

VESICLE COMPOSITION, AND EXTERNAL SKIN PREPARATION AND COSMETIC, EACH CONTAINING SAME

Technical Field

[0001]

The present invention relates to a vesicle composition, and an external skin preparation and a cosmetic, each containing the same.

Background Art

[0002]

Vesicles (closed cavities of an amphipathic substance, having a bimolecular membrane structure) are attracting attentions as a carrier, for example, for use in drug delivery system, as they incorporate active ingredients therein because of their specific structure.

[0003]

Typical known amphipathic substances constituting the vesicle include biological phospholipids (see, for example, Patent Documents 1 and 2). Vesicles of such phospholipids, which are also called liposomes, are natural components and thus intensively studied because of their biological safety. However, phospholipids are easily influenced by pH, temperature and also by electrolytes and there are many restrictions based on stability over time when they are used (see, for example, Nonpatent Document 1). Thus, Nonpatent Document 1 cites castor oil, soy bean oil, arginine, methionine, cholesterol, phytosterol, casein, monoglycerides, and diglycerides as the additive for stabilization.

In addition, known for improvement of storage stability when blended with electrolytes are cosmetic liquid emulsion preparations containing lysophospholipids, oils such as glyceryl tri(2-ethylhexanoate), cosmetic electrolytes, water, and additionally polyoxyethylene sterol ether (see, for example, Patent Document 3).

Alternatively, vesicles of a non-ionic synthetic surfactant such as a polyoxyethylene hydrogenated castor oil ether or a polyoxyethylene castor oil ether, which was used as the amphipathic substance other than phospholipids, were proposed (see, for example, Patent Document 4).

Citation List

Patent Documents

[0004]

[Patent Document 1] Japanese Unexamined Patent Application
Publication No. 2010-59066

[Patent Document 2] Japanese Unexamined Patent Application
Publication No. 2008-88133

[Patent Document 3] International Patent Application Publication
No. WO 2005/77322 pamphlet

[Patent Document 4] Japanese Unexamined Patent Application
Publication No. 59-16534

Nonpatent Document

[0005]

[Nonpatent Document 1] "development of advanced cosmetics,"
P.122-123, (2000)

Summary of Invention

Technical Problem

[0006]

However, phospholipids are compounds generally having fatty acids bound to the C-1,2 position of the glycerol skeleton by ester linkage. For that reason, phospholipids contained in a vesicle system are often hydrolyzed gradually over time, consequently releasing free fatty acids. In addition, the free fatty acids often lower the pH of the system and additionally reduce the dispersion stability of the vesicle. Additionally, the free fatty acids yellow the product and generate odor, leading to deterioration of product quality. Accordingly, although phospholipids are superior in the incorporation efficiency of scarcely water-soluble substances, and the penetration and storage efficiency in the skin, they are easily influenced by to external factors such as electrolytes and pH and contain an important problem of low stability over time.

In addition, they have a problem that they are less stable over time, even if a nonionic surfactant such as polyoxyethylene hydrogenated castor oil ether or polyoxyethylene castor oil ether is used, as will be shown in Comparative Example 3 below.

Thus, there exists a need for studies aimed at improving the stability of vesicles over time.

[0007]

An object of the present invention, which was made under the circumstance and to solve the problems above, is to provide a vesicle

composition superior in stability over time and an external skin preparation and a cosmetic, each containing the same.

Solution to Problem

[0008]

After intensive studies to solve the problems above, the inventors have found that it was possible to form a novel vesicle superior in stability over time, especially salt resistance and acid/alkali resistance, by using a vesicle composition containing an ether-based nonionic surfactant having a sterol skeleton and a monoalkyl glyceryl ether. It was also found that, if such a vesicle composition is used, the stability of the vesicle is easily retained even when it is used in an external skin preparation or a cosmetic normally containing electrolytes.

[0009]

Thus, the present invention relates to the following inventions [1] to [7].

[1] A vesicle composition including a vesicle having a constituent membrane containing

(A) an ether-based nonionic surfactant having a sterol skeleton and

(B) a monoalkyl glyceryl ether.

[0010]

[2] The vesicle composition according to [1], wherein the membrane component contains a vesicle-forming auxiliary additionally as component (C).

[0011]

[3] The vesicle composition according to [2], wherein the vesicle-forming auxiliary is one, two or more compounds selected from sterols and ceramides.

[4] The vesicle composition according to [2] or [3], wherein the content ratio of the component (A) to the component (C) by mass, (A):(C), is 1:4 to 4:1.

[5] The vesicle composition according to any one of [2] to [4], wherein the content ratio of the total mass of the components (A) and (C) to the mass of the component (B), ((A)+(C)):(B), is 12:1 to 1:12.

[0012]

[6] An external skin preparation including the vesicle composition according to any one of [1] to [5].

[7] A cosmetic including the vesicle composition according to any one of [1] to [5].

Advantageous Effects of Invention

[0013]

The present invention provides a vesicle composition superior in the stability of the vesicle over time and an external skin preparation and a cosmetic, each containing the same.

Brief Description of the Drawings

[0014]

Fig. 1 shows the result obtained by small-angle X-ray scattering (Saxs) measurement of the vesicle composition according to the present invention.

Fig. 2 shows the result obtained by transmission electron microscope

(TEM) observation of the vesicle composition according to the present invention.

Fig. 3 shows the result obtained by differential scanning calorimetry (DSC) measurement of the vesicle composition according to the present invention.

Fig. 4 shows the result obtained by fluorescence polarization measurement of the vesicle composition according to the present invention.

Fig. 5 shows the result obtained by fluorescence polarization measurement of the vesicle composition of a Comparative Example.

Fig. 6 shows the result obtained by fluorescence polarization measurement of the vesicle composition of another Comparative Example.

