DESCRIPTION

Title of Invention: 5-DEAZAFLAVIN COMPOUND-CONTAINING EMULSION AND METHOD FOR PRODUCING SAME

Technical Field

[0001]

The present invention relates to a 5-deazaflavin compound-containing emulsion and a method for producing the same.

Background Art

[0002]

In recent years, methods for preventing or treating diseases, in which dysfunction of energy production in cells is causative factors, such as Alzheimer's disease, Parkinson's disease, neurodegenerative diseases associated with cerebral hemorrhage or cerebral infarction, and depression, as well as methods for providing anti-aging care, by improving dysfunction of energy production in cells, have attracted attention. Accordingly, active ingredients for improving dysfunction of energy production in cells have been intensively investigated, and, as one of such active ingredients, a 5-deazaflavin compound has been reported in PTL 1.

[0003]

The 5-deazaflavin compound reported in PTL 1 has an excellent activating effect on the production of adenosine triphosphate (ATP) in cells, and is therefore greatly expected as an active ingredient for improving dysfunction of energy production in cells. However, the 5-deazaflavin compound is a condensed polycyclic aromatic heterocyclic compound, and therefore is poorly soluble in both water and oil (fat or oil), and therefore has a property of being difficult to formulate into a liquid preparation.

Citation List

Patent Literature

[0004]

PTL 1: JP6717989B

Summary of Invention

Technical Problem

[0005]

Accordingly, an object of the invention is to provide a 5-deazaflavin compound-containing emulsion and a method for producing the same.

Solution to Problem

[0006]

As a result of intensive studies conducted in view of the above points, the present inventors have found that a 5-deazaflavin compound-containing emulsion can be produced by dissolving a 5-deazaflavin compound using benzyl alcohol or phenoxyethanol and appropriately selecting and emulsifying the constituent components.

[0007]

As described in claim 1, a 5-deazaflavin compound-containing emulsion of the invention that has been made based on the above finding contains, as constituent components, at least:

(1) a 5-deazaflavin compound;

(2) benzyl alcohol and/or phenoxyethanol;

(3) a polysorbate and a lecithin;

(4) a pharmaceutically acceptable salt of an aromatic carboxylic acid;

(5) a fat or oil; and

(6) an aqueous medium.

Further, a 5-deazaflavin compound-containing emulsion described in claim 2 further contains, as a constituent

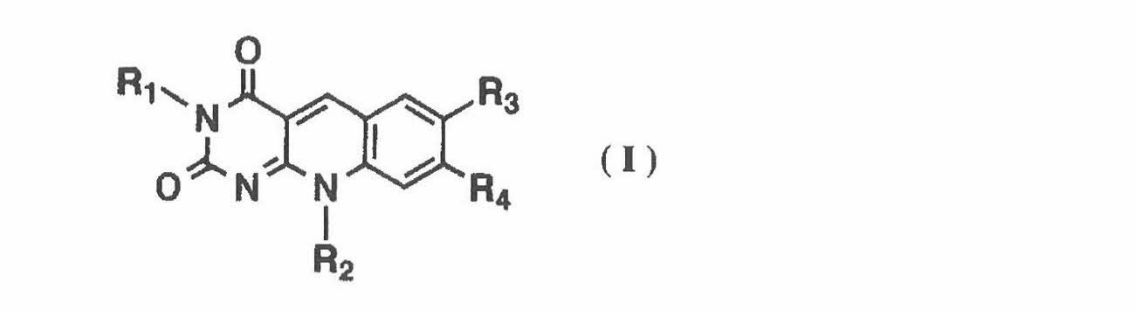
component, in the 5-deazaflavin compound-containing emulsion described in claim 1:

(7) an aromatic carboxylic acid.

Further, a 5-deazaflavin compound-containing emulsion described in claim 3 is configured such that, in the 5-deazaflavin compound-containing emulsion described in claim 1, the 5-deazaflavin compound is a compound represented by a general formula (I) below.

[0008]

[Chem. 1]



(I)

[0009]

[In the formula, R_1 represents any of a hydrogen atom, a lower alkyl group, and an optionally substituted phenyl group, R_2 represents any of a lower alkyl group, a lower cycloalkyl group, and an optionally substituted phenyl group, R_3 and R_4 are identical or different and represent any of a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a cyano group, a lower alkyl group, a lower alkoxy group, a lower alkylamino group, and a lower alkylsulfonyl group.]

