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(54) Title: LYOPHILIZED PREPARATION

(57) Abstract: It is provided a lyophilized preparation stably containing (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol or its pharmaceutically acceptable salt as an active ingredient. The present invention relates to a lyophilized preparation containing the above compound or its pharmaceutically acceptable salt as an active ingredient, and further containing: (a) at least one selected from sulfite, bisulfite, pyrosulfite, α-thioglycerol and cysteine, and (b) a β-cyclodextrin derivative.

DESCRIPTION

Lyophilized preparation

[Technical field]

[0001]

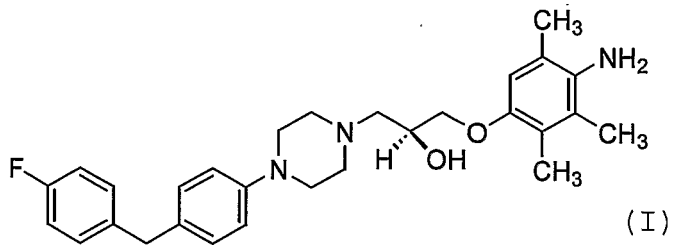
The present invention relates to a lyophilized preparation containing as an active ingredient, (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{ 4-[4-(4-fluorobenzyl)phenyl] -1-piperazinyl} -2-propanol or its pharmaceutically acceptable salt having remedial and therapeutic effect against symptoms based on ischemic disorder and neurodegenerative disease, symptoms from spasm, epilepsy and migraine, as well as various symptoms caused by diabetes, arteriosclerosis and inflammatory disease.

[Background art]

[0002]

(2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{ 4-[4-(4-fluorobenzyl)phenyl] -1-piperazinyl} -2-propanol shown by the formula (I):

[0003]



(I)

[0004]

or its pharmaceutically acceptable salt is a compound having remedial and therapeutic effect against symptoms based on ischemic disorder and neurodegenerative disease, symptoms from spasm, epilepsy and migraine, as well as various symptoms caused by diabetes, arteriosclerosis and inflammatory disease because it has not only an ability to block Na^+ and T-type Ca^{2+} channel of neuron, but also anti-oxidization activity. In particular, a dimethane sulfonic acid salt thereof is a clinically interested compound (Patent document 1 and Non-patent document 1).

[0005]

This compound and its pharmaceutically acceptable salt have very poor solubility around neutrality, and do not have good stability in solution. In consideration of clinically expected dose, and desirable preparation form of the compound, solubility of 5 mg/mL or higher is required. However, since solubility around neutrality is very low, it is difficult to develop an injectable preparation by usual formulation technique.

[0006]

In developing an injectable preparation, it is necessary to secure stability of an active ingredient contained therein during production or storage, as well as to avoid stimulus of the preparation at the time of administration. In particular, for use as a therapeutic drug against acute ischemic disorder for which emergent administration of drug is required, there is a need of developing a lyophilized preparation stably containing the above compound and its pharmaceutically acceptable salt, which serves as an injectable preparation stably containing the above compound and its pharmaceutically acceptable salt, and as a before-use preparative type preparation which is alternative for a liquid preparation.

[Patent document 1] International Patent Publication WO99/23072

[Non-patent document 1] J. Med. Chem., 2000, 43, 3372-3376

[Disclosure of the invention]

[Problem to be solved by the invention]

[0007]

Therefore, it is an object of the present invention to provide a lyophilized preparation stably containing a compound represented by the formula (I) or its pharmaceutically acceptable salt as an active ingredient.

[0008]

In order to solve the problem, the inventors of the present application made diligent effort and newly found that a lyophilized preparation which contains a specific antioxidant and a specific solubilizing agent comprising a β-cyclodextrin derivative, together

with a compound represented by the formula (I) or its pharmaceutically acceptable salt is stable by itself, and provides a uniform liquid formulation exhibiting stable dissolved state when prepared before use, and thus accomplished the present invention.

[Means for solving the problem]

[0009]

Therefore, a basic aspect of the present invention is:

(1) A lyophilized preparation comprising, as an active ingredient, (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)-phenyl]-1-piperazinyl}-2-propanol represented by the formula (I) or its pharmaceutically acceptable salt, the lyophilized preparation further comprising:

(a) at least one antioxidant selected from the group consisting of sulfite, bisulfite, pyrosulfite, α-thioglycerol and cysteine; and

(b) a β-cyclodextrin derivative.