Description of Embodiments

[0015]

The vesicle composition according to the present invention comprises a vesicle having a constituent membrane containing a component (A) an ether-based nonionic surfactant having a sterol skeleton and a component (B) a monoalkyl glyceryl ether.

[0016]

The component (A) of the present invention, i.e., the sterol skeleton-containing ether-based nonionic surfactant, is for example a polyoxyalkylene sterol ether and examples thereof include adducts of alkylene oxide to a sterol skeleton such as phytosterol skeleton or cholesterol skeleton. Because the component (A) is used mainly as the component forming the vesicle membrane, the vesicle composition is resistant to

hydrolysis even under acidic or alkaline condition and thus improved in stability over time.

[0017]

Examples of the structures of the sterol skeleton region include animal-derived sterol skeletons such as cholesterol, cholestanol, lanosterol, cerebrosterol, dehydrocholesterol and coprostanol; plant-derived sterol skeletons such as β -sitosterol, stigmasterol, campesterol and ergosterol, fucosterol, spinasterol, and brassicasterol; microbe-based sterol skeletons such as mycosterol and zymosterol; and the derivative thereof for example by hydrogenation or hydration.

Those having animal-derived sterol skeletons are obtained mainly from animals. They are prepared, for example, from wool fat, and examples thereof include lanolin alcohols containing cholesterol and lanosterol as the principal components, or the hydrogen adducts thereof, and the like.

Those having plant-derived sterol skeletons are obtained mainly from plants. Phytosterols are generally one, two or more compounds selected from β -sitosterol, stigmasterol, campesterol, fucosterol, spinasterol, brassicasterol, and ergosterol, and in particular a mixture of two or more compounds.

[0018]

Examples of the alkylene oxides to be added to the sterol include alkylenes having a carbon number of 2 to 5, such as ethylene oxide, propylene oxide, butylene oxide, and ethylene-propylene oxides. The average mole number of the alkylene oxides added is preferably 3 to 40, more preferably 5 to 30, and more preferably 5 to 10.

They may be used alone or in combination of two or more.

[0019]

In particular, those with ethylene oxides added to the sterol skeleton (also referred to as "POE sterols") are preferable. The sterol skeleton and the average mole number of ethylene oxide added are the same as those described above. Hereinafter, they can be used alone or in combination of two or more.

More specific examples thereof include polyoxyethylene cholesteryl ethers such as POE (5) cholesteryl ether, POE (10) cholesteryl ether, POE (15) cholesteryl ether, POE (20) cholesteryl ether, POE (24) cholesteryl ether, and POE (30) cholesteryl ether; polyoxyethylene cholestanols such as POE (20) cholestanol, POE (25) cholestanol, and POE (30) cholestanol; polyoxyethylene phytosterols such as POE (5) phytosterol, POE (10) phytosterol, POE (20) phytosterol, POE (25) phytosterol, and POE (30) phytosterol; polyoxyethylene phytostanols such as POE (20) phytostanol, POE (25) phytostanol, and POE (30) phytostanol, and the like. The numbers in parenthesis of the typical examples above are the average mole number of the ethylene oxides added. The same shall apply hereinafter.

In particular, polyoxyethylene cholesteryl ethers and polyoxyethylene phytosterols are preferable from the point of stability over time. More preferable are POE (5 to 30) cholesterol and POE (5 to 30) phytosterols. Further preferable are POE (5 to 10) cholesterol and POE (5 to 10) phytosterols.

[0020]

The amount of the component (A) sterol skeleton-containing

ether-based nonionic surfactant used in the present invention is not particularly limited, but preferably 0.01 to 10 mass %, more preferably 0.05 to 5 mass %, still more preferably 0.1 to 0.5 mass %, further more preferably 0.3 to 0.5 mass %, with respect to 100 mass % of all components used in preparing the vesicle composition (hereinafter, referred to also as "total amount used"), from the point of stability over time.

[0021]

The component (B) monoalkyl glyceryl ether according to the present invention is a derivative of glycerol etherified at the site-1 hydroxyl group. Because the component (B) is mainly used as the component for the vesicle membrane, the vesicle composition is resistant to hydrolysis even under acidic/alkaline condition and superior in stability over time.

For example, those represented by the following Formula are preferable.

[0022]



(wherein, R is a linear or branched alkyl group having a carbon number of 6 to 30).

[0023]

The alkyl group is preferably a linear or branched alkyl group having a carbon number of 8 to 24. Examples of such components (B) include batyl alcohol, chimyl alcohol, selachyl alcohol, monobehenyl glyceryl ether, mono-2-ethylhexyl glyceryl ether, monoisostearyl glyceryl ether, monocapryl glyceryl ether, monoisodecyl glyceryl ether, and the like.

Among them, those with an alkyl group having a carbon number of

12 to 22 are preferable and those having a carbon number of 16 to 22 are more preferable. Further among the components (B) above, batyl alcohol, chimyl alcohol, and selachyl alcohol are preferable.

The amount of the component (B) monoalkyl glyceryl ether used in the present invention is not particularly limited but preferably 0.01 to 5 mass %, more preferably 0.1 to 2 mass %, still more preferably 0.1 to 1 mass %, further more preferably 0.1 to 0.9 mass %, and yet more preferably 0.1 to 0.3 mass % with respect to the total amount used from the point of stability over time.

[0024]

The vesicle composition preferably comprises a component (C) vesicle-forming auxiliary from the point of stability over time.

The component (C) vesicle-forming auxiliary used in the present invention is a vesicle membrane forming component added to facilitate vesicle formation and improve the stability over time, and examples thereof include sterols and ceramides. They may be used alone or in combination of two or more. The sterols are preferably those insoluble in water but readily soluble in organic solvents such as lower alcohol.

