Description

Title of Invention: Tablet comprising limaprost and β-cyclodextrin

TECHNICAL FIELD

[0001]

The present invention relates to a tablet comprising limaprost and β-cyclodextrin.

BACKGROUND ART

[0002]

Limaprost is known as a preventive and/or treating agent of peripheral circulatory disturbance. Particularly, it is very useful for improving symptoms of thromboangitis obliterans and lumbar spinal canal stenosis etc. which are chronic diseases.

[0003]

Limaprost has hydroscopic nature and is easily decomposed by absorbing moisture. Therefore, a marketed limaprost alfadex tablet avoids the influence of humidity by being packed in an aluminum bag after packaged in a PTP sheet.

[0004]

As a stable tablet comprising limaprost, for example, a pharmaceutical composition for oral administration which is stable and reduces the adhesiveness comprising (1) a lyophilized composition comprising limaprost alfadex (α-cyclodextrin clathrate of limaprost) and glucans, (2) diluents, and optionally glucans, wherein the content of glucans is from 1% by mass to 15% by mass based on 100% by mass of the total pharmaceutical composition and the water activity value is 0.2 or less at 25°C has been reported (see Patent reference 1).

[0005]

On the other hand, cyclodextrin is generally used for the solubilization of drugs, the bitterness masking or the stabilization. For example, it is known that cyclodextrin stabilizes a principal agent by being dissolved in aqueous solution with the principal agent and forming the principal agent inclusion. However, the stabilization effect is not necessarily obtained by cyclodextrin clathrate. For example, limaprost alfadex is an α-cyclodextrin clathrate of limaprost. However, the decomposition of limaprost is not suppressed markedly when limaprost crystal forms inclusion complex with α-cyclodextrin. Further, generally, to form drug inclusion with cyclodextrin, four methods are known such as emulsifying method (e.g., adding a certain amount of a principal agent to 20-50% of cyclodextrin suspension and emulsifying the suspension by using a homogenizer), saturated solution method (e.g., mixing a principal agent in saturated cyclodextrin solution for 30 minutes to several days and evaporating water in the precipitating clathrate or drying the

precipitation taken out after the cooling), kneading method (e.g., preparing a paste with adding small amount of water to cyclodextrin, addind and kneading a principal agent therein by using a kneading machine and drying the paste by a method commonly employed) and mixing and milling method (e.g., milling cyclodextrin and a principal agent by using a vibrating mill) (Non-Patent reference 1). However, stability does not improve when a principal agent is not dissolved with cyclodextrin and is simply mixed without solvent, since the principal agent does not form inclusion with cyclodextrin.

[0006]

For example, it is reported that stability was improved by blending β-cyclodextrin with pravastatin (e.g., see Patent reference 2). The reference discloses a step in which β-cyclodextrin and pravastatin are mixed and milled with a physical force and kneaded with a solution to form pravastatin inclusion with β-cyclodextrin.

[0007]

Further, as a purpose of improving disintegration, it is known that cyclodextrin is used as an additive for the manufacturing of an oral disintegration tablet. For example, an oral disintegration tablet comprising 70% by mass or more of cyclodextrin in a tablet is disclosed as a tablet using cyclodextrin as an additive (e.g., see Patent reference 3). The cyclodexrin disclosed in the reference includes β-cyclodextrin. However, the reference does not describe or indicate that cyclodextrin was used as an additive to improve the principal agent stability.

Prior Art

Patent Reference

[0008]

[Patent Reference 1] Japanese Patent No. 3646310

[Patent Reference 2] JP-A-2003-517432

[Patent Reference 3] WO2005/004923

Non Patent Reference

[0009]

[Non Patent-Reference 1]

Foods & Food Ingredients Journal of Japan (FFI journal) Terao, Konishi et al. Vol.210, No.3, 222-243, 2005

Summary of the Invention

Problems to be solved by the invention

[0010]

In a clinical site, various medicines are often packaged into one bag made of polyethylene laminated glassine paper and the like for patient convenience in view of

preventing improper use. Therefore, a tablet is desired to be stable for about several days to 30 days or a month at least after taking out from a PTP sheet and in the state of being unpackaged. In view of this, a limaprost tablet is desired to further improve its stability.

Namely, an object of the present invention is to provide a tablet comprising limaprost which is very stable against humidity. To be specific, it is to provide a tablet comprising limaprost wherein the content of the decomposed product is 5% or less after preservation at 30°C, relative humidity of 75% for 30 days or a month.