[0010]

In more specific aspects, the present invention provides:

(2) The lyophilized preparation according to the above (1), comprising (a) at least one selected from the group consisting of sodium bisulfite, sodium pyrosulfite, α-thioglycerol, L-cysteine hydrochloride monohydrate and L-cysteine;

(3) The lyophilized preparation according to the above (1), comprising (a) sodium bisulfite;

(4) The lyophilized preparation according to the above (1), wherein an amount of the antioxidant is 0.05 to 2 times (weight ratio) that of the active ingredient;

(5) The lyophilized preparation according to the above (3), comprising sodium bisulfite in an amount of 0.1 to 1.0 times (weight ratio) that of the active ingredient;

(6) The lyophilized preparation according to the above (1), wherein the β-cyclodextrin derivative is β-cyclodextrin sulfobutyl ether sodium salt or hydroxypropyl β-cyclodextrin;

(7) The lyophilized preparation according to any one of the above (1) to (6), wherein an amount of the β-cyclodextrin derivative

relative to the active ingredient satisfies 1:4 to 1:8 (molar ratio) by active ingredient: β-cyclodextrin derivative; and

(8) The lyophilized preparation according to the above (7), wherein the amount of the β-cyclodextrin derivative relative to the active ingredient satisfies 1:5 to 1:6 (molar ratio) by active ingredient: β-cyclodextrin derivative.

[0011]

More specifically, the present invention provides:

(9) The lyophilized preparation according to the above (1), further comprising an excipient; and

(10) The lyophilized preparation according to the above (9), wherein the excipient is at least one selected from the group consisting of maltose, sucrose, mannitol, trehalose and lactose.

[0012]

Most specifically, the present invention provides:

(11) A lyophilized preparation comprising: (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol or its pharmaceutically acceptable salt as an active ingredient; sodium bisulfite in an amount of 0.1 to 1.0 times (weight ratio) that of the active ingredient; and β-cyclodextrin sulfobutyl ether sodium salt (representatively, 7 sodium salt) in such an amount relative to the active ingredient that satisfies 1:4 to 1:8 (molar ratio) by active ingredient: β-cyclodextrin derivative.

[Effect of the invention]

[0013]

According to the present invention, a stable lyophilized preparation comprising a compound represented by the formula (I) or its pharmaceutically acceptable salt as an active ingredient is provided.

The lyophilized preparation provided by the present invention stably contains a compound represented by the formula (I) or its pharmaceutically acceptable salt, which is an active ingredient, and forms a very stable and uniform solution when dissolved before use.

Since the compound represented by the formula (I) or its pharmaceutically acceptable salt has remedial and therapeutic effect

against symptoms based on ischemic disorder and neurodegenerative disease, symptoms from spasm, epilepsy and migraine, as well as various symptoms caused by diabetes, arteriosclerosis and inflammatory disease, a before-use-preparative type preparation which is very effective for therapy of these diseases can be realized.

[Best mode for carrying out the invention]

[0014]

As described above, a basic form of the present invention is a lyophilized preparation comprising as an active ingredient, (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{ 4-[4-(4-fluorobenzyl)phenyl] -1-piperazinyl} -2-propanol represented by the formula (1) or its pharmaceutically acceptable salt, further comprising:

(a) at least one antioxidant selected from the group consisting of sulfite, bisulfite, pyrosulfite, α-thioglycerol and cysteine; and

(b) a β-cyclodextrin derivative.

[0015]

As for a pharmaceutically acceptable salt of the compound represented by the formula (I), treatment of the compound of formula (I) which is free base, together with an inorganic acid or organic acid in a suitable solvent will give a corresponding salt. Examples of such inorganic acid include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, periodic acid and the like inorganic acids. Examples of organic acid include formic acid, acetic acid, lactic acid, oxalic acid, malonic acid, propionic acid, valeric acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, benzoic acid, p-toluene sulfonic acid, methane sulfonic acid, ethane sulfonic acid, trifluoromethane sulfonic acid, benzene sulfonic acid and the like organic acids.

In this case, a salt comprising one to three acid molecules may be selectively produced by increasing/decreasing the use amount of inorganic or organic acid within the range of 1 to 3 equivalents, depending on the number of basic nitrogen atom in the compound of formula (I).

[0016]

In the present invention, dimethane sulfonic acid salt is particularly preferred as the pharmaceutically acceptable salt of formula (I). This compound, namely (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol dimethane sulfonate is a compound for which clinical development is being examined under the development code number: SUN N8075.

Therefore, in the following explanation, as the compound represented by the formula (I) or its pharmaceutically acceptable salt, (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol dimethane sulfonate (hereinafter, simply referred to "SUN N8075") will be described as a representative example.

[0017]

The present invention will be explained more specifically by sequentially explaining the practice of formulation of SUN N8075 and formulation consideration by way of Test examples instead of Examples.

It is to be noted that these Test examples are given for understanding of the present invention, and the scope of the present will not be limited by these Test examples.

[0018]

In the lyophilized preparation provided by the present invention, a compound of the formula (I) represented by SUN N8075 or its pharmaceutically acceptable salt contained as an active ingredient has very low solubility at pH around neutrality, and an aqueous solution of the compound has properties such as stimulus property when administered as an injectable preparation, self-oxidation property, low stability against light and susceptibility to light decomposition.