[0025]

Known sterols can be used as the sterols and examples thereof include animal-derived sterols such as cholesterol, cholestanol, lanosterol, cerebrosterol, dehydrocholesterol, and coprostanol; one, two or more phytosterols selected from β -sitosterol, stigmasterol, campesterol, fucosterol, spinasterol, brassicasterol, and ergosterol; plant-derived sterols such as Macadamia nuts oil fatty acid cholesteryl and palm oil fatty acid cholesteryl;

microbe-derived sterols such as mycosterol and zymosterol; and the derivative thereof for example by hydrogenation or hydration.

In particular, animal- and plant-derived sterols are preferable; cholesterol and phytosterols are more preferable from the points of salt resistance and acid/alkaline resistance; and phytosterols are further more preferable. Generally cholesterol and phytosterols have low affinity to water and are thus oleophilic. More specifically, they are hardly soluble in water and soluble in organic solvents (such as lower alcohols having a carbon number of 1 to 3 (e.g., monovalent, bivalent)).

The sterols described above may be used alone or in combination of two or more.

[0026]

The ceramides above may be known ceramides and examples thereof include natural ceramides, synthetic ceramides, and pseudoceramide (synthetic pseudoceramide), and the like. Such ceramides are favorable from the points of stability over time and also from the efficiency to raise moisturizing action.

It is preferable to use synthetic ceramides and/or pseudoceramides, because they can be produced at low cost and the purity of them can be adjusted readily. Typical examples thereof include N-acylsphingosines, N-hydroxyacylphytosphingosines, N-acylphytosphingosines, type-1 to -4 ceramides, and the like. In particular, N-stearoylsphingosines (ceramide 2) are preferable.

The ceramides described above may be used alone or in combination of two or more.

[0027]

The amount of the component (C) vesicle-forming auxiliary used in the present invention is not particularly limited, but preferably 0.001 to 3 mass %, more preferably 0.05 to 2 mass %, still more preferably 0.05 to 1 mass %, further more preferably 0.05 to 0.5 mass %, particularly 0.2 to 0.5 mass %, yet particularly 0.3 to 0.5 mass % with respect to the total amount used, from the point of stability over time.

[0028]

The content ratio of the component (A) to the component (C) by mass, (A):(C), then is not particularly limited, but preferably 1:4 to 4:1, more preferably 1:2 to 2:1, further more preferably 2:3 to 3:2, from the points of stability over time, especially of salt resistance and acid/alkaline resistance.

The content ratio of the total of the components (A) and (C) to the component (B) by mass is also not particularly limited, but the ratio ((A)+(C)): (B) is preferably 12:1 to 1:12, more preferably 9:1 to 1:9, still more preferably 6:1 to 3:7, further more preferably 5:1 to 3:2, particularly preferably 5:1 to 3:1, from the point of stability over time, especially of salt resistance and acid/alkaline resistance.

[0029]

The vesicle composition according to the present invention may contain electrolytes and scarcely-soluble substances as needed as other components (D). The electrolytes are substances that dissociate into ions in solvents (in particular, water) and examples thereof include polyelectrolytes, low-molecular weight electrolytes, and the like.

These electrolytes are used, for example, for provision of

pharmacological actions (for example, dermatologically effective beauty care), improvement of stability and storage life, adjustment of viscosity and pH, and the like. The dermatologically effective beauty care includes moisturization, inflammation prevention, skin-whitening, ultraviolet protection and the like. The scarcely-soluble substance is a substance that is not readily soluble in polar solvents and/or non-polar solvents and used, for example, for the pharmacological action described above and also for improvement of stability and storage life, and it is possible to incorporate such a substance in the vesicle.

[0030]

The electrolyte (low-molecular weight electrolyte and polyelectrolyte) used is not particularly limited and may be any compound, organic or inorganic, if it is commonly used as pharmaceuticals or cosmetics. Examples thereof include, but are not limited to, salts of an alkali metal such as sodium or potassium, salts of an alkali-earth metal salt such as magnesium or calcium, and the like. The following electrolytes may be used alone or in combination of two or more.

[0031]

Examples of the low-molecular weight electrolytes for the moisturization application include inorganic electrolytes such as alkali-metal or alkali-earth metal salts including sodium chloride, magnesium chloride, calcium chloride, aluminum potassium sulfate, and sodium hydrogen phosphate; organic electrolytes such as organic acids, amino acids, and sugars including pyrrolidonecarboxylic acid salt, edetate salts, urea, citric acid, lactic acid, sodium lactate, citrate salts, lactate salts,

succinate salts, malate salts, L-alanine, β -alanine, L-arginine, L-arginine hydrochloride salts, L-asparagine monohydrate, L-aspartic acid, polyaspartic acid, L-citrulline, L-cysteine, L-cysteine hydrochloride salt monohydrate, L-cystine, L-DOPA, L-glutamic acid, N-acylglutamic acid, L-glutamic acid hydrochloride, L-glutamine, polyglutamic acid, glutamate salts, glycine, trimethylglycine, L-histidine, L-histidine hydrochloride monohydrate, L-hydroxyproline, L-isoleucine, L-leucine, L-lysine, L-lysine hydrochloride, L-methionine, L-ornithine hydrochloride, L-proline, L-phenylalanine, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine, L- α -aminobutyric acid, glucosamine hydrochloride, and sodium glucuronate; and the like.

Examples thereof for the inflammation prevention application include glycyrrhizate salts, glycyrrhetinate salts, salicylic acid, salicylate salts, and the like. Examples thereof for the skin-whitening and anti-oxidative applications include vitamins such as L-ascorbic acid, sodium L-ascorbic acid-2-phosphate, magnesium L-ascorbic acid-2-phosphate, L-ascorbic acid glucoside (e.g., L-ascorbic acid 2-glucoside), vitamin A's such as tranexamic acid, vitamin B's, vitamin C, vitamin E and the like.

Examples thereof for the ultraviolet protection application include phenylbenzimidazolesulfonate salts, hydroxymethoxybenzophenonesulfonate salts, and the like.

