

SPECIFICATION

Stable Lipid Emulsion Containing Prostaglandin E₁

Technical Field

[0001]

The present invention relates to a stable lipid emulsion containing prostaglandin E₁.

Background Art

[0002]

Prostaglandin E₁ (henceforth also abbreviated as "PGE₁"), of which nonproprietary name is "alprostadi", has potent vasodilatation action and antithrombotic action, and has been clinically used with indications of improvement of ulcers of extremities and pain at rest in chronic arterial occlusive diseases (Buerger's disease, arteriosclerosis obliterans), improvement of skin ulcer in progressive systemic sclerosis and the like, improvement of skin ulcer in diabetes and the like. As a preparation containing prostaglandin E₁, so-called lipid preparation in which PGE₁ is dissolved in fine lipid particles (for example, "Liple Injection", manufactured and sold by Mitsubishi Tanabe Pharma Corporation) is known. On the basis of the fact that lipid particles used as carrier of the drug are likely to distribute especially in injured vessels, these preparations are intended to efficiently accumulate PGE₁ in lesions, utilizing the idea of drug delivery system (DDS), and to be hard to occur the inactivation of the active ingredient in vivo. The preparation contains purified soybean oil, highly purified yolk lecithin, oleic acid, concentrated glycerin and sodium hydroxide as additives, and is adjusted to pH 4.5 to 6.0.

[0003]

However, since PGE₁ as the active ingredient of the aforementioned PGE₁ lipid preparation is easily decomposed in a solution, the preparation needs to be stored at a temperature of 5°C or lower under light shielding with avoiding freezing, and the validated period thereof is approved to be one year, which is shorter than that of ordinary preparations. Since such preparations may cause cost increase in drug management, during distribution or at clinical sites, it is desired to develop a preparation having longer validated period, thereby to reduce the drug management

cost. A means for suppressing the inactivation of prostaglandin E₁ due to passage through the lung by using a lipid emulsion is disclosed in Japanese Patent Publication (KOKAI) No. 58-222014 (Patent document 1), a means for improving chemical stability of the same by using a lipid emulsion is disclosed in Japanese Patent Unexamined Publication No. 60-149524 (Patent document 2), and an auxiliary agent for angiography prepared as a lipid emulsion is disclosed in Japanese Patent Unexamined Publication No. 4-66540 (Patent document 3). As for influence of pH on PGE₁ in a lipid emulsion, it is known that the substance is most stable around pH 5.0, and becomes unstable at a pH higher or lower than said pH (Pharmaceutical Research, 6, pp.210-215, 1989, Non-patent document 1).

Patent document 1: Japanese Patent Unexamined Publication No. 58-222014

Patent document 2: Japanese Patent Unexamined Publication No. 60-149524

Patent document 3: Japanese Patent Unexamined Publication No. 4-66540

Non-patent document 1: Pharmaceutical Research, 6, pp.210-215, 1989

Disclosure of the Invention

Object to be Achieved by the Invention

[0004]

An object of the present invention is to provide a preparation containing a compound having prostaglandin E₁ activity which has a longer validated period. More specifically, the object of the present invention is to provide a means for prolonging the validated period of lipid preparations marketed as prostaglandin E₁-containing preparations (e.g., "Liple Injection" and the like).

Means for Achieving the Object

[0005]

The inventors of the present invention conducted various researches to achieve the aforementioned object, and as a result, they found that when the preparation hermetically sealed in a glass ampoule (pH was adjusted to about 5.0 at the time of filling) was sterilized in an autoclave (125°C) at the final stage of manufacturing process of the preparation, alkaline components dissolved from the inner surface of the glass ampoule to increase the pH of the preparation higher than that before the sterilization. The inventors of the present invention continued further researches on the basis of this finding, and found that by employing a means for suppressing the dissolution of the alkaline components from a glass ampoule at

the time of sterilization, a preparation was easily producible without being influenced by characteristics of a glass ampoule (i.e., a material) to provide a lipid preparation stable over a long period of time.

[0006]

The present invention thus provides a lipid emulsion comprising a compound having prostaglandin E₁ activity which is sterilized by heating after hermetic sealing in a glass container, wherein a remaining prostaglandin E₁ activity after storage at 5°C for 16 months is 65% or more and 100% or less of the activity at the time of start of the storage.