Means for the solving the problems

[0011]

The present inventors made intensive studies to obtain a more stable tablet comprising limaprost than an existing tablet. As a result, they found the stability of limaprost improves particularly when β-cyclodextrin is blended among various additives. Further, they found that the stability of limaprost against humidity improves markedly by mixing β-cyclodextrin simply as an additive, without dissolving limaprost in a solvent with β-cyclodextrin. This finding is surprising because, although not wishing to be bound by any theory, it is not considered that limaprost forms inclusion with β-cyclodextrin when limaprost and β-cyclodextrin are mixed simply without solvent, according to previous findings. Further, limaprost is sometimes used as limaprost alfadex forming inclusion with α-cyclodextrin. However, this finding that the further blending of cyclodextrin to the drug which is already forming inclusion improves the drug stability cannot be easily expected by those skilled in the art regarding previous findings that the improvement of the limaprost stability is attributed to the inclusion forming of cyclodextrin and the like. Further, the present inventers found a tablet comprising limaprost and β-cyclodextrin has very improved stability against humidity compared with existing tablets comprising limaprost, and thus completed the present invention.

[0012]

Namely, the present invention relates to:

[0013]

1. A tablet comprising limaprost and β-cyclodextrin, wherein the content of β-cyclodextrin is from 30% by mass to 99% by mass based on 100% by mass of the total tablet content;

2. The tablet according to above 1, wherein the content of β-cyclodextrin is from 50% by mass to 95% by mass based on 100% by mass of the total tablet content;

3. The tablet according to above 1 or 2, which may further comprise 0.0165% by mass to 2.5% by mass of glucans;

4. The tablet according to any one of above 1 to 3 comprising limaprost as limaprost alfadex, wherein the tablet at least comprises a mixture comprising (1) lyophilized

composition comprising limaprost alfadex and (2) β-cyclodextrin;

5. The tablet according to above 4 which is manufactured through a step of admixing the β-cyclodextrin in (2) without a solvent;

6. The tablet according to above 5, which further comprises β-cyclodextrin in the lyophilized composition;

7. The tablet according to above 6, wherein the content of β-cyclodextrin in the lyophilized composition is from 0.1% by mass to 1% by mass based on 100% by mass of the total tablet content;

8. The tablet according to any one of above 4 to 7, which further comprises glucans in the lyophilized composition;

9. The tablet according to above 8, comprising limaprost alfadex and glucans with the ratio of 1:0.1 to 15;

10. The tablet according to above 8, comprising limaprost alfadex and glucans with the ratio of 1:0.1 to 6;

11. A tablet comprising limaprost alfadex, β-cyclodextrin and glucans, wherein the content of β-cyclodextrin is from 30% by mass to 99% by mass and the content of glucans is from 0.0165% by mass to 2.5% by mass based on 100% by mass of the total tablet content;

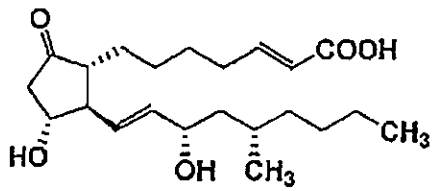
12. A tablet comprising a mixture of (1) lyophilized composition comprising limaprost alfadex, β-cyclodextrin and glucans and (2) β-cyclodextrin, wherein the content of β-cyclodextrin is from 30% by mass to 99% by mass and the content of glucans is from 0.0165% by mass to 1.0% by mass based on 100% by mass of the total tablet content;

13. The tablet according to any one of above 1 to 12 which does not comprise substantially 17S,20-dimethyl-trans-Δ^2-PGA_1 in the tablet or comprises 5% or less of 17S,20-dimethyl-trans-Δ^2-PGA_1 based on 100% of the total tablet content after preservation at 30°C, relative humidity of 75% for a month.

[0014]

Limaprost

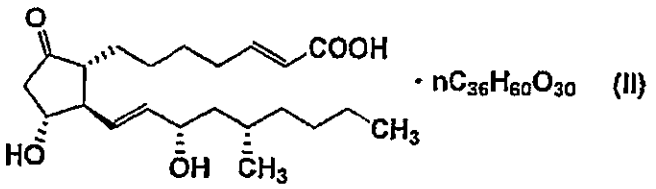
In the specification, limaprost is a compound represented by following formula (I) and its chemical name is (E)-7-[(1R,2R,3R)-3-hydroxy-2-[(3S,5S)-(E)-3-hydroxy-5-methyl-1-nonenyl]-5-oxocyclopentyl]-2-heptenoic acid (Registry No. 74397-12-9).



(I)

[0015]

Further, in the specification, limaprost may be comprised forming inclusion complex with an α-cyclodextrin. An α-cyclodextrin clathrate of limaprost is represented by following formula (II) (n represents the integer).



$\cdot nC_{36}H_{60}O_{30}$ (II)

Its chemical name is (E)-7-[(1R,2R,3R)-3-hydroxy-2-[(3S,5S)-(E)-3-hydroxy-5-methyl-1-nonenyl]-5-oxocyclopentyl]-2-heptenoic acid α-cyclodextrin clathrate (Registry No. 100459-01-6 (limaprost:α-cyclodextrin=1:1), 88852-12-4 (limaprost:α-cyclodextrin=1:n)), which is generally known as limaprost alfadex. This is used for the same meaning of "limaprost alfadex" listed in the Japanese Pharmacopoeia Sixteenth Edition.

[0016]

According to the present invention, unless otherwise indicated and as is apparent for those skilled in the art, each of symbols



indicates that it is bound to the opposite side of the sheet (namely α-configuration),



indicates that it is bound to the front side of the sheet (namely β-configuration).