[0032]

Examples of those for the pH (alkaline region) adjustment application include basic amino acids such as L-arginine; alkali or alkali-earth metal hydroxide or carbonate salts such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, and sodium

carbonate; amines such as monoethanolamine, diethanolamine, triethanolamine, isopropanolamine, diisopropanolamine, triisopropanolamine, and 2-amino-2-methyl-1,3-propanediol; and the like.

Examples of those for the pH (acid region) adjustment application include acidic amino acids such as L-aspartic acid and glutamic acid; organic or mineral acids such as lactic acid, malic acid, citric acid, tartaric acid, acetic acid, succinic acid, phosphoric acid, hydrochloric acid, sulfuric acid, and nitric acid; and the like .

[0033]

Among the low-molecular weight electrolytes above, inorganic electrolytes (in particular, alkali-metal salts), organic electrolytes (in particular, organic acids), and vitamins (in particular, vitamin C's) are preferable.

[0034]

Examples of the polyelectrolytes for example for the moisturization, skin-whitening, and antioxidation include animal-derived polysaccharides (acidic mucopolysaccharides, basic polysaccharides, etc.) such as hyaluronate salts and chitosan hydrochloride or the glycopeptides thereof, plant-derived polysaccharides such as galactomannan, seaweed-derived polysaccharides such as carrageenan; microbe-derived polysaccharides such as xanthan gum; nucleic acids such as DNA salts; polyacrylate salts, and the like.

[0035]

The vesicle composition according to the present invention may contain physiologically active substances such as enzymes, peptides, hormones, cell growth factors, placenta extracts, ATP, cyclic ATPs,

interferons, vitamins, royal jelly, microbial metabolites, prostaglandins, sphingosine derivatives, astaxanthine, and sugars, as they are incorporated in the vesicle particles in the range that does not impair the advantageous effects of the present invention. In addition, the vesicle composition according to the present invention may contain various additives such as surfactants, water-soluble polymers, in addition to the components above.

[0036]

The production method for the vesicle composition according to the present invention is not particularly limited and it may be produced by any general method. It can be prepared, for example, by vortexing method (A. D. Bangham, *J. Mol. Biol.*, 13, 238 (1965)), sonication method (C. Huang, *Biochem.*, 8, 344 (1969)), prevesicle method (H. Trauble, *Neurosci. Res. Prog. Bull.*, 9, 273 (1971)), ethanol-injection method (S. Batzri, *Biochem. Biophys. Acta.*, 298, 1015 (1973)), French press-extrusion method (Y. Barenholz, *FEBS Lett.*, 99, 210 (1979)), cholic acid-removal method (Y. Kagawa, *J. Biol. Chem.*, 246, 5477 (1971)), Triton X-100 batch method (W. J. Gerritsen, *Eur. J. Biochem.*, 85, 255 (1978)), Ca^{2+} fusion method (D. Papahadjopoulos, *Biochem. Biophys. Acta.*, 394, 483 (1975)), ether-injection method (D. Deazer, *Biochem. Biophys. Acta.*, 443, 629 (1976)), annealing method (R. Lawaczeck, *Biochem. Biophys. Acta.*, 443, 313 (1976)), freeze/thaw fusion method (M. Kasahara, *J. Biol. Chem.*, 252, 7384 (1977)), W/O/W emulsion method (S. Matsumoto, *J. Colloid Interface Sci.*, 62, 149 (1977)), reverse-phase evaporation method (F. Szoka, *Proc. Natl. Acad. Sci. USA*, 75, 4194 (1978)), polyvalent alcohol method (JP-A No. 60-7932) or the like.

[0037]

The vesicle composition according to the present invention is produced, for example, by using the components (A) and (B) and as needed the component (C) as the major components for the membrane of the vesicle particles, adding any other components as needed, forming vesicle particles of these components, and thus giving a vesicle composition.

Specifically, the vesicle composition is prepared by mixing the components (A) and (B) and additionally a component (E) dispersing solvent, dispersing these components under heat and agitation, and allowing the dispersion to cool to room temperature and thus forming vesicle particles.

The component (E) dispersing medium is not particularly limited and, for example, purified water and/or a hydrophilic organic solvent may be used. In particular, it is preferable to use purified water and a hydrophilic organic solvent in combination for preparation of the vesicle.

The concentration of the vesicle components, with respect to 100 mass % of the all components used for the vesicle composition can be adjusted by using the component (E) dispersing solvent (preferably purified water).

[0038]

More specifically, the vesicle composition according to the present invention is obtained by dispersing the components (A) and (B) in a component (E) hydrophilic organic solvent by agitating the mixture under heat at a temperature of 70°C or higher (preferably about 90 to 100°C) for about 2 to 10 minutes, adding a component (E) purified water to the dispersion, stirring the resulting dispersion at a temperature kept at 70°C or higher (preferably 70 to 80°C) for about 2 to 10 minutes, and cooling the

mixture gradually to room temperature (about 20 to 40°C).

When the components (C) and (D) are mixed with the components (A) and (B), it is preferable to add the components (C) and (D) to a component (E) hydrophilic organic solvent. Alternatively, the component (D) may be added to the component (E) purified water.

[0039]

Examples of the component (E) hydrophilic organic solvents include alcohols such as monovalent and polyvalent alcohols.

The monovalent alcohols are, for example, lower alcohol having a carbon number of 1 to 3 (for example, ethanol).

The polyvalent alcohol above has two or more hydroxyl groups in the molecule. Examples of those having two hydroxyl groups in the molecule (bivalent alcohols) include polypropylene glycols such as propylene glycol, dipropylene glycol, and tripropylene glycol; butylene glycols such as 1,3-butylene glycol and 1,4-butylene glycol; pentanediols such as 1,2-pentanediol and 1,3-pentanediol, and the like. Examples of those having three or more hydroxyl groups in the molecule include glycerol, polyglycerins such as diglycerin, triglycerin, and tetraglycerol; polyethylene derivatives, and the like.