Further, as described in claim 4, a method for producing a 5-deazaflavin compound-containing emulsion of the invention includes emulsifying constituent components including at least:

(1) a 5-deazaflavin compound;

(2) benzyl alcohol and/or phenoxyethanol;

(3) a polysorbate and a lecithin;

(4) a pharmaceutically acceptable salt of an aromatic carboxylic acid;

(5) a fat or oil; and

(6) an aqueous medium.

Advantageous Effects of Invention

[0010]

According to the invention, it is possible to provide a 5-deazaflavin compound-containing emulsion and a method for producing the same.

Description of Embodiments

[0011]

The 5-deazaflavin compound-containing emulsion of the invention contains, as constituent components, at least:

(1) a 5-deazaflavin compound;

(2) benzyl alcohol and/or phenoxyethanol;

(3) a polysorbate and a lecithin;

(4) a pharmaceutically acceptable salt of an aromatic carboxylic acid;

(5) a fat or oil; and

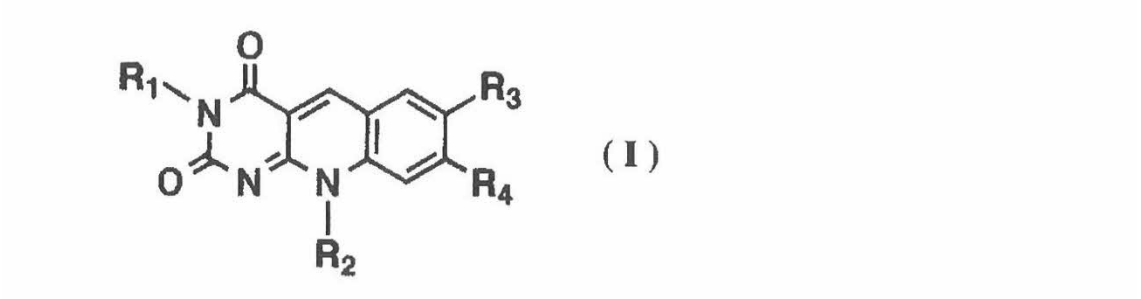
(6) an aqueous medium.

[0012]

In the invention, the 5-deazaflavin compound refers to a compound having a 5-deazaflavin skeleton (a skeleton in which the nitrogen atom at the 5-position of the flavin skeleton is replaced with a carbon atom), and specific examples thereof include a compound represented by a general formula (I) below described in PTL 1.

[0013]

[Chem. 2]



(I)

[0014]

[In the formula, R_1 represents any of a hydrogen atom, a lower alkyl group, and an optionally substituted phenyl group, R_2 represents any of a lower alkyl group, a lower cycloalkyl group, and an optionally substituted phenyl group, R_3 and R_4 are identical or different and represent any of a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a cyano group, a lower alkyl group, a lower alkoxy group, a lower alkylamino group, and a lower alkylsulfonyl group.]

[0015]

Here, the lower alkyl group refers to a linear or branched alkyl group having 1 to 6 carbon atoms, and specific examples thereof include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, and a tert-butyl group. The lower cycloalkyl group refers to a cycloalkyl group having 3 to 7 carbon atoms, and specific examples thereof include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, and a cycloheptyl group. Examples of the halogen atom include a fluorine atom, a chlorine atom, a bromine atom, and an iodine atom. The lower alkoxy group refers to a linear or branched alkoxy group having 1 to 6 carbon atoms, and specific examples thereof include a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, and a tert-butoxy group. The lower alkylamino group refers to an alkylamino group in which the lower alkyl moiety has the same meaning as described above, and specific examples thereof include a methylamino group, an ethylamino group, and a propylamino group. The lower alkylsulfonyl group refers to an alkylsulfonyl group in which the lower alkyl moiety has the same meaning as described above, and specific examples thereof include a methylsulfonyl group, an ethylsulfonyl group, and a propylsulfonyl group. Examples of the substituent that the optionally substituted phenyl group may have include a halogen atom, a hydroxy group, a nitro group,

a cyano group, a carboxyl group, an amino group, a lower alkyl group, a lower alkoxy group, and a lower alkylamino group. The lower alkyl group, the lower alkoxy group, and the lower alkylamino group have the same meanings as described above.

[0016]

In the invention, benzyl alcohol and/or phenoxyethanol are used because they are liquids that are poorly soluble in an aqueous medium and are capable of dissolving a 5-deazaflavin compound, and therefore benzyl alcohol and/or phenoxyethanol in which a 5-deazaflavin compound is dissolved is allowed to be present in an emulsion as droplets in which the 5-deazaflavin compound is dissolved (corresponding to fat particles in which a drug is dissolved in a drug-containing fat emulsion).