[0007]

According to preferred embodiments of the aforementioned invention, there are provided the aforementioned lipid emulsion, which contains 5 μ g or more of the compound having prostaglandin E₁ activity at the time of the start of the storage, and contains 4 μ g or more of the compound having prostaglandin E₁ activity remaining after the storage at 5°C for 16 months; and the aforementioned lipid emulsion, which contains 10 μ g or more of the compound having prostaglandin E₁ activity at the time of the start of the storage, and contains 8 μ g or more of the compound having prostaglandin E₁ activity remaining after the storage at 5°C for 16 months. There is also provided the aforementioned lipid emulsion, wherein a pH at the time of the start of the storage after the heat sterilization is in the range of 4.9 to 5.3.

[0008]

According to further preferred embodiments, there are provided the aforementioned lipid emulsion, wherein the glass container is a container of which inner surface is coated with a film; the aforementioned lipid emulsion, wherein the glass container is a glass ampoule of which inner surface is coated with a film; the aforementioned lipid emulsion, wherein the coated film is a silicon oxide coated film; the aforementioned lipid emulsion, wherein the container is a container from which alkali components on glass surface are removed by a chemical treatment; and the aforementioned lipid emulsion, wherein the container is a glass ampoule from which alkali components on glass surface are removed by a chemical treatment. There is also provided the aforementioned lipid emulsion, which contains 5 to 50 w/v % of vegetable oil based on the total volume of the lipid emulsion.

[0009]

From another aspect, the present invention provides a method for preparing a lipid emulsion comprising a compound having prostaglandin E₁ activity, which comprises the step of hermetically sealing a lipid emulsion in a glass container, wherein said emulsion contains a compound having prostaglandin E₁ activity and is adjusted to have a pH of 4.8 to 5.2, and sterilizing the lipid emulsion by heating, and wherein the container preferably comprises a means for suppressing an increase of the pH of the lipid emulsion after the heat sterilization.

[0010]

According to preferred embodiments of the aforementioned invention, there are provided the aforementioned method, wherein the glass container is a glass ampoule, and the means for suppressing the increase of the pH is a coated film on inner surface of the glass ampoule, preferably a coated film of silicon oxide; and the aforementioned method, wherein the glass container is a glass ampoule, and the means for suppressing the increase of the pH is removal of alkaline components on the surface of glass by a chemical treatment. There are also provided the aforementioned method, wherein the lipid emulsion has a pH of 4.9 to 5.3 after the heat sterilization; and the aforementioned method, wherein an amounts of the compound having PGE₁ activity remaining in the lipid emulsion in glass ampoules after the heat sterilization provides a relative standard deviation of 1.0% or smaller. The amount of the compound having PGE₁ activity referred to herein means an amount of "PGE₁" as an active ingredient in the case where a lipid emulsion contains "PGE₁" as the active ingredient, or means an amount of "a compound having PGE₁ activity other than PGE₁" as an active ingredient in the case where a lipid emulsion contains "the compound having PGE₁ activity other than PGE₁" as an active ingredient.

Effect of the Invention

[0011]

The lipid emulsion of the present invention has improved stability of the compound having prostaglandin E₁ activity compared with that observed in conventional lipid emulsions, and has a characteristic feature of no decrease of the content of the active ingredient even after storage over a prolonged period of time. Further, the preparation method of the present invention is characterized in that it can provide a product of which content of PGE₁ after the sterilization is not affected

(hardly affected) by a characteristic of the glass container (i.e., a material).

Best Mode for Carrying out the Invention

[0012]

The lipid emulsion of the present invention is a lipid emulsion containing a compound having prostaglandin E₁ activity, and it is sterilized by heating after being hermetically sealed in a container, and characterized in that an amount of remaining PGE₁ activity in the lipid emulsion after the storage of the lipid emulsion at 5°C for 16 months is 65% or more and 100% or less of that observed at the time of start of the storage. As the compound having PGE₁ activity, any compound may be used so long that a compound having PGE₁ activity and acceptable as an active ingredient of medicaments is chosen. For example, PGE₁ derivatives disclosed in Japanese Patent Unexamined Publication Nos. 59-206349, 59-216820, and the like are preferably used. Among them, for example, 7-[(1R,2R,3R)-3-hydroxy-2-[(1E,3S)-3-hydroxyoct-1-en-1-yl]-5-oxocyclopentyl]heptanoic acid (nonproprietary name "alprostadil") is particularly preferred.