[0040]

Among the alcohols above, polyvalent alcohols are preferable; among them, bivalent alcohols are preferable; butylene glycols, especially 1,3-butylene glycol, are preferable for providing a vesicle superior in stability over time.

[0041]

The alcohols above may be used alone or in combination of two or more. The amount of the alcohol used is not particularly limited, but preferably at least thrice larger (by mass) than the total amount of the components (A) and (B) or components (A) to (C). More specifically, it is preferably 0.01 to 50 mass %, more preferably 0.1 to 20 mass %, still more preferably 1 to 10 mass %, particularly 3 to 8 mass % with respect to the total amount used.

[0042]

Vesicle particles formed with conventional vesicle compositions (in particular, vesicle compositions containing phospholipid) were lower in salt resistance and acid/alkali resistance and thus unfavorable in stability over time.

In contrast, as shown in Examples below, it is possible to form a new vesicle by using the components according to the present invention, even if no phospholipid is used. The vesicle formed according to the present invention can accommodate electrolytes, scarcely-soluble substances and others therein and thus can be used, for example, for transportation of active ingredients in the body and for improvement of penetration and storage of such an active ingredient in the skin.

The vesicle according to the present invention is stable thermodynamically, even if there are electrolytes inside or outside the vesicle (for example, in the copresence of a basic/acidic drug, high-conductivity solution, alkaline solution, or acidic solution). It is thus very excellent in stability over time. It is also superior in membrane flowability, which makes it possible to make an active ingredient penetrate and stored in the

skin and to enhance the action of the active ingredient.

[0043]

For that reason, the vesicle composition according to the present invention can be used in wide application shapes and can incorporate various active ingredients internally. In particular, they are possibly superior in stability over time, even if the electrolytes described above are contained in the vesicle composition. The vesicle according to the present invention is expected to have the operations and effects of the further electrolytes and scarcely-soluble substances and show not only its inherent vesicle characteristics, but also the synergic effect. Because the components (A), (B), and (C) are inexpensive, reliably available raw materials, it is possible to provide the vesicle composition inexpensively and reliably. It is thus possible to use it in wide areas, including the areas of pharmaceuticals, external skin preparations, and cosmetics, by making the most of the favorable characteristics of the vesicle.

[0044]

The vesicle composition according to the present invention preferably has a pH (20°C) of 2 to 11, more preferably 3 to 10. As described above, the vesicle composition according to the present invention is superior in stability over time not only in the neutral region of 6 to 7, but also in an acidic region of 3 to 5 and an alkaline region of 8 to 10.

The vesicle composition normally has an electric conductivity (20°C) of less than about 0.001 S/m. Even if electrolytes are present, i.e., even if the vesicle composition according to the present invention has an electric conductivity higher than that of normal vesicle, for example in the range of

0.001 to 3 S/m, more specifically 0.001 to 1 S/m, further 0.001 to 0.5 S/m, it is advantageously superior in stability over time compared to conventional vesicle compositions. The electric conductivity is a value determined at 20°C by using a conductivity meter.

[0045]

The vesicle composition according to the present invention described above can be used, as it is, in various applications, for example as pharmaceuticals, quasi drugs, external skin preparations, and cosmetics.

The vesicle composition according to the present invention may be used, as it is contained in products in the various applications above, and the content of the vesicle composition according to the present invention therein is not particularly limited, but is preferably 1.0 to 90 mass %, and more preferably 3.0 to 50 mass % in the product. The ranges of pH and electric conductivity of the product are advantageously in the ranges described above from the point of the stability of vesicle over time.

[0046]

The method of producing the product is not particularly limited, and it can be produced for example by preparing a vesicle composition and then mixing it with any other components. Alternatively, it is also possible to obtain the vesicle composition, simultaneously as the product is prepared in accordance with the method of producing the vesicle composition as described above.

[0047]

In addition, various additives normally used in the pharmaceuticals, external skin preparations, and cosmetics described above (e.g., water,

alcohol, oils, surfactants, thickeners, powders, chelating agents, pH adjusters, moisturizers, whiteners, various drugs such as antiinflammatory agents and cell activators, plant-, animal-, and microbe-derived extracts, flavoring agents, and the like) may be used as other arbitrary components in the range that does not impair the advantageous effects of the invention.

[0048]

The product according to the present invention may be used in any shape. The vesicle composition according to the present invention is higher in skin permeability, which is a characteristic inherent to vesicles, and thus preferably used in external skin preparations and cosmetics.

Examples of the forms of the external skin preparations and cosmetics used include cosmetics in the forms of emulsion, cream, skin lotion, beauty-care liquid, pack, cleaning agent, and make-up cosmetics, external drugs in the forms of dispersion, ointment, liquid, aerosol, patch, poultice, and liniment.

Examples

[0049]

Hereinafter, the present invention will be described specifically with reference to Examples and Test Examples, but it should be understood that the present invention is not restricted by these Examples.

[0050]

(Vesicle compositions of Examples 1 to 15)

Vesicle compositions were prepared by using the components shown in the columns of Examples 1 to 15 of Table 1 by the following production

process.

A vesicle composition of Example 13 (sample B in Fig. 3) was prepared in a manner similar to that of the vesicle composition of Example 2 (sample A in Fig. 3), except that the contents of the component (A) polyoxyethylene (5 mole) phytosterol, the component (B) batyl alcohol, and the component (C) cholesterol were altered.

Step 1: Components selected from the components 1 to 17 were fused into a solution under heat at 95°C.

Step 2: Purified water was added to the solution obtained in step 1, as the mixture was kept constant at 75°C, and the mixture was agitated in a disperser, to give a dispersion.

Step 3: The dispersion obtained in step 2 was cooled gradually to 40°C, to give each of the vesicle compositions of Examples 1 to 15.