[0017]

In the invention, a polysorbate (a polyoxyethylene sorbitan fatty acid ester) and a lecithin serve as emulsifiers for dispersing, in an emulsion, droplets formed of benzyl alcohol and/or phenoxyethanol in which the 5-deazaflavin compound is dissolved. It is essential that both a polysorbate and a lecithin are used in admixture. This is because when either of these is used alone, a 5-deazaflavin compound-containing emulsion having excellent stability cannot be produced (the emulsion undergoes phase separation immediately after production, or precipitates or sediments are generated in the emulsion). As the polysorbate, polysorbate 20, 40, 60, 65, 80, or the like can be used (these may be used alone or two or more types may be used in admixture). As the lecithin, egg yolk lecithin, soy lecithin, hydrogenated egg yolk lecithin, hydrogenated soy lecithin, or the like can be used (these may be used alone or two or more types may be used in admixture).

[0018]

In the invention, specific examples of the pharmaceutically acceptable salt of an aromatic carboxylic acid include pharmaceutically acceptable salts of benzoic acid,

salicylic acid, phthalic acid, isophthalic acid, or terephthalic acid, for example, alkali metal salts such as sodium salts and potassium salts, and alkaline earth metal salts such as magnesium salts and calcium salts (these may be used alone or two or more types may be used in admixture).

[0019]

In the invention, specific examples of the fat or oil include known fats and oils that can be used as the fat or oil, including vegetable oils such as soybean oil, corn oil, palm oil, safflower oil, perilla oil, olive oil, castor oil, and cottonseed oil, as well as animal oils such as lanolin, egg yolk oil, fish oil, mineral oils such as liquid paraffin, medium-chain fatty acid triglycerides, chemically synthesized triglycerides, and gelled hydrocarbons (these may be used alone or two or more types may be used in admixture).

[0020]

In the invention, specific examples of the aqueous medium include water (such as pure water, purified water, and water for injection), as well as buffers adjusted to a predetermined pH, for example, a pH in the range of 3.5 to 9.0, desirably 5.0 to 8.5, and more desirably 6.5 to 8.0, by adding, to water, acetic acid–sodium acetate, boric acid–sodium carbonate, boric acid–sodium tetraborate, hydrochloric acid–sodium tetraborate, phosphoric acid–sodium phosphate, sodium dihydrogen phosphate–disodium hydrogen phosphate, citric acid–sodium hydroxide, hydrochloric acid–potassium hydrogen phthalate, sodium hydroxide–potassium hydrogen phthalate, citric acid–disodium hydrogen phosphate, succinic acid–sodium tetraborate, ammonia–ammonium chloride, potassium dihydrogen phosphate–disodium hydrogen phosphate–phosphoric acid, potassium dihydrogen phosphate–disodium hydrogen phosphate–sodium hydroxide, potassium dihydrogen phosphate–disodium hydrogen phosphate, potassium dihydrogen phosphate–sodium hydroxide, disodium hydrogen phosphate–sodium hydroxide, Tris (an abbreviation for

tris(hydroxymethyl)aminomethane, the same applies hereinafter)–hydrochloric acid, Tris–EDTA, Tris–acetic acid–EDTA, trisodium citrate–sodium hydroxide–sodium chloride, sodium dihydrogen phosphate–EDTA–sodium chloride, or the like.

[0021]

In the 5-deazaflavin compound-containing emulsion of the invention, an aromatic carboxylic acid may further be incorporated. By further incorporating an aromatic carboxylic acid, the dissolving power for the 5-deazaflavin compound in benzyl alcohol and/or phenoxyethanol can be enhanced. Specific examples of the aromatic carboxylic acid include benzoic acid, salicylic acid, phthalic acid, isophthalic acid, and terephthalic acid (these may be used alone or two or more types may be used in admixture).

[0022]

The content of the 5-deazaflavin compound in the 5-deazaflavin compound-containing emulsion of the invention may be, for example, 0.01 to 30 mg/g (the upper limit is desirably 20 mg/g, and more desirably 10 mg/g). The content of benzyl alcohol and/or phenoxyethanol is desirably 5 times or more the content of the 5-deazaflavin compound, and more desirably 10 times or more. When the content is less than 5 times, there is a risk that the entire amount of the 5-deazaflavin compound cannot be dissolved even if an aromatic carboxylic acid is further incorporated to enhance the dissolving power for the 5-deazaflavin compound in these solvents. However, the upper limit thereof is desirably 250 mg/g, more desirably 150 mg/g, and still more desirably 100 mg/g. The total content of the polysorbate and the lecithin is desirably 0.5 to 5 times the content of benzyl alcohol and/or phenoxyethanol. When the total content is less than 0.5 times, emulsification may become difficult. However, the upper limit thereof is desirably 200 mg/g, and more desirably 150 mg/g. The proportion of the content of the polysorbate with respect to the total content of the