[0019]

Therefore, the problems to be solved by the present lyophilized preparation is to ensure sufficient solubility as a before-use-dissolving type lyophilized preparation which is to be dissolved in a distilled water for injection; to ensure dilution stability; to reduce stimulus at the time of vessel administration

in administration; to prevent oxidation and light decomposition of the active ingredient during storage; and to prevent generation of insoluble matters when dissolved.

In the following, examinations for these points will be explained sequentially.

[0020]

Test example 1: Examination of solubilizing agent (Part 1)

The present inventors of the present application examined properties of the SUN N8075 itself, and found that this compound had very low solubility at pH around neutrality.

Therefore, for examination of a lyophilized preparation containing SUN N8075 as an active ingredient, it is necessary to add a solubilizing agent for improving the solubility of the active ingredient in addition to the active ingredient.

[0021]

In view of this, solubility of SUN N8075 was examined using compounds listed in Table 1 below which are conventionally used as a solubilizing agent.

[Method]

8 mg/mL aqueous solution of SUN N8075 was prepared. On the other hand, for each solubilizing agent, an aqueous solution having approximately 0.4% of solubilizing agent was prepared.

10 mL of SUN N8075 aqueous solution and 10 mL of solution of each solubilizing agent were mixed to give Mixture A, and Mixture A was filtered through a filter of 0.22 μm.

6.24 g of sodium dihydrogen phosphate and 16.4 g of sodium chloride were weighed and water was added to make the volume precisely 1,000 mL. To this solution, 1 mol/L sodium hydroxide test solution was added dropwise and the pH value was adjusted to 7.4, which was named Mixture B.

[0022]

Mixture of each 2.5 mL of Mixture A and Mixture B was provided as a test solution (in each test solution, the concentration of SUN N8075 corresponds to 2 mg/mL, and the concentration of solubilizing agent corresponds to 0.1%).

The test solution was shaken in a reciprocating shaker at 24°C

for 30 minutes, filtered through a filter of 0.22 μm, and the concentration of SUN N8075 in the filtrate was measured by HPLC method to determine its solubility.

As for a solubilizing agent of which degree of improving solubility of SUN N8075 was high, tests with concentrations of the added solubilizing agent varied were additionally executed in accordance with the method as described above.

[0023]

[Results]

The results are collectively shown in Table 1.

[0024]

[Table 1]

Solubilizing agent	Adding Conc. (%)	pH	Appearance of solution	Concentration (μg/mL)
No additive	-	6.8	colorless and clear	ND
Glycerin	0.1	6.8	colorless and clear	ND
Macrogol 4000*1	0.1	6.8	colorless and clear	ND
Mannitol	0.1	6.8	colorless and clear	ND
Ethylene diamine*5	0.1	-	-	-
Nicotinic amide	0.1	6.8	colorless and clear	ND
Propylene glycol	0.1	6.9	colorless and clear	ND
Meglumine*5	0.1	-	-	-
β-cyclodextrin	0.1	6.9	colorless and clear	26
Human serum albumin	0.1	6.8	colorless and clear	14
HCO-60*2	0.1	6.8	colorless and clear	184
	0.2	6.9	colorless and clear	334
	0.5	6.8	colorless and clear	395
Tween80*3	0.1	6.8	clouded	745
	0.2	6.8	clouded	1830
	0.5	6.8	clouded	1790
	1.0	6.8	colorless and clear	1820
β-cyclodextrin derivative*4	0.1	6.8	colorless and clear	ND
	0.5	6.8	colorless and clear	98
	1.0	6.8	colorless and clear	240
	5.0	6.9	colorless and clear	1425
	10	6.5	colorless and clear	4851

[0025]

*1: polyethylene glycol 4000

*2: polyoxyethylene hardened castor oil

*3: polyoxyethylene (20) sorbitan monooleate

*4: β-cyclodextrin sulfobutyl ether sodium salt

*5: Test was halted because solubilizing agent solution clouded

ND: Not detected

[0026]

From these examinations, it was found that polyoxyethylene (20) sorbitan monooleate (Tween80) and β-cyclodextrin sulfobutyl ether sodium salt, which is a β-cyclodextrin derivative, are effective as a solubilizing agent.

[0027]

Test example 2: Examination of solubilizing agent (Part 2)

An objective preparation of the present invention is a before-use-dissolving type lyophilized preparation which is to be dissolved in distilled water for injection, diluted as appropriate, and administered typically in the form of an injection preparation (intravenous, drip or the like). Therefore, it is requested to give no stimulus in tissues at the site of administration when administered.