[0051]

The pH (20°C) of each vesicle composition obtained was approximately 4 to 5 and the electric conductivity (20°C) was equal to or less than 0.001 (S/m).

[0052]

(Vesicle compositions of Test Examples 1 to 3)

As shown in the columns of Test Examples 1 to 3 of Table 2, components selected from the components 18 to 20 were added to the vesicle compositions obtained by the production processes 1 to 3, to give vesicle compositions of Test Examples 1 to 3.

The vesicle composition of Test Example 1 had an electric conductivity (20°C) of 0.36 (S/m).

The vesicle composition of Test Example 2 had a pH (20°C) of 3.2 and an electric conductivity (20°C) of 0.07 (S/m).

The vesicle composition of Test Example 3 had a pH (20°C) of 9.7 and an electric conductivity (20°C) of 0.03 (S/m).

[0053]

[Table 1]

(mass %)

No.	Component	Example														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	(A) Polyoxyethylene (5 mole) phytosterol [*1]	0.4	0.4	0.4	0.4	0.4	0.1	0.45	0.05			0.4	0.4	0.3		
2	(A) Polyoxyethylene (10 mole) phytosterol [*2]														0.4	
3	(A) Polyoxyethylene (30 mole) phytosterol [*3]									0.4						
4	(A) Polyoxyethylene (5 mole) cholesterol ether [*4]										0.4					
5	(A) Polyoxyethylene (10 mole) cholesterol ether [*5]															0.4
6	Polyoxyethylene (20 mole) hydrogenated castor oil [*6]															
7	Hydrogenated soy bean phospholipid 80%, cholesterol 20% [*7]															
8	N-stearoylalanine sodium															
9	(B) Butyl alcohol	0.2	0.2	0.2	0.2	0.2	0.7	0.1	0.9	0.3	0.2			0.4	0.2	0.2
10	(B) Selaohyl alcohol											0.2				
11	(B) Chlmvl alcohol												0.2			
12	Cetearyl alcohol															
13	(C) Cholesterol		0.4				0.2	0.45	0.05	0.3	0.4	0.4	0.4	0.3		
14	(C) Phytosterol			0.4												
15	(C) Ceramide 2				0.4											
16	Vitamin A oil					0.02										
17	(E) 1,3-butylene glycol	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
18	(D) L-ascorbic acid 2-glucoside															
19	(D) Citric acid															
20	(D) Sodium hydroxide															
21	(E) Purified water															
	Component (A) : component (C)	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance
	Component (A) + component (C) : component (B)	-	1:1	1:1	1:1	-	1:2	1:1	1:1	1:1.3	1:1	1:1	1:1	1:1	-	-
	<Evaluation>	2:1	4:1	4:1	4:1	2:1	3:7	9:1	1:9	2:3:1	4:1	4:1	4:1	3:2	2:1	2:1
(i)	(Immediately after preparation) Maltose cross image	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
(ii)	(40°C, 2W) Maltose cross image	B	A	A	B	B	B	B	B	B	A	A	A	B	B	B
(iii)	(40°C, 2W) Presence of precipitation	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A

*1 NIKKOL BPS-5 (produced by Nihon Surfactant Kogyo K. K.)

*2 NIKKOL BPS-10 (produced by Nihon Surfactant Kogyo K. K.)

*3 NIKKOL BPS-30 (produced by Nihon Surfactant Kogyo K. K.)

*4 EMALLEX CS-5 (produced by Nihon Emulsion Co., Ltd.)

*5 EMALLEX CS-10 (produced by Nihon Emulsion Co., Ltd.)

*6 NIKKOL HCO-20 (produced by Nihon Surfactant Kogyo K. K.)

*7 PRESOME CSII-101 (produced by Nippon Fine Chemical Co., Ltd.)

[0054]

[Table 2]

(mass %)

No.	Component	Test Example			Comparative Example						
		1	2	3	1	2	3	4	5	6	7
1	(A) Polyoxyethylene (5 mole) phytosterol [*1]	0.4	0.4	0.4		0.4		0.4			
2	(A) Polyoxyethylene (10 mole) phytosterol [*2]										
3	(A) Polyoxyethylene (30 mole) phytosterol [*3]										
4	(A) Polyoxyethylene (5 mole) cholesteryl ether [*4]										
5	(A) Polyoxyethylene (10 mole) cholesteryl ether [*5]										
6	Polyoxyethylene (20 mole) hydrogenated castor oil [*6]						0.4			0.4	
7	Hydrogenated soy bean phospholipid 80%, cholesterol 20% [*7]										0.4
8	N-stearoylalanine sodium								0.4		
9	(B) Batyl alcohol	0.2	0.2	0.2	0.2		0.2		0.2		
10	(B) Selachyl alcohol										
11	(B) Chimyl alcohol										
12	Cetearyl alcohol							0.2			
13	(C) Cholesterol	0.4	0.4	0.4	0.4	0.4	0.4	0.4			
14	(C) Phytosterol										
15	(C) Ceramide 2										
16	Vitamin A oil										
17	(E) L,3-butylene glycol	5	5	5	5	5	5	5	5	5	5
18	(D) L-ascorbic acid 2-glucoside	2									
19	(D) Citric acid		0.1								
20	(D) Sodium hydroxide	0.25		0.02					0.02	0.25	0.25
21	(E) Purified water	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance
	Component (A) : component (C)	1:1	1:1	1:1	-	-	-	-	-	-	-
	Component (A) + component (C) : component (B)	4:1	4:1	4:1	-	-	-	-	-	-	-
	<Evaluation>										
(i)	(Immediately after preparation) Maltose cross image	A	A	A	C	C	C	C	C	B	C
(ii)	(40°C, 2W) Maltose cross image	B	B	B	C	C	C	C	C	C	C
(iii)	(40°C, 2W) Presence of precipitation	A	A	A	C	C	C	C	C	C	C

*1 NIKKOL BPS-5 (produced by Nihon Surfactant Kogyo K. K.)