[0017]

In the present invention, it is preferable to comprise limaprost as α-cyclodextrin inclusion complex represented by above formula (II), that is limaprost alfadex.

[0018]

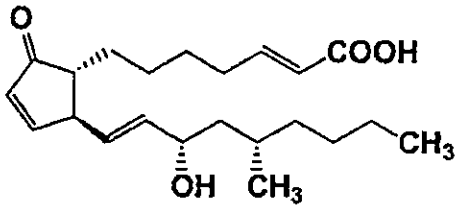
In a preferred embodiment, a tablet of in the present invention comprises about 5 to 10μg of limaprost in a tablet. Further, it is preferable to comprise limaprost alfadex which is equivalent to about 5 to 10μg of limaprost when a tablet comprises limaprost as limaprost alfadex.

[0019]

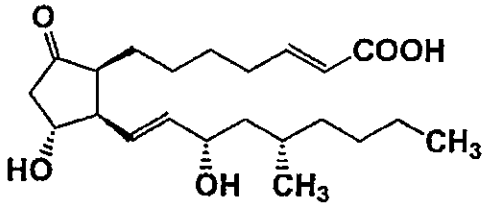
Limaprost and limaprost alfadex are known compounds and can be manufactured by known methods such as the disclosed methods in JP-A-55-100360 and the like.

[0020]

When limaprost is decomposed, the compound represented by following formula, 17S,20-dimethyl-trans-Δ^2-PGA_1 (hereafter abbreviated as 11-deoxy)



or the one represented by following formula, 17S,20-dimethyl-trans-Δ^2-8-iso-PGE_1 (hereafter abbreviated as 8-iso) and the like are generated as decomposed products.



It is known that a decomposed product mainly generated is 11-deoxy. The drug efficacy may be weakened when the content of these decomposed products are increased. Since the tablet comprising limaprost of the present invention is very stable, it is capable to reduce the content of 11-deoxy at above limit of detection and about 10% or less, preferably at above limit of detection and about 8% or less detection, and more preferably at above limit of detection and about 5% or less. Further, the tablet of the present invention can reduce the content of 11-deoxy at low level in a stability study under humid and high temperature conditions which is conducted to predict the preservation stability in a clinical site. For example, the tablet of the present invention can reduce the content of 11-deoxy, preferably at above limit of detection and about 5% or less, more preferably at above limit of detection and about 3.5% or less after preservation at 30°C, relative humidity of 75% for 30 days or a month. Further, the tablet of the present invention can reduce the content of 11-deoxy, preferably at above limit of detection and about 5% or less, more preferably at above limit of detection and about 3.5% or less after preservation at 60°C for 30 days or a month.

[0021]

For example, the yield of 11-deoxy can be represented as the ratio (mass ratio) of

the amount of 11-deoxy in a composition to the total amount of limaprost, 11-deoxy and 8-iso.

The yield of 11-deoxy can be calculated based on 100 of the total amount of limaprost and the decomposed products after determination of limaprost and its decomposed products (8-iso, 11-deoxy).

The amount of limaprost, 11-deoxy and 8-iso can be measured by known analytical methods (e.g., high performance liquid chromatography, gas chromatography, thin-layer chromatography and the like). Particularly, it is preferable to be measured by high performance liquid chromatography. By using high performance liquid chromatography, the amount of limaprost, 11-deoxy and 8-iso can be measured with high sensitivity under the same test condition and with the same sample. High performance liquid chromatography can be performed by a known method.

[0022]

To be specific, the measurement is performed under the following high performance liquid chromatography (HPLC) test condition. Under the following test condition, the amount of limaprost and decomposed product can be measured and the ratio of limaprost and the decomposed product can be calculated.

[0023]

HPLC Test Condition

Detector: ultraviolet absorptiometer (measurement wavelength: 215 nm)

Column: pack 3 to 5 μm of octadecylsilyl-sylicagels for liquid chromatography into stainless steel tube of which internal diameter is about 5 mm and length is 10 to 20 cm

Mobile phase: 0.02M potassium dihydrogen phosphate (pH 4.3)/acetonitrile/isopropanol mixed liquid (9:5:2)

Flow rate: adjust to the rate which makes the retention time of limaprost about 12 minutes

Internal standard solution: testosterone solution of acetonitrile (13→20000)

[0024]

As described, the amount of the decomposed product can be determined by known methods other than high performance liquid chromatography and also can be determined under other test conditions of high performance liquid chromatography and evaluated by other calculation methods (e.g., external standard method and the like). The present invention includes a tablet in which even more than 5% of 11-deoxy is determined by a method other than the above high performance liquid chromatography method when above limit of detection and about 5% or less of 11-deoxy is determined by the above-mentioned method after preservation at 30°C, relative humidity of 75% for 30 days or a month in a stability test. Further, the present invention includes a tablet in which the amount of 11-deoxy cannot be measured substantially.