[0013]

A particularly preferred example of the compound having prostaglandin E₁ activity according to the present invention includes 7-[(1R,2R,3R)-3-hydroxy-2-[(1E,3S)-3-hydroxyoct-1-en-1-yl]-5-oxocyclopentyl]heptanoic acid (alprostadil) as described above. However, this compound is likely to change into 7-[(1R,2S)-2-[(S,E)-3-hydroxyoct-1-enyl]-5-oxocyclopent-3-enyl]heptanoic acid (prostaglandin A₁) after a dehydration reaction. It is considered that the pharmacological activity of the lipid emulsion of the present invention decreases due to the change into prostaglandin A₁. According to the present invention, an amount of prostaglandin A₁ in 1 ml of the lipid emulsion of the present invention after the storage at 5°C for 16 months is desirably 3.0 μg or less. Most desirably, the amount is 0 μg or more and 1.5 μg or less.

[0014]

Lipid emulsions containing a compound having the PGE₁ activity are disclosed in, for example, Japanese Patent Unexamined Publication Nos. 58-222014, 60-149524, 4-66540, and the like, and those skilled in the art can easily prepare such lipid emulsions. Lipid emulsions can be prepared so as to contain, for example, vegetable oil, a phospholipid, water, and the compound having PGE₁ activity. Furthermore, emulsification aids, stabilizers, polymer substances, isotonic agents,

and the like can also be added, if needed.

[0015]

Although the lipid emulsions can be prepared by various methods, they can be prepared by the following method, for example. Given amounts of a vegetable oil (preferably soybean oil), a phospholipid, a compound having PGE₁ activity, the aforementioned additives and the like can be mixed, heated as required, and then subjected to a homogenization treatment using a conventionally used homogenizer (e.g., pressurized injection type homogenizer, ultrasonic homogenizer and the like) to prepare a water-in-oil type dispersion, and then this dispersion can be added with a necessary amount of water, and converted into an oil-in-water type emulsion by homogenization using a homogenizer to prepare a lipid emulsion. After the preparation of the lipid emulsion, the emulsion may be further added with additives such as stabilizers and isotonic agents. The lipid emulsion is prepared so as to have a pH in the range of 4.8 to 5.2 before heat sterilization. For the adjustment of pH, an appropriate amount of a basic substance such as sodium hydroxide may be used. Osmotic pressure ratio thereof can be adjusted to be about 1 as a ratio to physiological saline.

[0016]

Mean particle diameter of particles in the lipid emulsion of the present invention can be measured by using a particle size measuring apparatus based on the principle of dynamic light scattering. In the present invention, mean particle diameter of particles in the lipid emulsion is preferably 0.1 μ m or larger and 0.4 μ m or smaller.

[0017]

The lipid emulsion of the present invention can be prepared by, for example, hermetically sealing a lipid emulsion prepared as described above in a glass container, and subjecting it to heat sterilization. As the glass container, an arbitrary glass container may be used so long as a container is chosen which is suitable for the hermetic sealing and has a characteristic feature that it does not allow dissolution of alkaline components into the lipid emulsion filled in the container during the heat sterilization. For example, a glass container having a means for suppressing an increase of pH of the lipid emulsion after the heat sterilization is preferred, and a glass ampoule having a means as described above is particularly preferred.

[0018]

The means for suppressing the increase of pH of the lipid emulsion after the heat sterilization is not particularly limited. For example, a means for preventing dissolution of alkaline components into the lipid emulsion at the time of the heat sterilization, a means for dissolving acidic components into the lipid emulsion at the time of the heat sterilization and the like may be used. A means for preventing the dissolution of alkaline components into the lipid emulsion at the time of the heat sterilization is preferred. Examples of the means for preventing the dissolution of alkaline components into the lipid emulsion at the time of the heat sterilization include, for example, coating of inner surface of the container with a film. Coating of inner surface of a glass ampoule with a silicon oxide film can be preferably employed. Alternatively, as the means for suppressing the increase of pH, it is also possible to employ removal of alkaline components on the surface of glass with a chemical treatment. Such technique is described in, for example, Japanese Patent Unexamined Publication No. 2-175630 and the like, and those skilled in the art can easily employ said technique.