polysorbate and the lecithin is, for example, 5 to 96%. As the proportion of the content of the polysorbate with respect to the total content of the polysorbate and the lecithin increases, the viscosity of the 5-deazaflavin compound-containing emulsion to be produced decreases. The content of the pharmaceutically acceptable salt of an aromatic carboxylic acid is desirably 0.5 to 5 times the content of benzyl alcohol and/or phenoxyethanol. However, the upper limit thereof is desirably 200 mg/g, more desirably 150 mg/g, and still more desirably 100 mg/g. The content of the fat or oil is desirably 0.01 to 1 times the content of benzyl alcohol and/or phenoxyethanol. Since the fat or oil is miscible with benzyl alcohol and/or phenoxyethanol, when the content of the fat or oil increases, there is a risk that the dissolution of the 5-deazaflavin compound by benzyl alcohol and/or phenoxyethanol may be impaired. When an aromatic carboxylic acid is further incorporated, the upper limit of the content thereof is desirably 0.5 times the content of benzyl alcohol and/or phenoxyethanol.

[0023]

A method for producing a 5-deazaflavin compound-containing emulsion of the invention is not particularly limited, and examples thereof include a method in which the contents of a 5-deazaflavin compound, benzyl alcohol and/or phenoxyethanol, a polysorbate and a lecithin, a pharmaceutically acceptable salt of an aromatic carboxylic acid, a fat or oil, and an aromatic carboxylic acid (when further incorporated) are set within the above numerical ranges, an oil phase component is prepared by dissolving the 5-deazaflavin compound, the fat or oil, and the aromatic carboxylic acid (when further incorporated) in benzyl alcohol and/or phenoxyethanol, an aqueous phase component is prepared by dissolving the polysorbate and the lecithin, the pharmaceutically acceptable salt of an aromatic carboxylic acid in an aqueous medium, and the oil phase component and the aqueous phase component are mixed and emulsified. The emulsification

of the mixed liquid of the oil phase component and the aqueous phase component may be performed by manual shaking, or by using an apparatus such as a stirrer (mixer), an ultrasonic emulsifier, or an ultrasonic cleaner. The emulsification time may be, for example, 1 to 30 minutes. The average particle diameter of the droplets formed of benzyl alcohol and/or phenoxyethanol in which the 5-deazaflavin compound is dissolved (when an aromatic carboxylic acid is further incorporated, the aromatic carboxylic acid is also contained in the droplets) is desirably 300 nm or less, more desirably 200 nm or less, and still more desirably 100 nm or less. The lower limit is, for example, 1 nm (which can be adjusted, for example, by adjusting the emulsification conditions).

[0024]

The 5-deazaflavin compound-containing emulsion of the invention can easily undergo filtration sterilization and can also undergo high-pressure steam sterilization by setting the average particle diameter of the droplets to, for example, 200 nm or less. High-pressure steam sterilization may be performed under general conditions (for example, 120 to 122°C × 10 to 15 minutes) after filling the 5-deazaflavin compound-containing emulsion of the invention into a glass ampoule, a synthetic resin container, or the like.

[0025]

The 5-deazaflavin compound-containing emulsion of the invention may have its pH adjusted (for example, to 3.5 to 9.0) and/or its osmotic pressure adjusted by addition of a per se known pH adjusting agent or osmotic pressure adjusting agent. Further, a per se known preservative, antioxidant, stabilizer, or the like may be added to the 5-deazaflavin compound-containing emulsion of the invention as necessary.

[0026]

The 5-deazaflavin compound-containing emulsion of the invention has excellent stability, and therefore can be stored

at room temperature (for example, 5 to 30°C). Further, the 5-deazaflavin compound-containing emulsion of the invention has transparency (a turbidity of 0.5 or less), and therefore facilitates visual inspection of deterioration, foreign matter contamination, and compatibility changes, and also provides a sense of reassurance to patients being administered. These effects function effectively particularly when the 5-deazaflavin compound-containing emulsion of the invention is used as a liquid preparation such as an injection, an oral preparation, a lotion, an eye drop, a nasal drop, an ear drop, or an inhalant (which may be diluted in an aqueous medium as necessary).

Examples

[0027]

The invention will be described in detail below with reference to Examples, but the invention is not to be construed as being limited to the following description.