[0025]

In the present invention, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and hydroxypropyl β-cyclodextrin and the like are used as cyclodextrin to be blended with limaprost. Among them, β-cyclodextrin is particularly used.

As a method for blending β-cyclodextrin, β-cyclodextrin may be blended with limaprost or α-cyclodextrin clathrate of limaprost (limaprost alfadex) by a known method. In the present invention, β-cyclodextrin can be mixed without adding any solvents *etc.* and β-cyclodextrin can be added and mixed without solvents.

Further, as a method for blending β-cyclodextrin, a lyophilized composition comprising limaprost or limaprost alfadex and β-cyclodextrin can be produced and milled. The lyophilized composition comprising limaprost or limaprost alfadex and β-cyclodextrin can be produced by a conventional method of solubilizing limaprost or limaprost alfadex and β-cyclodextrin in a solvent (e.g., water, organic solvents (e.g., ethanol, acetone and the like) and the like). Further, as a method for blending β-cyclodextrin, β-cyclodextrin can be further admixed with lyophilized composition comprising limaprost or limaprost alfadex and β-cyclodextrin. For example, the lyophilized composition produced by the above-mentioned method is milled and then β-cyclodextrin can be further mixed thereto.

As a method for blending β-cyclodextrin in the present invention, β-cyclodextrin can be blended by any methods. β-cyclodextrin is preferred to be mixed without solvents such as water and organic solvents. Particularly, it is preferred that β-cyclodextrin is further mixed after milling lyophilized composition comprising limaprost or limaprost alfadex and β-cyclodextrin.

[0026]

The blended content of β-cyclodextrin is preferably from about 30% by mass to 99% by mass, more preferably from about 50% by mass to 95% by mass, further preferably from about 50% by mass to 85% by mass based on 100% by mass of the total tablet content. The blended content of β-cyclodextrin represents the total content of β-cyclodextrin added at producing the lyophilized composition and β-cyclodextrin added and mixed, namely, the total content of β-cyclodextrin comprised in a whole tablet.

[0027]

When a lyophilized composition comprising limaprost and β-cyclodextrin is milled and β-cyclodextrin is mixed thereto, the content of β-cyclodextrin used for producing the lyophilized composition may be minute, namely, from about 0.1% by mass to 1% by mass and preferably from about 0.1% by mass to 0.5% by mass based on 100% by mass of the total tablet content. On the other hand, the content of β-cyclodextrin added and mixed is from about 30% by mass to 99% by mass, preferably from about 50% by mass to 95% by mass, more preferably from about 50% by mass to 85% by mass based on 100% by mass of the total tablet content.

[0028]

Although a tablet comprising limaprost and β-cyclodextrin is very stable against humid, and glucans (dextran and the like) may be further blended. Blending glucans improves the stability against heat. In the specification, glucans represent glucan or glucan treated chemically or with an enzyme. Glucan is any of polysaccharide comprising of D-glucose and categorized to α-glucan or β-glucan. α-glucans include α-glucan which has α-1, 4 glucoside bonds (e.g., starch, glycogen and the like); which has α-1, 6 glucoside bonds (dextran and the like); and which has α-1, 4 and α-1, 6 glucoside bonds (e.g., pullulan and the like). Representative β-glucans are such as cellulose which has β-1, 4 glucoside bonds. Glucans treated chemically or with an enzyme are such as starch treated chemically or with an enzyme, for example, dextrin or pregelatinized starch and the like. In the present invention, preferable glucans are such as dextran (e.g., dextran, dextran 40, dextran 70 and the like), dextrin, pullulan, corn starch, potato starch, wheat starch, rice starch and pregelatinized starch and the like. Among them, dextran is particularly preferable. Glucans can be blended by simple mixing or, for example, blended by dissolving limaprost, β-cyclodextrin and glucans in a solvent (e.g., water, organic solvents (e.g., ethanol, acetone and the like) and the like) and producing lyophilized composition by a method commonly employed. When glucans are blended, the stability against heat tends to be improved and, on the other hand, the stability against humidity tends to be worsened. Therefore, the amount of the blended glucans can be minute, namely, from about 0.0165% by mass to about 2.5% by mass, preferably from about 0.0165% by mass to about 1.0% by mass, more preferably from about 0.08% by mass to 1.0% by mass, based on 100% by mass of the total tablet content. Further, when glucans are blended in a tablet, a preferable blending ratio of limaprost alfadex and dextran is 1:0.1 to 15; more preferable ratio is 1:0.1 to 6; further preferable ratio is 1:0.5 to 6. Further, blending glucans increases the hardness of a lyophilized composition and improves the molding of a tablet.

[0029]

The tablet of the present invention (e.g., uncoated tablet, dry coated tablet, coated tablet, three-layer tablet and the like) may also further comprise additives except the aforementioned additives. Any additives commonly employed for a tablet production can be used, for example, one or two or more of excipients, lubricants, disintegrants, fluidizers, binders, corrigents, flavorings, surfactants, aromas, colorants, antioxidants, masking agents, antistatic agents or wetting agents and the like can be blended appropriately.

