Test Method

Example 1

The resin container obtained in the section of "2. Production of Resin Container" was subjected to a sterilization treatment with ethylene oxide gas (sterilization with ethylene oxide at a concentration of

20% (v/v), at a temperature of 40°C and a relative humidity of 50% for 3 hours), and then, in the container, Eye drop 1 obtained in the section of "1. Preparation of Eye Drop" was charged. The container containing this eye drop was stored at a temperature of 40°C and a relative humidity of 75% for 30 days. The concentration of the present compound in the container was measured by high performance liquid chromatography before the initiation of storage and after 30-day storage. The content of the present compound was calculated taking the concentration of the present compound at the time of initiation of storage as a standard (100%). The results are shown in Table 1. Incidentally, each value in Table 1 is expressed as an average of three cases.

Comparative example 1

Except that the sterilization treatment with ethylene oxide gas was altered into a sterilization treatment with gamma rays (32 kGy), the content of the present compound was calculated in the same manner as in Example 1.

Comparative example 2

Except that the sterilization treatment with ethylene oxide gas was altered into a sterilization treatment with electron rays (23 kGy), the content of the present compound was calculated in the same manner as in

Example 1.

Comparative example 3

Except that a container with no sterilization treatment was used as the container, the content of the present compound was calculated in the same manner as in Example 1.

Comparative example 4

Except that Eye drop 1 was altered into Eye drop 2, the content of latanoprost was calculated in the same manner as in Example 1.

Comparative example 5

Except that Eye drop 1 was altered into Eye drop 2 and the sterilization treatment with ethylene oxide gas was altered into a sterilization treatment with gamma rays (32 kGy), the content of latanoprost was calculated in the same manner as in Example 1.

Comparative example 6

Except that Eye drop 1 was altered into Eye drop 2 and the sterilization treatment with ethylene oxide gas was altered into a sterilization treatment with electron rays (23 kGy), the content of latanoprost was calculated in the same manner as in Example 1.

Comparative example 7

Except that Eye drop 1 was altered into Eye drop 2 and a container with no sterilization treatment was used

as the container, the content of latanoprost was calculated in the same manner as in Example 1.

[Table 1]

	Liquid charged	Sterilization treatment method	Content (%) 30 days
Example 1	Eye drop 1	Ethylene oxide gas sterilization	96.5
Comparative example 1	Eye drop 1	Gamma-ray sterilization	78.4
Comparative example 2	Eye drop 1	Electron-ray sterilization	84.5
Comparative example 3	Eye drop 1	No treatment	96.6
Comparative example 4	Eye drop 2	Ethylene oxide gas sterilization	103.2
Comparative example 5	Eye drop 2	Gamma-ray sterilization	99.4
Comparative example 6	Eye drop 2	Electron-ray sterilization	101.1
Comparative example 7	Eye drop 2	No treatment	103.2

4. Test Results and Discussion

As is clear from Table 1, when an eye drop containing the present compound was stored in a container made of a propylene/ethylene random copolymer subjected to a sterilization treatment with ethylene oxide gas, the content of the present compound in the eye drop after a predetermined period of time was higher in comparison with the case where it was stored in a container subjected to a sterilization treatment with gamma rays or electron rays. Further, as is clear from Example 1 and Comparative example 3, when an eye drop containing the present compound was stored in a container subjected to a sterilization treatment with ethylene oxide gas, the content of the present compound in the eye drop after a predetermined period of time was comparable even if it was

compared with the case with no sterilization treatment. Thus, it was confirmed that when the present compound is stored in a resin container subjected to a sterilization treatment with ethylene oxide gas, a decrease in the present compound in an aqueous liquid preparation can be inhibited.

Further, as is clear from Comparative examples 4 to 7, even if an eye drop containing latanoprost which is a prostaglandin derivative having no fluorine atom in its molecule was stored in a container subjected to a sterilization treatment with gamma rays, electron rays or ethylene oxide gas, the content of latanoprost in the eye drop did not decrease in any of the cases, and moreover, even if it was compared with the case where it was stored in a container with no sterilization treatment, the content of latanoprost in the eye drop was comparable. Thus, it was confirmed that even if an aqueous liquid preparation containing a prostaglandin derivative having no fluorine atom in its molecule such as latanoprost is stored in a container subjected to any sterilization treatment, it is stable.

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CLAIMS:

1. A prostaglandin-containing product comprising an aqueous liquid preparation containing 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α or an
5 alkyl ester thereof or a salt thereof stored in a resin container made of propylene/ethylene copolymer and subjected to a sterilization treatment, wherein a decrease in the content of the 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α or the alkyl ester thereof or the salt
10 thereof in the aqueous liquid preparation is inhibited by performing the sterilization treatment of the container with ethylene oxide gas.
2. The prostaglandin-containing product according to claim 1, wherein the aqueous liquid preparation is an eye drop.
- 15 3. A method for producing a prostaglandin-containing product comprising an aqueous liquid preparation containing 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α or an alkyl ester thereof or a salt thereof stored in a resin container made of propylene/ethylene
20 copolymer and subjected to a sterilization treatment, comprising performing the sterilization treatment of the container with ethylene oxide gas to inhibit the content of the 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranor-prostaglandin F2 α or the alkyl ester thereof or the salt
25 thereof in the aqueous liquid preparation from decreasing.
4. The method according to claim 4, wherein the aqueous liquid preparation is an eye drop.