[0019]

The lipid emulsion of the present invention can be prepared by hermetically sealing the aforementioned lipid emulsion adjusted to a pH in the range of 4.8 to 5.2 in a container and then subjecting the emulsion to heat sterilization. The heat sterilization can be performed, for example, in an autoclave at 125°C for about several minutes to 10 minutes. However, temperature and time are not particularly limited, and any treatment can be employed so long that sufficient sterilization can be attained. The lipid emulsion preferably has a pH in the range of 4.9 to 5.3 after the heat sterilization. The increase of pH after the heat sterilization compared with that before the heat sterilization is preferably less than 0.3, more preferably less than 0.2, most preferably less than 0.1. As for variation of PGE₁ amounts (μ g) in ampoules after the sterilization, relative standard deviation of the amounts is desirably 1.0% or less, more desirably 0.5% or less.

[0020]

The lipid emulsion containing a compound having prostaglandin E₁ activity of the present invention can be provided as, for example, a preparation containing 5 μ g or 10 μ g of a compound having prostaglandin E₁ activity filled in an ampoule.

In the present invention, it is desirable that, in an ampoule with 5 μ g of filling, the compound is filled in an amount corresponding to 80 to 125% of the amount.

Specifically, it is meant that 4 μ g or more and 6.25 μ g or less of the compound is filled in the ampoule. Also according to the present invention, it is desirable that, in an ampoule with 10 μ g of filling, the compound is filled in an amount corresponding to 80 to 125% of said amount. Specifically, it is meant that 8 μ g or more and 12.5 μ g or less of the compound is filled in the ampoule.

[0021]

Diseases to which the lipid emulsion of the present invention is applicable, method for using the lipid emulsion and the like are specifically described in detail in, for example, the package insert of "Liple Injection 5 μ g" (Mitsubishi Tanabe Pharma Corporation, 16th edition, revised on April, 2008).

Examples

[0022]

The present invention will be more specifically explained with reference to examples. However, the scope of the present invention is not limited by the following examples.

Example 1

Alprostadiol (PGE₁), oleic acid and yolk lecithin from which phosphatidylethanolamine (PE) was removed were dissolved in purified soybean oil, the solution was added with a mixture of glycerol and water for injection separately prepared, and the resulting mixture was stirred with a homomixer to prepare a suspension. The suspension obtained was emulsified with a Manton Gaulin homogenizer (produced by Manton Gaulin), and the emulsion was adjusted to pH 4.90 using sodium hydroxide and hydrochloric acid. The prepared emulsion was filled in a Silicoat Ampoule (Fuji Glass, glass ampoule of which inner surface is coated with silicon oxide film having a thickness of 70 to 100Å) and the inside of the ampoule was substituted with nitrogen, and then the opening of the ampoule was closed by melting to hermetically seal the emulsion. The resulting ampoule was subjected to sterilization at 125°C for 2.2 minutes using a high pressure steam sterilizer to obtain a lipid emulsion of the present invention.

[0023]

Example 2

An emulsion was prepared in the same manner as that of Example 1, adjusted to pH 5.01 using sodium hydroxide, then filled and sealed in a Silicoat Ampoule, and subjected to sterilization in the same manner as that of Example 1 to obtain a lipid emulsion of the present invention.

Example 3

An emulsion was prepared in the same manner as that of Example 1, adjusted to pH 5.15 using sodium hydroxide, then filled and sealed in a Silicoat Ampoule, and subjected to sterilization in the same manner as that of Example 1 to obtain a lipid emulsion of the present invention.

[0024]

Example 4 (Comparative Example)

The emulsion prepared in Example 1 was filled in an ordinary glass ampoule (glass ampoule not having silicon oxide coated film), the inside of the ampoule was substituted with nitrogen, and the opening of the ampoule was closed by melting to hermetically seal the emulsion. The resulting ampoule was subjected to sterilization at 125°C for 2.2 minutes using a high pressure steam sterilizer to obtain a lipid emulsion.

[0025]

Example 5

Emulsion was prepared in the same manner as that of Example 1, adjusted to pH 5.09 to 5.15 using sodium hydroxide, then filled and sealed in Silicoat Ampoules in the same manner as that of Example 1. Nine samples were prepared in this manner, and subjected to sterilization to obtain a lipid emulsion of the present invention.

[0026]

Example 6 (Comparative Example)

Ten samples were prepared in the same manner as that of Example 5 using ordinary glass ampoules, and subjected to sterilization in the same manner as that of Example 5 to obtain a lipid emulsion.