[0030]

As an excipient, for example, glucose, fructose, maltose, lactose (lactose hydrate, spray-dryed lactose, fluidized-bed granulation lactose, isomerized lactose, reduced lactose and the like), sucrose, D-mannitol, erythritol, maltitol, xylitol, palatinose, trehalose, sorbitol, crystalline cellulose, talc, light anhydrous silicic acid, anhydrous calcium

phosphate, precipitated calcium carbonate, calcium silicate and the like can be mentioned.

As a lubricant, for example, magnesium stearate, calcium stearate, sucrose fatty acid ester, sodium stearyl fumarate, stearic acid, talc, polyethyleneglycol and the like can be mentioned.

As a disintegrant, for example, low substituted hydroxypropyl cellulose, carmellose, carmellose calcium, carboxymethyl starch sodium, croscarmellose sodium, crospovidone, hydroxypropyl starch, corn starch and the like can be mentioned.

As a fluidizer, for example, light anhydrous silicic acid, talc, water-containing silicon dioxide and the like can be mentioned.

As a binder, for example, hydroxypropyl cellulose, hydroxypropyl methylcellulose, povidone, polyvinylpyrrolidone, methylcellulose, polyvinyl alcohol, carboxymethylcellulose, sodium alginate, gum arabic powder, gelatin and the like can be mentioned. One or two or more of these may be blended appropriately.

As a corrigent, for example, saccharose, D-sorbitol, xylitol, citric acid, ascorbic acid, tartaric acid, malic acid, aspartame, acesulfame potassium, thaumatin, saccharin sodium, glycyrrhizin dipotassium, sodium glutamate, 5'-inosinic acid sodium, 5'-guanylic acid sodium and the like can be mentioned.

As a flavor, for example, trehalose, malic acid, maltose, potassium gluconate, anise essential oil, vanilla essential oil, cardamom essential oil and the like can be metioned.

As a surfactant, for example, polysorbates (polysorbate 80 and the like), polyoxyethylene-polyoxypropylene copolymer, sodium lauryl sulfate and the like can be mentioned.

As an aroma, for example, lemon oil, orange oil, menthol, peppermint oil and the like can be mentioned.

As a colorant, for example, titanium oxide, Food Color Yellow No. 5, Food Color Blue No. 2, iron sesquioxide, yellow iron sesquioxide and the like can be mentioned.

As an antioxidant, for example, sodium ascorbate, L-cysteine, sodium sulfite, vitamin E can be mentioned. As a masking agent, for example, titanium oxide and the like can be mentioned.

As an antistatic agent, for example, talc, titanium oxide and the like can be mentioned. As a wetting agent, for example, polysorbate 80, lauric acid sodium sulfate, sucrose fatty acid ester, macrogol, hydroxypropyl cellulose (HPC) and the like can be mentioned.

[0031]

The tablet of the present invention can be manufactured by the method described below. For example, limaprost and limaprost alfadex or milled lyophilized composition comprising limaprost is granulated by using a tumbling granulator, an agitation granulation machine, a fluiduized bed dryer granulator, a centrifugal tumbling granulator, a dry

granulator and the like. Additives are uniformly blended with the obtained granules as necessary followed by making tablet by using a rotary tableting machine for compression molding and the like to give uncoated tablets. Uncoated tablets may be used as it is or, where necessary, may be coated with coating agents. Further, a tablet can be prepared without a granulation step, by mixing limaprost, limaprost alfadex or a milled lyophilized composition comprising limaprost and additives and making the mixed powder into tablet with a rotary tableting machine and the like. Surprisingly, the tablet of the present invention has an advantage that the tablet does not have difficulty with tablet molding although the tablet comprises relatively large amount of β-cyclodxtrin which is likely to make tablets fragile.

[0032]

Further, a lubricant can be blended by an internal or external lubrication.

The blended powder or tablets may be dried before or after tableting. As a tablet drying method, hot air drying, drying under reduced pressure and heated air drying under reduced pressure are preferable.

[0033]

As a tablet drying method, drying under reduced pressure and heated air drying under reduced pressure are preferable.

The tablet of the present invention is useful for a treatment of peripheral circulatory failure such as thromboangiitis obliterans or lumbar spinal canal stenosis and the like.

Effect of the Invention

[0034]

The tablet of the present invention is very stable against humidity and can be preserved for a long period since it suppresses the generation of limaprost decomposed product. Further, the present invention does not have difficulty with tablet molding. Therefore, the tablet of the present invention can be packaged into one bag with other medicines in a clinical site.

Mode for Carrying Out the Invention

[0035]

Although the following describes the present invention in detail with preparation examples and examples, those are described for well understanding of the present invention and the present invention is not limited thereto.

[0036]

Example 1: Comparison of the stabilizing effect among various additives

(1) Preparation of lyophilized composition

In 37.5 g of purified water, 1 g of limaprost alfadex was dissolved and 7 g of dextran 40 was dissolved thereto. The prepared solution was transferred to a metal tray and lyophilized by a method commonly employed. After the lyophilization, the lyophilized composition was ground with a mortar. The ground powder was passed through a sieve (42 mesh) to give lyophilized composition powder.