Stimulus property in administration was examined for polyoxyethylene (20) sorbitan monooleate (Tween80) and β-cyclodextrin sulfobutyl ether sodium salt, which is a β-cyclodextrin derivative, which were found, as a result of the examination of Test example 1, to be an effective solubilizing agent for improvement of solubility of SUN N8075.

[0028]

[Method]

Saline, a solution in saline to which 0.1% of Tween80 was added, and a solution in saline to which 0.5, 1.0, 2.0 or 3.0% of β-cyclodextrin sulfobutyl ether sodium salt dissolving various concentrations described in Table 2 below of SUN N8075 were prepared, and administered to aorta of rat, and precipitation of SUN N8075 and presence of stimulus (blood vessel stimulus) on tissues at the site of administration were evaluated.

[0029]

[Results]

These results are collectively shown in Table 2.

Table 2: Blood vessel stimulus by SUN N8075 and stimulus suppressing effect by β-cyclodextrin sulfobutyl ether sodium salt [hereinafter referred to as Captisol (registered trademark)] (rat)

[0030]

[Table 2]

Solubilizing agent concentration in saline	Drug conc. (mg/mL)	Administ. Time (hour)	Preciptation at administration site	Blood vessel stimulation
None	0.23	72	Detected*1	Detected
	0.7	72	Detected*1	Detected
	2.3	72	Detected*1	Detected
0.1% Tween80	0.23	72	None*2	Detected
	0.7	72	None*2	Detected
3.0% Captisol	0.23	72	None*2	None
	0.7	72	None*2	None
2.0% Captisol	0.7	24	None*2	None
2.0% Captisol	0.7	24	None*2	None
2.0% Captisol	0.7	24	None*2	None

*1: Observed on polarization microscope

*2: Finding by naked eyes at autopsy and result of pathological examination

[0031]

From these results, as to the administration solution in which Captisol which is a β-cyclodextrin derivative was added as a solubilizing agent, precipitation of crystals of SUN N8075 was not observed at the site of administration, and no blood vessel stimulus was observed.

β-cyclodextrin sulfobutyl ether sodium salt, which is a β-cyclodextrin derivative, is commercially available from CyDex Inc. in U.S. in the name of "Captisol (registered trademark)".

[0032]

A β-cyclodextrin derivative which may be used in the present invention has improved water solubility compared to β-cyclodextrin by introducing a substituent such as a sulfoalkyl group or hydroxyalkyl group into β-cyclodextrin, and hydroxypropyl β-cyclodextrin can be exemplified in addition to the aforementioned β-cyclodextrin sulfobutyl ether sodium salt. Products having various average degrees of substitution are commercially available. Among others, those having degree of substitution by sulfobutyl group is about 7 are preferred, and Captisol (registered trademark) is exemplified as such a product.

[0033]

It was demonstrated that a preferred use amount, relative to the active ingredient, satisfies 1:4 to 1:8 (molar ratio) by active

ingredient: β-cyclodextrin derivative, and preferred concentration of β-cyclodextrin derivative when dissolved before use is 7.5 to 13.5% (w/v).

[0034]

Test example 3: Examination of antioxidant

In the lyophilized preparation provided by the present invention, a compound of the formula (I) represented by SUN N8075 or its pharmaceutically acceptable salt, which is an active ingredient, is easy to be oxidized.

Therefore, it is necessary to prevent a content of SUN N8075 in the lyophilized preparation from reducing due to oxidation, and further to prevent oxidation in various processes such as in the process of preparing the lyophilized preparation, in the process of lyophilizing SUN N8075 dissolved in an aqueous solution, or to prevent oxidization of SUN N8075 in a reconstituted solution.

In view of the above, addition of an antioxidant is essential in a lyophilized preparation of the present invention, and various antioxidants were examined for the anti-oxidizing ability for SUN N8075.

[0035]

[Method]

In this examination, hydrochloride of the compound of formula (I) was used instead of SUN N8075. Approximately 400 mg of the hydrochloride of compound of formula (I) were precisely weighed and water was added to make the volume precisely 200 mL, which was provided as an original drug aqueous solution.

Approximately 400 mg of each antioxidant shown in Table 3 below were precisely weighed and dissolved by adding 20 mL of water. As to butylhydroxy anisole, 10.7 mg was precisely weighed and dissolved in 100 mL of water.

15 mL of each antioxidant solution was mixed with 15 mL of solution of drug substance to prepare a stock sample (in the sample, the concentration of the hydrochloride compound of formula (I) corresponds to 1 mg/mL and the concentration of antioxidant corresponds to 10 mg/mL).

[0036]

After dispensing each stock sample into 15 brown glass ampules, the ampules were sealed and stored at 60°C.

As a control sample, 15 mL of solution of drug substance added with 15 mL of water were stored in the same condition.

The remaining three ampules for each sample solution were used for measurement at the start of tests.