*2 NIKKOL BPS-10 (produced by Nihon Surfactant Kogyo K. K.)

*3 NIKKOL BPS-30 (produced by Nihon Surfactant Kogyo K. K.)

*4 EMALOX CS-5 (produced by Nihon Emulsion Co., Ltd.)

*5 EMALOX CS-10 (produced by Nihon Emulsion Co., Ltd.)

*6 NIKKOL HCO-20 (produced by Nihon Surfactant Kogyo K. K.)

*7 PRESOME CSII-101 (produced by Nippon Fine Chemical Co., Ltd.)

[0055]

(Vesicle compositions of Comparative Examples 1 to 7)

Vesicle compositions of Comparative Examples 1 to 7 were prepared by using the components shown in the column of Comparative Examples 1 to 7 of Table 2 by the production process of the Examples 1 to 15.

[0056]

(Tests for confirmation of maltese cross image by vesicle composition and on stability over time)

For first screening, samples immediately after production and after storage still at 40°C for 2 weeks were observed under the crossed Nicol of an polarization microscope (produced by Olympus Corporation) for determination of whether there were maltese cross images observable from the respective vesicle composition. The criteria for judgment are shown below and the results in Table 1.

In addition, each vesicle composition was observed under microscope after it is stored still at 40°C for 2 weeks in order to determine whether there is precipitation.

[0057]

(i) Criteria of maltese cross image

A: There were many maltese cross images observed

B: There were maltese cross images easily observable, although the number was not many.

C: There was no maltese cross image observed.

(ii) Criteria of precipitation

A: There was no precipitation observed.

B: There was precipitation observable under microscope, but the amount thereof is limited.

C: There was intensive precipitation observed, possibly causing problems
[0058]

The vesicle composition of Example 2, which was superior in stability over time, was subjected to small-angle X-ray scattering spectrum measurement in a high-brightness small-angle X-ray scattering device SAXS (produced by Anton Paar). As shown in Fig. 1, the vesicle composition showed peaks characteristic of lamellar structure in the small-angle X-ray scattering spectrum.

In addition, the presence of multilamellar vesicles was examined by using a transmission electron microscope (TEM) (phosphotungstic acid coating). As shown in Fig. 2, the TEM observation also gave a multilamellar vesicle image indicating a multilayer structure.

[0059]

The results above demonstrate that the vesicle compositions according to the present invention (vesicle compositions of Examples 1 to 15 and Test Examples 1 to 3) had a multilamellar structure. They also exhibited excellent stability over time.

[0060]

(Test for confirmation of thermodynamic stability of vesicles)

The vesicle compositions of Examples 2 and 13 were subjected to differential scanning calorimetry (DSC) in a heat-flux differential scanning calorimeter (SII NanoTechnology Inc.) The samples of Example 2 and 13 were referred to respectively as samples A and B.

Vesicle compositions of Examples 2 and 13 did not have the endothermic peak corresponding to the gel/liquid crystal transition temperature in the vicinity of 40 to 50°C, suggesting that they had a thermodynamically stable structure.

The results above suggested that the vesicles according to the present invention (vesicle compositions of Examples 1 to 15 and Test Examples 1 to 3) are thermodynamically stable.

[0061]

(Influence of electrolytes on vesicle compositions according to present invention)

The results of the tests on the vesicle compositions of Test Examples 1 to 3 according to the evaluation criteria (i) and (ii) are shown in Table 1.

Separately, NaCl was added to the vesicle composition of Example 2 to a concentration of 0.5 mass % and the stability over time of the mixture when stored at 50°C for 14 days was examined by monitoring the transmission coefficient. There was almost no change in transmission coefficient, indicating that the composition was favorably stable over time.

As shown in Test Examples 1 to 3, the vesicle compositions were favorably stable over time, even when an electrolyte, L-ascorbic acid 2-glucoside, citric acid, or sodium hydroxide, was added thereto.

As obvious from the results above, the vesicles according to the present invention (vesicle compositions of Examples 1 to 15 and Test Examples 1 to 3) were superior in stability over time even in the copresence of electrolytes or in the acidic/alkaline region.

[0062]

(Tests on membrane flowability of vesicle)

The membrane flowability of the vesicle composition of Example 2 was examined by measurement of fluorescence polarization value.

Separately, vesicle compositions of Comparative Examples 8 and 9 were prepared similarly to the vesicle compositions of Comparative Examples 6 and 7, except that L-ascorbic acid 2-glucoside and sodium hydroxide were not added, and the membrane flowability of them was evaluated. Each sample was adjusted to a NaCl concentration of 0, 0.3 or 0.5%.

The device used for determination of the fluorescence polarization value was a fluorescence photometer RF-5300 (manufactured by Shimadzu Corporation). The reagents used were DPH (1,6-diphenyl-1,3,5-hexatriene, excitation light: 360 nm, fluorescence detection: 430 nm) as oleophilic fluorescence probe and ANS (1-anilinonaphthalene-8-sulfonic acid, excitation light: 380 nm, fluorescence detection: 465 nm) as hydrophilic fluorescence probe. The fluorescence polarization value was calculated according to the formula below and plotted along the left axis in Fig. 4 (DPH: □ in Fig. 4, ANS: ◇ in Fig. 4). In addition, the ratio (P_{ANS}/P_{DPH}) of the fluorescence polarization value (P_{DPH}) when DPH was used to the fluorescence polarization value (P_{ANS}) when ANS was used was determined and plotted along the right axis of Fig. 4 (△ in Fig. 4).