[0037]

(2) Preparation of blended powder

Above-mentioned lyophilized composition powder (200 mg) of limaprost alfadex/dextran 40 was blended with each additive (15 g) by a mortar. The blended powder was divided into glass bottles with the portion of 1 g. After drying the divided samples by reduced pressure drying machine (50°C, 12 hours or more), those were placed in a stability test chamber at 30°C, relative humidity of 75% with keeping a plug in opened state and sampled periodically to be evaluated.

[0038]

(3) Purity test

The production rate of the decomposed product (11-deoxy) of limaprost was measured by high performance liquid chromatography (HPLC).

[0039]

The results are shown below.

[Table 1]

Additives	Initial	2 weeks	1 month
Lactose	0.9	6.6	13.9
Dicalcium Phosphate Anhydrous	0.5	4	7.6
Hydrogenated Canola Oil	1.3	3.8	7.4
Stearic Acid	0.9	4.2	8.2
Dextran 70	0.6	3.8	6.8
Aspartic Acid	1.7	4.3	8.6
α-cyclodextrin	1.8	4.8	9.9
β-cyclodextrin	-	2.6	4.4

In case where β-cyclodextrin was mixed, the content of the decomposed product was 3% or less after preservation for two weeks and 5% or less after preservation for a month. On the other hand, in powders for which other additives such as α-cyclodextrin was mixed, the content of the decomposed product was increased with time and largely exceeded 5% after preservation for a month.

Therefore, it was suggested that the stability of limaprost is improved in a blended powder of β-cyclodextrin and limaprost.

[0040]

Example 2: Effect of the amount of β-cyclodextrin in a tablet

<Preparation Example 1: tablet comprising 30% β-cyclodextrin>

In 62.25 g of purified water, 1.67 g of limaprost alfadex was dissolved, followed by dissolving 1.67 g of β-cyclodextrin and then dissolving 3.32 g of dextran 40. The thus prepared solution was transferred to a metal tray and lyophilized by a method commonly employed. After the lyophilization, the lyophilized composition was ground with a mortar, followed by passing through a sieve (30 mesh) to give a lyophilized composition powder.

[0041]

With 0.664 g of the above-mentioned lyophilized composition powder, 20 g of carmellose, 30 g of β-cyclodextrin, 50 g of lactose, 0.2 g of light anhydrous silicic acid and 2 g of stearic acid were mixed, followed by making into tablet at 800-1000 kg/cm^2 (102.9 mg/tablet, 6.5 mmϕ) with a rotary tableting machine (manufactured by Kikusui Seisakusho Ltd.) to give 1000 tablets each of which comprises 5 μg of limaprost.

[0042]

<Preparation Example 2: tablet comprising 50% β-cyclodextrin>

With 0.664 g of the lyophilized composition powder as described in Preparation Example 1, 20 g of carmellose, 50 g of β-cyclodextrin, 30 g of lactose and 0.2 g of light anhydrous silicic acid were mixed, followed by making into tablet at 800-1000 kg/cm^2 (100.9 mg/tablet, 6.5 mmϕ) with a rotary tableting machine (manufactured by Kikusui Seisakusho Ltd.) to give 1000 tablets each of which comprises 5 μg of limaprost. Magnesium stearate was sprayed to the rotary tableting machine by using an external luburication machine (manufactured by Kikusui Seisakusho Ltd.).

[0043]

<Preparation Example 3: tablet comprising 60% β-cyclodextrin>

With 0.664 g of the lyophilized composition powder as described in Preparation Example 1, 20 g of carmellose, 60 g of β-cyclodextrin, 20 g of lactose and 0.2 g of light anhydrous silicic acid were mixed, followed by making into tablet at 800-1000 kg/cm^2 (100.9 mg/tablet, 6.5 mmϕ) with a rotary tableting machine (manufactured by Kikusui Seisakusho Ltd.) to give 1000 tablets each of which comprises 5 μg of limaprost. Magnesium stearate was sprayed to the rotary tableting machine by using an external luburication machine (manufactured by Kikusui Seisakusho Ltd.).

[0044]

<Preparation Example 4: tablet comprising 70% β-cyclodextrin>

With 0.664 g of the lyophilized composition powder as described in Preparation Example 1, 20 g of carmellose, 70 g of β-cyclodextrin, 10 g of lactose and 0.2 g of light anhydrous silicic acid were mixedfollowed by making into tablet at 800-1000 kg/cm^2 (100.9 mg/tablet, 6.5 mmϕ) with a rotary tableting machine (manufactured by Kikusui Seisakusho

Ltd.) to give 1000 tablets each of which comprises 5 μg of limaprost. Magnesium stearate was sprayed to the rotary tableting machine by using an external luburication machine (manufactured by Kikusui Seisakusho Ltd.).