The results of stability test for PGE₁ are shown in Table 1, in which the samples of the lipid emulsion adjusted to various pH values before the heat sterilization were stored at 25°C. Remaining ratio of PGE₁ was measured by high performance liquid chromatography using a post column reaction (measured

according to the method described in JP Forum, 15 (3), pp.233-235, 2006). The results of the stability tests for PGE₁ in which the storage was performed at 30°C and 40°C are shown in Table 2. As can be understood from these results, even under the storage at 30°C and 40°C, the PGE₁ stability of the lipid emulsion of the present invention filled and hermetically sealed in Silicoat ampoules was superior to that of the lipid emulsion of Example 5 filled and hermetically sealed in ordinary glass ampoules. PGE₁ stability at 5°C in the lipid emulsion prepared to have a pH of around 5.0 was calculated by the Arrhenius plotting using the aforementioned results. As shown in Table 3, in the lipid emulsion of the present invention filled and hermetically sealed in Silicoat ampoules, 65% or more of the content was successfully maintained after 16 months compared with the content at the time of the start of the storage.

[0027]

PGE₁ amounts remained in each sample after the sterilization, averages, standard deviations, and relative standard deviations thereof are shown in Table 4. The standard deviation of the PGE₁ amounts remained in the lipid emulsion of the present invention filled and sealed in Silicoat ampoules was smaller than the relative standard deviation of the PGE₁ amounts remained in the lipid emulsion of Example 7 filled and hermetically sealed in ordinary glass ampoules, and thus it was demonstrated that the lipid emulsion of the present invention was a stable product having less variation of the amounts in samples.

[0028]

[Table 1]

	pH		Remaining ratio of PGE1 (%)		
	After pH adjustment	After sterilization	25°C		
			Storage period (day)		
			0	14	28
Example 1	4.90	4.99	100.0	89.0	78.1
Example 2	5.01	5.08	100.0	89.3	76.2
Example 3	5.15	5.25	100.0	88.1	75.7
Example 4	5.01	5.32	100.0	86.1	73.1

[0029]

[Table 2]

	pH		Remaining ratio of PGE1 (%)			
	After pH adjustment	After sterilization	30℃	40℃		
			Storage period (day)			
			21	36	7	14
Example 2	5.01	5.08	70.8	54.5	72.6	49.8
Example 4	5.01	5.32	63.4	47.6	65.1	44.4

[0030]

[Table 3]

	Remaining ratio of PGE1 (%)		
	Estimated value after storage at 5°C		
	Storage period (month)		
	0	12	16
Example 2	100.0	74.1	67.1

[0031]

[Table 4]

	Content (μ g)										Average	Standard deviation	Relative standard deviation (%)
Example 5	11.58	11.60	11.69	11.60	11.61	11.73	11.64	11.74	11.66		11.65	0.06	0.5
Example 6	11.60	11.89	11.64	11.77	11.91	11.83	11.98	11.94	11.69	11.57	11.78	0.15	1.3

[0032]

Example 7

An emulsion prepared in the same manner as that of Example 2 was taken in a volume of 1 ml, and added with 1 ml of an internal standard solution (prepared by dissolving 50 mg of 1-naphthol in 20 ml of 99.5% ethanol and adding a mobile phase to 3 ml of this solution to make the total volume 100 ml), and they were mixed to obtain a sample solution. Separately, an alprostadil standard solution was dried in a desiccator, and 10 mg of the solid was taken, accurately weighed and dissolved in 99.5% ethanol to make the total volume 100 ml and thereby obtained a standard stock solution (E1). Further, a prostaglandin A1 standard solution was dried in a desiccator, and 10 mg of the solid was taken, accurately weighed and dissolved in 99.5% ethanol to make the total volume 100 ml and thereby obtained a standard stock solution (A1). Each of E1 and A1 was taken in a volume of 2.5 ml, and added with a mobile phase to make the total volume 50 ml, and 1 ml of this mixture was taken and mixed with 1 ml of an internal standard solution to obtain a standard solution. The sample solution and the standard solution in a volume of 40 μ l each were subjected to liquid chromatography.

[0033]

A ratio of the peak area of prostaglandin A1 to the peak area of the internal standard substance was calculated. The area ratio of prostaglandin A1 for the sample solution is represented as QT, and the area ratio of prostaglandin A1 for the standard solution was represented as QS. By using these area ratios, an amount of prostaglandin A1 converted as an amount of alprostadil was calculated in accordance with the following equation.