[0037]

Each prepared sample was sampled in time series. 1 mL of sample solution was precisely measured, change in appearance and solution state of the sample were observed, and then added with methanol to make the volume precisely 10 mL. For this solution, residual percentage of the hydrochloride of compound of formula (I) was calculated by HPLC method. Furthermore, the pH value of the sample solution remaining after completion of test was measured.

[0038]

[Results]

These results are collectively shown in Table 3 below.

[0039]

[Table 3]

Antioxidant	Storage period	Appearance	pH	Residual degree (%)	Purity (%)
No additive	At start	colorless and clear	2.8	100	100
	1 day	colorless and clear	2.8	98.7	98.4
	7 days	colorless and clear	3.0	84.4	82.5
	21 days	pale yellow	2.9	43.1	51.2
Sodium Bisulfite	At start	colorless and clear	3.5	100	97.2
	1 day	colorless and clear	3.2	99.9	98.5
	7 days	colorless and clear	2.8	97.3	98.3
	21 days	colorless and clear	2.8	91.2	98.4
α-thioglycerol	At start	colorless and clear	2.7	100	100
	1 day	colorless and clear	2.8	97.5	100
	7 days	colorless and clear	2.9	97.1	99.2
	21 days	colorless and clear	2.8	89.0	96.8
L-cysteine HCl monohydrate	At start	colorless and clear	1.7	100	100
	1 day	colorless and clear	1.7	97.9	100
	7 days	colorless and clear	1.7	100.6	99.7
	21 days	colorless and clear	1.7	94.0	99.6
Sodium edetate	At start	colorless and clear	4.0	100	100
	1 day	colorless and clear	3.8	94.1	97.9
	7 days	colorless and clear	4.1	68.5	81.2
	21 days	colorless and clear	4.2	31.9	53.8
Citric acid	At start	colorless and clear	2.1	100	100
	1 day	colorless and clear	2.2	98.0	99.2
	7 days	colorless and clear	2.2	89.8	88.6
	21 days	colorless and clear	2.2	57.3	63.6
Sodium pyrosulfite	At start	colorless and clear	3.6	100	94.4
	1 day	colorless and clear	3.1	102.4	98.2
	7 days	colorless and clear	2.9	97.2	97.3
	21 days	colorless and clear	2.7	89.8	97.6
Butyl hydroxy anisole	At start	colorless and clear	2.8	100	100
	1 day	colorless and clear	2.8	99.2	96.8
	7 days	colorless and clear	2.8	80.3	80.6
	21 days	Brown precipitates	2.8	41.2	53.5

[0040]

From these results, it was found that sodium bisulfite, sodium pyrosulfite, L-cysteine hydrochloride monohydrate and α-thioglycerol provide desired anti-oxidation effect on the solution of SUN N8075. In addition to sodium bisulfite and sodium pyrosulfite, sulfites such as sodium sulfite, potassium sulfite and calcium sulfite, bisulfites such as potassium bisulfite and ammonium bisulfite, pyrosulfites such as potassium pyrosulfite and the like may be used, and in addition to L-cysteine hydrochloride monohydrate, cysteine such as L-cysteine, DL-cysteine and hydrochlorides thereof may also be used.

These antioxidants may be used singly or in combination, and

from the viewpoint of the amount used as an ingredient in parental dosage form for clinical use as the experience, sodium bisulfite is particularly preferably added as an antioxidant.

[0041]

When sodium bisulfite is used as an antioxidant, the added amount is 0.05 to 2 times, preferably 0.1 to 1.0 times (weight ratio), that of SUN N8075 which is an active ingredient, and the concentration when reconstituted is desirably in a range of from 0.02 to 1.0%(w/v), and preferably in a range of from 0.1 to 0.50%(w/v).

[0042]

When an added amount of sodium bisulfite is less than 0.05 times (weight ratio) the amount of the active ingredient, antioxidant activity cannot be exerted including the case of administration, and if the amount exceeding 2 times (weight ratio) the amount of the active ingredient is used, no more effect is observed.

[0043]

The preparation provided by the present invention is a lyophilized preparation comprising a compound represented by the formula (I) or its pharmaceutically acceptable salt, for example, SUN N8075, which is parenterally administered, for example, in the form of a before-use-dissolving type injection preparation. The dose is not uniquely defined because it differs depending on various factors, including condition of the patient to be treated, degree of severity, age, presence/absence of complication and the like.

However, from the result of study for clinical use amount of SUN N8075, it was found that by preparing a preparation containing 1 to 7 mg/mL, preferably 1 to 5 mg/mL of SUN N8075 as a before-use preparative preparation and appropriately adjusting the dose, it can be used in therapy of target disease.

Among others, it is particularly preferred to prepare a before-use preparative preparation containing 5 mg/mL of SUN N8075 and use it in therapy of target disease while appropriately diluting and adjusting the dose, for example, with saline.