[0045]

<Preparation Example 5: tablet comprising 80% β-cyclodextrin>

With 0.664 g of the lyophilized composition powder as described in Preparation Example 1, 20 g of carmellose, 80 g of β-cyclodextrin and 0.2 g of light anhydrous silicic acid were mixed, followed by making into tablet at 800-1000 kg/cm^2 (100.9 mg/tablet, 6.5 mmϕ) with a rotary tableting machine (manufactured by Kikusui Seisakusho Ltd.) to give 1000 tablets each of which comprises 5 μg of limaprost. Magnesium stearate was sprayed to the rotary tableting machine by using an external luburication machine (manufactured by Kikusui Seisakusho Ltd.).

[0046]

<Preparation Example 6: tablet comprising 90% β-cyclodextrin>

With 0.664 g of the lyophilized powder as described in Preparation example 1, 10 g of carmellose, 90 g of β-cyclodextrin and 0.2 g of light anhydrous silicic acid were mixed, followed by making into tablet at 800-1000 kg/cm^2 (100.9 mg/tablet, 6.5 mmϕ) with a rotary tableting machine (manufactured by Kikusui Seisakusho Ltd.) to give 1000 tablets each of which comprises 5 μg of limaprost. Magnesium stearate was sprayed to the rotary tableting machine by using an external luburication machine (manufactured by Kikusui Seisakusho Ltd.).

[0047]

<Comparative Preparation Example 1>

Comparative preparation 1 was obtained by the same method described in Example 13 of Japanese Patent No. 3646310.

[0048]

<Comparative Preparation Example 2: tablet comprising 0.2% β-cyclodextrin (0% of added and mixed amount)>

With 0.664 g of the lyophilized composition powder described in Preparation Example 1, 20 g of carmellose, 80 g of lactose and 0.2 g of light anhydrous silicic acid were mixed, followed by making into tablet at 800-1000 kg/cm^2 (102.9 mg/tablet, 6.5 mmϕ) with a rotary tableting machine (manufactured by Kikusui Seisakusho Ltd.) to give 1000 tablets each of which comprises 5 μg of limaprost.

[0049]

The formulation of the above-mentioned Preparation Examples 1-6 and Comparative examples 1 and 2 are following.

[Table 2]

(mg/tablet)	Comparative Example 1	Comparative Example 2	Preparation Example 1	Preparation Example 2	Preparation Example 3	Preparation Example 4	Preparation Example 5	Preparation Example 6
Limaprost Alfadex	0.167	0.167	0.167	0.167	0.167	0.167	0.167	0.167
β-cyclodextrin	-	0.167	0.167	0.167	0.167	0.167	0.167	0.167
Dextran	1.162	0.332	0.332	0.332	0.332	0.332	0.332	0.332
Total of Lyophilized Composition	1.328	0.664	0.664	0.664	0.664	0.664	0.664	0.664
Carmellose	-	20	20	20	20	20	20	10
β-cyclodextrin	-	-	30	50	60	70	80	90
Light Anhydrous Silicic Acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Stearic Acid	-	2	2	-	-	-	-	-
Magnesium Stearate	-	-	-	Trace amount	Trace amount	Trace amount	Trace amount	Trace amount
Lactose	85	80	50	30	20	10	-	-
Dextrin	9	-	-	-	-	-	-	-
Corn Starch	5	-	-	-	-	-	-	-
Stearic Acid	0.5	-	-	-	-	-	-	-
Total	101	102.9	102.9	100.9	100.9	100.9	100.9	100.9
Content of β-cyclodextrin (%)	0	0.2	30	50	60	70	80	90

About 100 tablets of each formulation were placed in a glass bottle and preserved in a stability test chamber at 30°C, relative humidity of 75% with keeping a plug in open state. The tablets were sampled periodically to be evaluated. The production rate of the decomposed product of limaprost (11-deoxy) was measured by high performance liquid chromatography (HPLC).

[0050]

The production rate of the decomposed product was calculated based on 100 of the total of limaprost and decomposed products. The results of measurement are shown below.

[Table 3]

	Content of β-cyclodextrin	Initial	1 month
Comparative Preparation Example 1	0	0.3	9.1
Comparative Preparation Example 2	0.2	1.1	6.7
Preparation Example 1	30	0.3	3.9
Preparation Example 2	50	0.9	3.1
Preparation Example 3	60	0.8	2.9
Preparation Example 4	70	0.8	2.7
Preparation Example 5	80	0.7	2.4
Preparation Example 6	90	0.7	2.6

A tablet comprising 30% or more of β-cyclodextrin (Preparation Examples 1-6) improved its stability markedly compared with the tablet described in Example 13 of Patent reference 1 which does not comprise β-cyclodextrin in the tablet (Comparative Preparation Example 1) and Comparative Preparation Example 2 comprising the same amount of β-cyclodextrin with α-cyclodextrin forming inclusion with limaprost in the lyophilized composition.

[0051]

Therefore, it was suggested that the tablet comprising 30% or more of β-cyclodextrin improves its preservation stability.