[0028]

Examples and Comparative Examples:

The contents of a test tube charged with predetermined amounts of each of the four constituent components: (1) a 5-deazaflavin compound; (2) benzyl alcohol or phenoxyethanol; (5) a fat or oil; and (7) an aromatic carboxylic acid were dissolved until uniform using an ultrasonic cleaner (ASU-30) manufactured by AS ONE Corporation filled with water at 50°C (operating time: 15 minutes) (oil phase component). In addition, the contents of a test tube charged with predetermined amounts of each of the three constituent components: (3) a polysorbate and a lecithin; (4) a pharmaceutically acceptable salt of an aromatic carboxylic acid; and (6) an aqueous medium were dissolved until uniform using an ultrasonic emulsifier (UH-50) manufactured by SMT Corporation (operating time: 5 minutes) (aqueous phase component). The aqueous phase component was added to the test tube containing the oil phase component and mixed, and the

mixture was emulsified for 5 minutes using a test tube stirrer (HM-10) manufactured by AS ONE Corporation to produce a 5-deazaflavin compound-containing emulsion. The types and amounts of use of the seven constituent components are shown in Table 1. In Table 1, T-MAC used as the (1) 5-deazaflavin compound is 10-ethyl-3-methylpyrimido[4,5-b]quinoline-2,4(3H,10H)-dione (a compound in which R_1 = a methyl group, R_2 = an ethyl group, and R_3 = R_4 = a hydrogen atom in the general formula (I)), and TN1160 is 8-chloro-3-methyl-10-phenylpyrimido[4,5-b]quinoline-2,4(3H,10H)-dione (a compound in which R_1 = a methyl group, R_2 = a phenyl group, R_3 = a hydrogen atom, and R_4 = a chlorine atom in the general formula (I)) (both are compounds described in PTL 1). As the (3) polysorbates 20, 60, and 80, those manufactured by NOF Corporation were used. As the egg yolk lecithin, PL-100M manufactured by Kewpie Corporation was used. As the (5) MCT (medium-chain fatty acid triglyceride), MCT oil manufactured by Nisshin OilliO Group, Ltd. was used. As the soybean oil, one manufactured by Croda International plc was used. The (6) aqueous medium is pure water (1 mL = 1000 mg). "None" means that the component was not used as a constituent component. The "Polysorbate ratio" indicates the proportion of the content of the polysorbate with respect to the total content of the polysorbate and the lecithin.

[0029]

[Table 1]

	(1)	(2)	(7)	(3)	(4)	(5)	(6) Pure water	Poly-sorbate ratio
Example 1	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 300/100mg	Na salicylate 300mg	MCT 40mg	5mL	75%
Example 2	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 250/100mg	Na salicylate 240mg	MCT 40mg	5mL	71%
Example 3	T-MAC 16mg	Benzyl alcohol 200mg	Salicylic acid 40mg	Polysorbate 80/egg yolk lecithin 300/100mg	Na salicylate 300mg	MCT 40mg	5mL	75%

	(1)	(2)	(7)	(3)	(4)	(5)	(6) Pure water	Poly-sorbate ratio
Example 4	T-MAC 12mg	Phenoxyethanol 200mg	Salicylic acid 40mg	Polysorbate 80/egg yolk lecithin 300/100mg	Na salicylate 300mg	Soybean oil 40mg	5mL	75%
Example 5	T-MAC 6mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 250/100mg	Na benzoate 240mg	MCT 40mg	5mL	71%
Example 6	TN1160 1mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 300/100mg	Na salicylate 300mg	MCT 40mg	5mL	75%
Comparative Example 1	T-MAC 10mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/polysorbate 20/egg yolk lecithin 200/50/100mg	None	MCT 40mg	2.5mL	71%
Example 7	T-MAC 10mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/polysorbate 20/egg yolk lecithin 200/50/100mg	Na salicylate 300mg	MCT 40mg	2.5mL	71%
Comparative Example 2	T-MAC 10mg	Benzyl alcohol 200mg	Benzoic acid 60mg	Polysorbate 80/polysorbate 60 100/150mg	Na salicylate 300mg	MCT 20mg	2.5mL	100%
Example 8	T-MAC 10mg	Benzyl alcohol 200mg	Benzoic acid 60mg	Polysorbate 80/polysorbate 60/egg yolk lecithin 100/150/100mg	Na salicylate 300mg	MCT 20mg	2.5mL	71%
Comparative Example 3	T-MAC 3mg	Benzyl alcohol 100mg	None	Egg yolk lecithin 200mg	None	None	4mL	0%
Comparative Example 4	T-MAC 10mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Egg yolk lecithin 300mg	Na salicylate 300mg	None	2.5mL	0%
Comparative Example 5	T-MAC 10mg	Benzyl alcohol 200mg	None	Egg yolk lecithin 300mg	Na salicylate 300mg	None	2.5mL	0%
Comparative Example 6	T-MAC 10mg	Benzyl alcohol 200mg	None	Egg yolk lecithin 300mg	Na salicylate 300mg	MCT 40mg	2.5mL	0%
Comparative Example 7	T-MAC 10mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Egg yolk lecithin 150mg	Na salicylate 300mg	MCT 40mg	2.5mL	0%
Example 9	T-MAC 16mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 400/50mg	Na salicylate 300mg	MCT 40mg	4mL	89%
Example 10	T-MAC 16mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 400/100mg	Na salicylate 300mg	MCT 40mg	4mL	80%