Amount of prostaglandin A1 (μ g) = (accurate weight of weighed prostaglandin A1 (mg)) $\times$ QT/QS $\times$ 0.5 $\times$ 1.054

[0034]

As for the emulsion prepared in the same manner as that of Example 2, the accurate weight of the taken prostaglandin A1 was 10.05 mg, the ratio of the peak area of prostaglandin A1 to the peak area of the internal standard substance for the sample solution (QT) was 0.180931, and the ratio of the peak area of prostaglandin A1 to the peak area of the internal standard substance for the standard solution (QS) was 0.778099. Calculation was performed by introducing these values into the

aforementioned equation, and the amount of prostaglandin A1 in the emulsion was calculated to be 1.23 μ g.

Industrial Applicability

[0035]

In the lipid emulsion of the present invention, stability of a compound having prostaglandin E₁ activity is improved compared with that in conventional lipid emulsions, and thus content of the active ingredient does not decrease even after storage over a prolonged period of time. Therefore, the lipid emulsion of the present invention is extremely useful as a prostaglandin-E₁ containing preparation.

What is claimed is:

- [1] A lipid emulsion comprising a compound having prostaglandin E₁ activity, which is sterilized by heating after hermetical sealing in a glass container, wherein a remaining prostaglandin E₁ activity after storage at 5°C for 16 months is 65% or more and 100% or less of the activity at the time of start of the storage.
- [2] The lipid emulsion according to claim 1, which contains 5 μ g or more of the compound having prostaglandin E₁ activity at the time of the start of the storage, and contains 4 μ g or more of the compound having prostaglandin E₁ activity remaining after the storage at 5°C for 16 months.
- [3] The lipid emulsion according to claim 1, which contains 10 μ g or more of the compound having prostaglandin E₁ activity at the time of the start of the storage, and contains 8 μ g or more of the compound having prostaglandin E₁ activity remaining after the storage at 5°C for 16 months.
- [4] The lipid emulsion according to claim 2 or 3, wherein the compound having prostaglandin E₁ activity remains after the storage at 5°C for 16 months in an amount corresponding to 80.0 to 125.0% of 5 μ g or 10 μ g of the compound having prostaglandin E₁ activity.
- [5] The lipid emulsion according to any one of claims 1 to 4, which has a pH in the range of 4.9 to 5.3 at the time of the start of the storage after the heat sterilization.
- [6] The lipid emulsion according to any one of claims 1 to 5, wherein the glass container is a container of which inner surface is coated with a film.
- [7] The lipid emulsion according to claim 6, wherein the glass container is a glass ampoule.
- [8] The lipid emulsion according to claim 6 or 7, wherein the coated film is a silicon oxide coated film.
- [9] The lipid emulsion according to any one of claims 1 to 5, wherein the container is a container from which alkali components on glass surface are removed by a chemical treatment.
- [10] The lipid emulsion according to claim 9, wherein the glass container is a glass ampoule.
- [11] The lipid emulsion according to any one of claims 1 to 10, which contains 5 to 50 w/v % of a vegetable oil based on the total volume of the lipid emulsion.

[12] The lipid emulsion according to any one of claims 1 to 11, which contains 5 μ g of the compound having prostaglandin E₁ activity, 100 mg of a purified soybean oil, 18 mg of a highly purified yolk lecithin, 2.4 mg of oleic acid, and 22.1 mg of a concentrated glycerin in 1 mL of the lipid emulsion.

[13] The lipid emulsion according to any one of claims 1 to 11, which contains 10 μ g of the compound having prostaglandin E₁ activity, 200 mg of a purified soybean oil, 36 mg of a highly purified yolk lecithin, 4.8 mg of oleic acid, and 44.2 mg of a concentrated glycerin in 2 mL of the lipid emulsion.

[14] The lipid emulsion according to any one of claims 1 to 13, wherein the compound having prostaglandin E₁ activity is 7-[(1R,2R,3R)-3-hydroxy-2-[(1E,3S)-3-hydroxyoct-1-en-1-yl]-5-oxocyclopentyl]heptanoic acid.

[15] A method for preparing the lipid emulsion according to any one of claims 1 to 14, which comprises the step of hermetically sealing in a glass container a lipid emulsion which contains a compound having prostaglandin E₁ activity and is adjusted to have pH 4.8 to 5.2, and then sterilizing the lipid emulsion by heating.

[16] The method according to claim 15, wherein the container comprises a means for suppressing an increase of pH of the lipid emulsion after the heat sterilization.

[17] The method according to claim 15, wherein an amount of the compound having prostaglandin E₁ activity remaining in the lipid emulsion in glass ampoules after the heat sterilization has a relative standard deviation of 1.0% or smaller.