[0052]

Example 3: Effect of blending glucans on heat stability

Tablets comprising various amount of dextran as shown below, Preparation Examples 7-13 were prepared by using the same method described in Preparation Example 1.

[Table 4]

(mg/tablet)	Preparation Example 7	Preparation Example 8	Preparation Example 9	Preparation Example 10	Preparation Example 11	Preparation Example 12	Preparation Example 13
Limaprost Alfadex	0.167	0.167	0.167	0.167	0.167	0.167	0.167
β-cyclodextrin	0.167	0.167	0.167	0.167	0.167	0.167	0.167
Dextran	0	0.0167	0.0835	0.167	0.332	0.664	0.996
Total of Lyophilized Composition	0.334	0.3507	0.4175	0.501	0.666	0.998	1.33
Carmellose	20	20	20	20	20	20	20
β-cyclodextrin	70	70	70	70	70	70	70
Light Anhydrous Silicic Acid	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Magnesium Stearate	trace amount	trace amount	trace amount	trace amount	trace amount	trace amount	trace amount
Lactose	10	10	10	10	10	10	10
Total	100.53	100.55	100.6	100.7	100.66	101.19	101.53
Limaprost Alfadex:Dextran	1:0	1:0.1	1:0.5	1:1	1:2	1:4	1:6

Obtained tablets were placed in glass bottles and the glass bottles were preserved in a stability test chambers of (1) 30°C, relative humidity of 75% with keeping a plug in open state (2) 60°C in closed state. The tablets were sampled periodically and the production rate of the decomposed product of limaprost (the production rate (%) of 11-deoxy) were measured by high performance liquid chromatography (HPLC). The production rate of the decomposed product was calculated based on 100 of the total of limaprost and decomposed products. The results of measurement are shown below.

[Table 5]

	30°C 75%RH		60°C in closed state	
	Initial	1 month	Initial	1 month
Preparation Example 7	0.4	2.4	0.4	5.5
Preparation Example 8	0.3	2.3	0.3	4.5
Preparation Example 9	0.4	2.2	0.4	3.3
Preparation Example 10	0.4	2.3	0.4	3.2
Preparation Example 11	0.3	2.4	0.3	2.2
Preparation Example 12	0.5	2.7	0.5	1.6
Preparation Example 13	0.5	2.8	0.5	1.6

As shown above, the tablet stability against heat was improved according with the increase of the content of dextran in a lyophilized composition.

INDUSTRIAL APPLICABILITY

[0053]

The tablet comprising limaprost of the present invention is very stable against humidity. Therefore, the tablet of the present invention is very useful because the tablet can be packaged in one bag with other tablets and provided in a clinical site without being deteriorated.

Claims

1. A tablet comprising a mixture of (1) limaprost alfadex and (2) β-cyclodextrin, wherein the content of β-cyclodextrin is from 30% by mass to 99% by mass based on 100% by mass of the total tablet content.

2. The tablet according to claim 1, wherein the content of β-cyclodextrin is from 50% by mass to 95% by mass based on 100% by mass of the total tablet content.

3. The tablet according to claim 1 or 2, which may further comprise 0.0165% by mass to 2.5% by mass of glucans.

4. The tablet according to any one of claims 1 to 3, wherein the tablet at least comprises a mixture comprising (1) lyophilized composition comprising limaprost alfadex and (2) β-cyclodextrin.

5. The tablet according to claim 4 which is manufactured through a step of admixing the β-cyclodextrin in (2) without a solvent.

6. The tablet according to claim 5, which further comprises β-cyclodextrin in the lyophilized composition.

7. The tablet according to claim 6, wherein the content of β-cyclodextrin in the lyophilized composition is from 0.1% by mass to 1% by mass based on 100% by mass of the total tablet content.

8. The tablet according to any one of claims 4 to 7, which further comprises glucans in the lyophilized composition.

9. The tablet according to claim 8, comprising limaprost alfadex and glucans with the ratio of 1:0.1 to 15.

10. The tablet according to claim 8, comprising limaprost alfadex and glucans with the ratio of 1:0.1 to 6.

11. A tablet comprising limaprost alfadex, β-cyclodextrin and glucans, wherein the content of β-cyclodextrin is from 30% by mass to 99% by mass and the content of glucans is from 0.0165% by mass to 2.5% by mass based on 100% by mass of the total tablet content.

12. A tablet comprising a mixture of (1) lyophilized composition comprising limaprost alfadex, β-cyclodextrin and glucans and (2) β-cyclodextrin, wherein the content of β-cyclodextrin is from 30% by mass to 99% by mass and the content of glucans is from 0.0165% by mass to 1.0% by mass based on 100% by mass of the total tablet content.

13. The tablet according to any one of claims 1 to 12 which does not comprise substantially 17S,20-dimethyl-trans-Δ^2-PGA_1 in the tablet or comprises less than 5% of 17S,20-dimethyl-trans-Δ^2-PGA_1 based on 100% of the total tablet content after preservation at 30°C, relative humidity of 75% for a month.