[0044]

Therefore, the lyophilized preparation provided by the present invention is preferably a preparation that is reconstituted in, for example, saline, and ensure the aforementioned dose. Concretely, a lyophilized preparation containing 50 mg of SUN N8075 as an active ingredient is reconstituted in 9 mL of saline to prepare a before-use-prepared solution preparation containing 5 mg/mL of SUN N8075 having its pH value of 3 to 5.

It should be appreciated that it goes without saying that a content of SUN N8075 in the lyophilized preparation provided by the present invention is not limited to the above, but a preparation that ensures objective dose may be provided as appropriate.

[0045]

The lyophilized preparation provided by the present invention is produced by preparing a uniform solution stably containing SUN N8075 which is an active ingredient, and further containing an antioxidant and a solubilizing agent, and lyophilizing the solution.

In preparing a lyophilized preparation, a solution of distilled water or the like for injection for dissolving SUN N8075 is desirably used as a solution in which dissolved oxygen is removed as much as possible in order to prevent oxidation of the SUN N8075. In doing so, it is preferred that dissolved oxygen is removed by bubbling with inert gas (for example, nitrogen gas, argon gas and the like).

[0046]

Besides this, it is essential that the lyophilized preparation provided by the present invention will not generate insoluble matters at the time of before-use preparation or when dissolved in distilled water for injection which is a solvent, and will provide a uniform solution in which the lyophilized preparation is completely dissolved. However, it was found that a uniform solution is not always obtained when reconstituted.

We supposed that the filled active ingredient SUN N8075 remains unsolved in the form of free base which has lower solubility due to volatilization of mesylate or the like during storage.

The following experiments were carried out for examining a suitable added amount of β-cyclodextrin sulfobutyl ether sodium salt

(Captisol) which is the most preferable solubilizing agent, namely an added ratio of Captisol relative to SUN N8075.

[0047]

Test example 4: Examination of added ratio of Captisol relative to SUN N8075

[Method]

Lyophilized preparations according to Formulations 1 to 3 in Table 4 below were prepared in the following manner.

Approximately 1.0 g of SUN N8075 bulk drug was precisely weighed and dissolved in 20 mL of water to give an original drug solution.

10.0 g, 15.0 g and 20.0 g each of β-cyclodextrin sulfobutyl ether sodium salt (Captisol), and 200 mg of sodium bisulfite (Japanese Pharmacopoeia; available from JUNSEI CHEMICAL) were precisely weighed and dissolved in 100 mL water to give three kinds of additive solutions containing different amounts of Captisol.

To each solution in which the original drug solution and each of the three additive solutions were mixed, water was added to make the volume precisely 200 mL, which was provided as a formulation solution. Each of the three kinds of formulation solutions was filtered through a filter of 0.22 μm (Commercial name: Stericup GV, available from Millipore) and dispensed by 10 mL into a 25 mL-volume vial (specification V-N25, available from FUJI GLASS CO., LTD.) and half plugged.

Each formulation solution thus dispensed was conveyed into a vacuum lyophilization dryer (Type FZ-6, available from Laboconco) and then lyophilized in the following conditions.

[0048]

Cooling: room temperature to -34°C (0.32°C/min.)

Lyophilization: -34°C, retained for 4 hours

Heating: -34°C to -20°C (0.12°C/min.)

Primary drying: -20°C (retained for 40 hours)

Heating: -20°C to 30°C (0.42°C/min.)

Secondary drying: 30°C, retained 20 hours or more

After lyophilization, vials were plugged and preparations of Formulations 1 to 3 were conveyed out of the lyophilization dryer.

[0049]

Each of these lyophilized preparations was reconstituted in 10 mL of saline, and appearance of the obtained solution was observed to evaluate generation of insoluble contaminants.

Each lyophilized preparation was tested four times, and evaluation of presence of insoluble contaminants in solution was made by observation under 1,000 Lux.

[0050]

[Result]

Results are collectively shown in Table 5 below.

Marks used in this Table represent the following meanings.

×: insoluble matters observed at the time of reconstitution

○: insoluble matters not observed at the time of reconstitution

-: not executed

[0051]

[Table 4]

Active Ingredient and Additive	Formulation		
	1	2	3
Ratio of Active ingredient : Captisol	1:10	1:15	1:20
SUN N8075 (Active ingredient) Sodium bisulfite Captisol	50mg 10mg 500mg	50mg 10mg 750mg	50mg 10mg 1000mg
Amount of solvent (saline)	10mL	10mL	10mL

[0052]

[Table 5]

Formulation No.	Ratio of Active ingredient : Captisol	1st	2nd	3rd	4th
1	1:10	×	-	×	×
2	1:15	-	○	○	○
3	1:20	-	○	○	○

[0053]

These results demonstrated that in a lyophilized preparation of the present invention, a preferred use amount of Captisol which is a solubilizing agent is 15 to 20 times by weight part, relative to the SUN N8075 which is an active ingredient.