	(1)	(2)	(7)	(3)	(4)	(5)	(6) Pure water	Poly-sorbate ratio
Example 11	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 200/200mg	Na salicylate 240mg	MCT 40mg	2mL	50%
Example 12	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 100/250mg	Na salicylate 240mg	MCT 40mg	4mL	29%

[Table 1] (continued)

	(1)	(2)	(7)	(3)	(4)	(5)	(6) Pure water	Poly-sorbate ratio
Example 13	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 300/200mg	Na salicylate 240mg	MCT 40mg	2mL	60%
Example 14	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 400/20mg	Na salicylate 240mg	MCT 40mg	4mL	95%
Example 15	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 30/270mg	Na salicylate 240mg	MCT 40mg	2mL	10%
Example 16	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 15/285mg	Na salicylate 240mg	MCT 40mg	2mL	5%
Comparative Example 8	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80 400mg	Na salicylate 240mg	MCT 40mg	4mL	100%
Example 17	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 160/240mg	Na salicylate 240mg	MCT 40mg	2mL	40%
Example 18	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 80/320mg	Na salicylate 240mg	MCT 40mg	2mL	20%
Comparative Example 9	T-MAC 12mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 250/100mg	Na salicylate 240mg	None	5mL	71%
Example 19	T-MAC 6mg	Benzyl alcohol 200mg	None	Polysorbate 80/egg yolk lecithin 250/100mg	Na salicylate 240mg	MCT 40mg	5mL	71%
Example 20	TN1160 2mg	Benzyl alcohol 200mg	Benzoic acid 60mg	Polysorbate 80/egg yolk lecithin 300/100mg	Na salicylate 300mg	MCT 40mg	5mL	75%

	(1)	(2)	(7)	(3)	(4)	(5)	(6) Pure water	Poly-sorbate ratio
Example 21	TN1160 1mg	Benzyl alcohol 200mg	None	Polysorbate 80/egg yolk lecithin 300/100mg	Na salicylate 300mg	MCT 40mg	5mL	75%
Example 22	T-MAC 6mg	Benzyl alcohol 150mg	Benzoic acid 50mg	Polysorbate 80/egg yolk lecithin 250/100mg	Na salicylate 240mg	MCT 40mg	5mL	71%
Example 23	TN1160 1mg	Benzyl alcohol 150mg	Benzoic acid 50mg	Polysorbate 80/egg yolk lecithin 300/100mg	Na salicylate 300mg	MCT 40mg	5mL	75%

[0030]

The average particle diameter of the droplets contained in the 5-deazaflavin compound-containing emulsions immediately after production was measured with a particle diameter measuring apparatus (Zetasizer Nano ZS) manufactured by Malvern Instruments using the photon correlation method. Further, test tubes containing the 5-deazaflavin compound-containing emulsions were capped and allowed to stand indoors for 12 hours, and thereafter the properties of the emulsions were visually evaluated. The results are shown in Table 2. As is apparent from Table 2, the 5-deazaflavin compound-containing emulsions produced in Examples 1 to 10, 14, and 19 to 23 had a polysorbate ratio (the proportion of the content of the polysorbate with respect to the total content of the polysorbate and the lecithin) of more than 60%, and therefore were emulsions having a low viscosity. Accordingly, it was possible to measure the average particle diameter of the droplets contained in the emulsions, and all of the average particle diameters were 100 nm or less. Since the 5-deazaflavin compound-containing emulsions produced in Examples 11 to 13 and 15 to 18 had a polysorbate ratio of 60% or less and therefore were emulsions having a high viscosity. Accordingly, the average particle diameter of the droplets contained in the emulsions could not be measured by the particle diameter measuring apparatus using the photon correlation