[0063]

[Formula 1]

$$P = [(I_{//} - I_{\perp}) / (I_{//} + I_{\perp})]$$

P: fluorescence polarization value; $I_{//}$: parallel polarization intensity; and $I_{\perp}$:

vertical polarization intensity

[0064]

It is thus possible to determine mobility of the hydrophilic and lipophilic groups in the vesicle, allowing evaluation of microscopic membrane flowability.

As shown in Fig. 4, in the case of the vesicle composition according to the present invention of Example 2, the P_{ANS}/P_{DPH} remained almost without any change even when an electrolyte NaCl was added, indicating that the balance of membrane flowability by the hydrophilic and lipophilic groups are preserved.

On the other hand, as shown in Figs. 5 and 6, the vesicle compositions of Comparative Examples 8 and 9 had a significantly fluctuating P_{ANS}/P_{DPH} ratio. It indicates that the balance of membrane flowability by the hydrophilic and lipophilic groups is disturbed significantly by addition of an electrolyte NaCl and that the vesicle compositions were inferior to the vesicle compositions of the Examples.

Because the balance of membrane flowability in the vesicle particles according to the present invention was preserved, it is possible by using the vesicle according to the present invention to make an active ingredient penetrate and stored in the skin and enhance the action of the active ingredient.

[0065]

The results above demonstrated that the vesicle compositions according to the present invention (those of Examples 1 to 15 and Test Examples 1 to 3) were superior in stability over time, particularly in salt

resistance and acid/alkali resistance.

Thus, the vesicle composition according to the present invention is considered to be a preparation that can possibly incorporate an active ingredient under a wide range of conditions.

It was also found that it is possible to form a vesicle, using at least a sterol skeleton-containing nonionic surfactant and a monoalkyl glyceryl ether as raw materials, even if phospholipids such as lecithin are not used substantially.

[0066]

Example 16: Ointment

An ointment was prepared with the components and by the production method described below.

[0067]

(Component)	(mass %)
1 Stearic acid	18.0
2 Cetanol	4.0
3 Triethanolamine	2.0
4 Glycerol	5.0
5 Dipotassium glycyrrhizate (Note 1)	0.5
6 Vesicle composition of Example 2	1.0
7 dl- α -Tocopherol acetate (Note 2)	0.2
8 Methyl paraoxybenzoate	0.1
9 Purified water	balance

(Note 1) produced by Wako Pure Chemical Industries, Ltd.

(Note 2) produced by Eisai Co., Ltd.

[0068]

(Production method)

A: Components (3) and (4) and part of component (9) were mixed and kept under heat at 75°C.

B: Components (1), (2), (7), and (8) are mixed and kept under heat at 75°C.

C: B was added gradually to A; component (5) dissolved in the balance of component (9) was added, as the mixture was cooled; and component (6) was added thereto, to give an ointment.

[0069]

The ointment of Example 16 was an ointment superior in stability of the vesicle composition.

[0070]

Example 17: Skin lotion

A skin lotion was prepared with the components and by the production method described below.

[0071]

(Component)	(mass %)
1 Glycerol	5.0
2 1,3-Butylene glycol	5.0
3 Lactic acid	0.05
4 Sodium lactate	0.1
5 Monooleic acid polyoxyethylene (20 mole) sorbitan	1.2
6 Ethanol	8.0
7 Methyl paraoxybenzoate	0.1
8 Flavoring agent	0.05

9 Vesicle composition of Example 3	10.0
10 Purified water	balance

[0072]

(Production method)

A: Components (5) to (8) were mixed, to give a solution.

B: Components (1) to (4) and (10) were mixed, to give a solution.

C: A was added to and mixed with B; and component (9) was added thereto, to give a skin lotion.

[0073]

The skin lotion of Example 17 was a skin lotion superior in stability of the vesicle composition.

[0074]

Example 18: Emulsion

An emulsion was prepared with the components and by the production method described below.

[0075]

(Component)	(mass %)
1 Monostearic acid polyoxyethylene (20 mole) sorbitan	1.0
2 Trioleic acid polyoxyethylene (20 mole) sorbitan	0.5
3 Glyceryl monostearate	1.0
4 Stearic acid	0.5
5 Behenyl alcohol	0.5
6 Squalane	8.0
7 Carboxyvinyl polymer	0.1
8 Methyl paraoxybenzoate	0.1

9 Sodium hydroxide	0.05
10 Ethanol	5.0
11 Vesicle composition of Example 9	5.0
12 Purified water	balance
13 Flavoring agent	0.05
14 Purified water	5.0

[0076]

(Production method)

A: Components (7) to (9) were added to component (12) and the mixture was mixed uniformly at 70°C.

B: Components (1) to (6) were mixed uniformly at 70°C.

C: B was added to A and the mixture was emulsified and cooled to room temperature.

D: Components (10), (11), (13) and (14) were added thereto, and the mixture was mixed uniformly, to give an emulsion.

[0077]

The emulsion of Example 18 was an emulsion superior in stability of the vesicle composition.

CLAIMS:

1. A vesicle composition, comprising a vesicle having a constituent membrane containing
(A) an ether-based nonionic surfactant having a sterol skeleton and
(B) a monoalkyl glyceryl ether.
2. The vesicle composition according to Claim 1, wherein the constituent membrane contains a vesicle-forming auxiliary additionally as component (C).
3. The vesicle composition according to Claim 2, wherein the component (C) vesicle-forming auxiliary is one, two or more compounds selected from sterols and ceramides.
4. The vesicle composition according to Claim 2 or 3, wherein the content ratio of the component (A) to the component (C) by mass, (A):(C), is 1:4 to 4:1.
5. The vesicle composition according to any one of Claims 2 to 4, wherein the content ratio of the total mass of the components (A) and (C) to the mass of the component (B), ((A)+(C)):(B), is 12:1 to 1:12.
6. An external skin preparation, comprising the vesicle composition according to any one of Claims 1 to 5.

7. A cosmetic, comprising the vesicle composition according to any one of Claims 1 to 5.