This amount corresponds to 1:4 to 1:8 (molar ratio) by SUN N8075: Captisol which is preferred as a use amount of the solubilizing agent relative to the active ingredient, and additionally corresponds to 7.5 to 13.5%(w/v) of Captisol at the time of before-use dissolution.

[0054]

In this manner, a lyophilized preparation of the present invention which will not generate insoluble contaminates at the time of reconstitution while offering a before-use preparative solution is provided. The solution after reconstitution may be diluted appropriately in saline and administered intravenously or by drip.

Therefore, stability should be ensured also for the solution after dilution.

We examined stability of a solution after dilution.

[0055]

Test example 5: Examination of stability of diluted solution of reconstituted solution

[Method]

A lyophilized preparation according to Formulation 3 of Test example 4 was dissolved in 10 mL of saline. The solution was diluted in saline so that concentration of the main drug, SUN N8075 was 30 μg/mL, to give a blend solution.

55 mL of the resultant blend solution was collected in a syringe and stored under 25°C/1,000 Lux (D65 lamp) exposure and under 25°C/light protection.

Each stored blend solution was sampled at the start of test, after 6 hours and 24 hours, and observation of appearance of blend solution (under 1,000 Lux), content remaining rate measurement by HPLC method and pH measurement were executed to evaluate stability.

[0056]

[Result]

The results are collectively shown in Table 6 below.

[0057]

[Table 6]

Storage condition	Storage time (hours)	Evaluation items		
		Appearance	pH	% of initial assay
Under light exposure	0 (At start)	Clear and colorless	4.81	100
	6	Clear and colorless	4.78	99.3
	24	Clear and colorless	4.79	98.4
Under light protection	0 (At start)	Clear and colorless	4.87	100
	6	Clear and colorless	4.88	99.8
	24	Clear and colorless	4.88	99.4

[0058]

As is apparent from the above result, stability of a lyophilized preparation of the present invention is not problematic even in a blend solution, which is obtained by diluting a reconstituted solution at the time of before-use preparation.

The present preparation is usually stored for a long term in the form of lyophilized product until it is reconstituted before use. We examined long-term stability of the lyophilized product.

[0059]

Test example 6: Examination of stability in long-term storage of lyophilized product

[Method]

A lyophilized preparation according to Formulation 3 of Test example 4 was stored at 25°C/60%RH, or 40°C/75%RH. Each of the preparation stored in each storage condition was sampled in time-series, and observation of appearance (under room diffused light), measurement of content remaining rate/related substance mass by HPLC method and water content measurement were conducted for evaluating stability.

[0060]

[Result]

The results are collectively shown in Table 7.

[0061]

[Table 7]

Storage condition	Storage period	Evaluation items			
		Appearance	% of initial assay	Quantity of related substance (%)	Water content (%)
25°C/60%RH	0 (At start)	Slightly yellowish white mass	100.0	0.86	0.72
	12 months	Slightly yellowish white mass	97.3	0.89	0.83
	24 months	Slightly yellowish white mass	98.2	0.83	0.81
	36 months	Slightly yellowish white mass	98.2	0.85	0.82
40°C/75%RH	0 (At start)	Slightly yellowish white mass	100.0	0.86	0.72
	1 month	Slightly yellowish white mass	99.2	0.85	0.74
	3 months	Slightly yellowish white mass	99.4	0.87	0.78
	6 months	Slightly yellowish white mass	99.8	0.85	0.93

[0062]

These results demonstrated that the present preparation is stable when it is stored in long-term in the form of a lyophilized product.

[0063]

From the foregoing test examples, a lyophilized preparation comprising a compound of the formula (I) represented by SUN N8075 or its pharmaceutically acceptable salt, provided by the present invention has a basic mode which contains:

(a) at least one selected from the group consisting of sulfite, bisulfite, pyrosulfite, α-thioglycerol and cysteine; and

(b) a β-cyclodextrin derivative.

Among others, in particular, those using sodium bisulfite serving as an antioxidant and Captisol serving as a solubilizing agent are preferable.

[0064]

More specifically, the present invention is a lyophilized preparation which comprises, as an active ingredient, a compound of the formula (I) represented by SUN N8075 or its pharmaceutically acceptable salt, sodium bisulfite in an amount of 0.1 to 1.0 times (weight ratio) that of the active ingredient, and β-cyclodextrin sulfobutyl ether sodium salt in such an amount that satisfies 1:4 to

1:8 (molar ratio) by active ingredient: β-cyclodextrin derivative.

[0065]

The lyophilized preparation provided by the present invention may contain a variety of excipients such as maltose, sucrose, mannitol, trehalose and lactose. A plurality of kinds of these excipients may be blended.