method; however, the average particle diameter of the droplets could be measured by diluting the emulsions 5-fold with pure water. The 5-deazaflavin compound-containing emulsions produced in all of the Examples were stable yellow transparent liquids or yellow slightly turbid liquids that neither underwent phase separation nor generated precipitates or sediments even 12 hours after production, and no visually observable change in properties was observed even when they were subsequently allowed to stand indoors for one month or longer. The turbidity of the 5-deazaflavin compound-containing emulsions immediately after production in Examples 1 to 10, 14, and 19 to 23 was measured at a wavelength λ = 620 nm by placing each sample in a measurement cell having a cell width of 1 cm using an ultraviolet spectrophotometer (UV1800) manufactured by Shimadzu Corporation (pure water being used as a blank). As a result, the turbidity was 0.1 or less in most cases, and even when exceeding 0.1, it was 0.2 or less. The turbidity of the 5-deazaflavin compound-containing emulsions produced in Examples 11 to 13 and 15 to 18 was mostly 0.3 to 0.4, and even when exceeding 0.4, it was 0.5 or less (the turbidity decreased upon dilution).

[0031]

Further, it was found that, by further incorporating an aromatic carboxylic acid such as benzoic acid or salicylic acid as a constituent component of the emulsion, the dissolving power for the 5-deazaflavin compound in benzyl alcohol or the like is enhanced, so that the same amount of the 5-deazaflavin compound can be dissolved with a smaller amount of benzyl alcohol or the like (comparison between Example 19 and Example 22, and comparison between Example 21 and Example 23), or a larger amount of the 5-deazaflavin compound can be dissolved with the same amount of benzyl alcohol or the like (comparison between Example 2 and Example 19, and comparison between Example 20 and Example 21).

[0032]

The 5-deazaflavin compound-containing emulsions produced in all Comparative Examples underwent phase separation or generated precipitates or sediments immediately after production, and therefore the average particle diameter of the droplets contained in the emulsions was not measured. It was considered that the poor stability of the 5-deazaflavin compound-containing emulsions produced in the Comparative Examples was attributable to the fact that a polysorbate and a lecithin were not used as constituent components (emulsifiers) of the emulsion, that a pharmaceutically acceptable salt of an aromatic carboxylic acid such as sodium salicylate or sodium benzoate was not used as a constituent component of the emulsion, or that a fat or oil such as MCT or soybean oil was not used as a constituent component of the emulsion.

[0033]

[Table 2]

	Average particle diameter of droplets immediately after production	Properties of emulsion 12 hours after production	Remarks	Evaluation
Example 1	21nm	Yellow transparent liquid		○
Example 2	41nm	Yellow transparent liquid		○
Example 3	25nm	Yellow transparent liquid		○
Example 4	85nm	Yellow slightly turbid liquid		○
Example 5	38nm	Yellow transparent liquid		○
Example 6	30nm	Yellow transparent liquid		○
Comparative Example 1	Not measured	Yellow turbid liquid with precipitates		×
Example 7	25nm	Yellow transparent liquid		○
Comparative Example 2	Not measured	Yellowish white turbid liquid with precipitates		×
Example 8	77nm	Yellow transparent liquid		○
Comparative Example 3	Not measured	Yellow transparent liquid with precipitates		×
Comparative Example 4	Not measured	Phase separation with precipitates		×
Comparative Example 5	Not measured	Phase separation with precipitates		×
Comparative Example 6	Not measured	Phase separation with precipitates		×
Comparative Example 7	Not measured	Phase separation		×
Example 9	15nm	Yellow transparent liquid		○
Example 10	16nm	Yellow transparent liquid		○
Example 11	Not measurable due to high viscosity	Yellow transparent liquid	Properties after 5-fold dilution: yellowish white slightly turbid liquid with average droplet particle diameter of 244nm	○
Example 12	Not measurable due to high viscosity	Yellow slightly turbid liquid	Properties after 5-fold dilution: yellowish white slightly turbid liquid with average droplet particle diameter of 268nm	○
Example 13	Not measurable due to high viscosity	Yellow transparent liquid	Properties after 5-fold dilution: yellowish white slightly turbid liquid with average droplet particle diameter of 288nm	○
Example 14	17nm	Yellow transparent liquid		○
Example 15	Not measurable due to high viscosity	Yellow transparent liquid	Properties after 5-fold dilution: yellowish white slightly turbid liquid with average droplet particle diameter of 573nm	○
Example 16	Not measurable due to high viscosity	Yellow transparent liquid	Properties after 5-fold dilution: yellowish white slightly turbid liquid with average droplet particle diameter of 516nm	○

Comparative Example 8	Not measured	Yellow transparent liquid with precipitates		×
Example 17	Not measurable due to high viscosity	Yellow slightly turbid liquid	Properties after 5-fold dilution: yellowish white slightly turbid liquid with average droplet particle diameter of 245nm	○
Example 18	Not measurable due to high viscosity	Yellow transparent liquid	Properties after 5-fold dilution: yellowish white slightly turbid liquid with average droplet particle diameter of 355nm	○
Comparative Example 9	Not measured	Yellow transparent liquid with sediments		×
Example 19	19nm	Yellow transparent liquid		○
Example 20	78nm	Yellow transparent liquid		○
Example 21	43nm	Yellow transparent liquid		○
Example 22	68nm	Yellow transparent liquid		○
Example 23	22nm	Yellow transparent liquid		○

[0034]

Further, 5-deazaflavin compound-containing emulsions of the invention having the types and amounts of use of constituent components shown in Table 3 were produced, and their stability and transparency were checked.

[0035]

[Table 3]

	(1)	(2)	(7)	(3)	(4)	(5)	(6) Pure water	Poly-Sorbate ratio
Example 24	T-MAC 30mg	Benzyl alcohol 200mg	Benzoic acid 60mg	Polysorbate 80/egg yolk lecithin 480/20mg	Na salicylate 240mg	MCT 10mg	4mL	96%
Example 25	TN1160 1mg	Benzyl alcohol 200mg	None	Polysorbate 80/soy lecithin 95/25mg	Na salicylate 240mg	MCT 40mg	4mL	79%
Example 26	T-MAC 2mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 150/300mg	Na salicylate 100mg	MCT 40mg	4mL	33%
Example 27	T-MAC 1mg	Benzyl alcohol 100mg	None	Polysorbate 80/egg yolk lecithin 240/160mg	Na salicylate 300mg	MCT 15mg	4mL	60%
Example 28	T-MAC 1mg	Benzyl alcohol 100mg	None	Polysorbate 80/egg yolk lecithin 380/20mg	Na salicylate 300mg	MCT 100mg	4mL	95%

Example 29	TN1160 2mg	Benzyl alcohol 200mg	Benzoic acid 40mg	Polysorbate 80/egg yolk lecithin 380/20mg	Na salicylate 300mg	MCT 10mg	4mL	95%
Example 30	T-MAC 1mg	Benzyl alcohol 200mg	None	Polysorbate 80/soy lecithin 95/5mg	Na salicylate 240mg	MCT 40mg	4mL	95%

Industrial Applicability

[0036]

The invention has industrial applicability in that it can provide a 5-deazaflavin compound-containing emulsion and a method for producing the same.

CLAIMS

[Claim 1]

A 5-deazaflavin compound-containing emulsion comprising, as constituent components, at least:

(1) a 5-deazaflavin compound;

(2) benzyl alcohol and/or phenoxyethanol;

(3) a polysorbate and a lecithin;

(4) a pharmaceutically acceptable salt of an aromatic carboxylic acid;

(5) a fat or oil; and

(6) an aqueous medium.

[Claim 2]

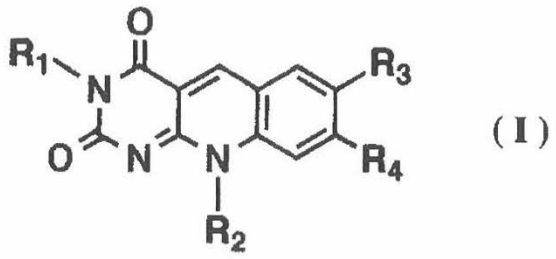
The 5-deazaflavin compound-containing emulsion according to claim 1, further comprising, as a constituent component:

(7) an aromatic carboxylic acid.

[Claim 3]

The 5-deazaflavin compound-containing emulsion according to claim 1, wherein the 5-deazaflavin compound is a compound represented by a general formula (I) below:

[Chem. 1]



(I)

[wherein R_1 represents any of a hydrogen atom, a lower alkyl group, and an optionally substituted phenyl group, R_2 represents any of a lower alkyl group, a lower cycloalkyl group, and an optionally substituted phenyl group, R_3 and R_4 are identical or different and represent any of a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a cyano group, a lower alkyl group, a lower alkoxy group, a lower alkylamino group, and a lower alkylsulfonyl group].

[Claim 4]

A method for producing a 5-deazaflavin compound-containing emulsion, the method comprising emulsifying constituent components including at least:

(1) a 5-deazaflavin compound;

(2) benzyl alcohol and/or phenoxyethanol;

(3) a polysorbate and a lecithin;

(4) a pharmaceutically acceptable salt of an aromatic carboxylic acid;

(5) a fat or oil; and

(6) an aqueous medium.