[0066]

The lyophilized preparation provided by the present invention may be produced by a process of producing lyophilized preparation which is commonly used in pharmacy. Examinations made by the present inventors revealed that the lyophilized preparation may be desirably prepared in the following steps.

Concretely it is a method of producing a lyophilized preparation which comprises the steps of:

(a) dissolving a compound of the formula (I) represented by SUN N8075 or its pharmaceutically acceptable salt in an injection solvent in which dissolved oxygen has been reduced by inert gas replacement, to prepare an original drug solution;

(b) dissolving a solubilizing agent, for example, a β-cyclodextrin derivative, in an injection solvent, replacing dissolved oxygen by inert gas replacement, and dissolving at least one selected from sulfite, bisulfite, pyrosulfite, α-thioglycerol and cysteine, to prepare a sub material solution;

(c) adding and mixing the original drug solution to the sub material solution under inert gas flow; and

(d) charging the resultant mixture solution into a vial and lyophilizing the same by a lyophilization machine.

[0067]

The vial filled with the resultant lyophilized preparation was plugged and windingly fastened, for example, with a butyl rubber plug (available from Daikyo Seiko Co., Ltd.) laminated with Teflon (registered trademark) and an aluminum cap (Flip cap 20; available from Hisa Kinzoku Kogyo Co., Ltd.) for provision as an actual product.

[0068]

The lyophilized preparation of the present invention thus

provided is dissolved in saline before use, diluted as necessary for appropriately adjusting the dose, and administered by injection or administered by drip, whereby it can be used in therapy of a target disease.

[Industrial applicability]

[0069]

According to the present invention, there is provided a stable lyophilized preparation containing a compound represented by the formula (I) and its pharmaceutically acceptable salt which has poor solubility around neutrality as an active ingredient.

The lyophilized preparation provided by the present invention stably contains a compound represented by the formula (I) and its pharmaceutically acceptable salt as an active ingredient, and since such compound and its pharmaceutically acceptable salt have excellent remedial and therapeutic ability against symptoms based on ischemic disorder and neurodegenerative disease, symptoms from spasm, epilepsy and migraine, as well as various symptoms caused by diabetes, arteriosclerosis and inflammatory disease, the lyophilized preparation is highly effective for therapy of these diseases, and thus provides great industrial applicability.

CLAIMS

1. A lyophilized preparation comprising, as an active ingredient, (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol or its pharmaceutically acceptable salt, the lyophilized preparation further comprising:

(a) at least one antioxidant selected from the group consisting of sulfite, bisulfite, pyrosulfite, α-thioglycerol and cysteine; and

(b) a β-cyclodextrin derivative.

2. The lyophilized preparation according to claim 1, comprising (a) at least one antioxidant selected from the group consisting of sodium bisulfite, sodium pyrosulfite, α-thioglycerol, L-cysteine hydrochloride monohydrate and L-cysteine.

3. The lyophilized preparation according to claim 1, comprising (a) sodium bisulfite.

4. The lyophilized preparation according to claim 1, wherein an amount of the antioxidant is 0.05 to 2 times (weight ratio) that of the active ingredient.

5. The lyophilized preparation according to claim 3, comprising sodium bisulfite in an amount of 0.1 to 1.0 times (weight ratio) that of the active ingredient.

6. The lyophilized preparation according to claim 1, wherein the β-cyclodextrin derivative is β-cyclodextrin sulfobutyl ether sodium salt or hydroxypropyl β-cyclodextrin.

7. The lyophilized preparation according to any one of claims 1 to 6, wherein an amount of the β-cyclodextrin derivative relative to the active ingredient satisfies 1:4 to 1:8 (molar ratio) by active ingredient: β-cyclodextrin derivative.

8. The lyophilized preparation according to claim 7, wherein the amount of the β-cyclodextrin derivative relative to the active ingredient satisfies 1:5 to 1:6 (molar ratio) by active ingredient: β-cyclodextrin derivative.

9. The lyophilized preparation according to claim 1, further comprising an excipient.

10. The lyophilized preparation according to claim 9, wherein the excipient is at least one selected from the group consisting of maltose, sucrose, mannitol, trehalose and lactose.

11. A lyophilized preparation comprising: (2S)-1-(4-amino-2,3,5-trimethylphenoxy)-3-{4-[4-(4-fluorobenzyl)phenyl]-1-piperazinyl}-2-propanol or its pharmaceutically acceptable salt as an active ingredient; sodium bisulfite in an amount of 0.1 to 1.0 times (weight ratio) that of the active ingredient; and β-cyclodextrin sulfobutyl ether sodium salt in such an amount relative to the active ingredient that satisfies 1:4 to 1:8 (molar ratio) by active ingredient: β-cyclodextrin derivative.