

DESCRIPTION

TITLE OF INVENTION: PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

[0001]

The present invention relates to pharmaceutical compositions containing N,N-dimethyl-2-oxo-N-(2-oxo-2-(phenylamino)ethyl)-2-(phenylamino)ethan-1-aminium (hereinafter referred to as Compound A) and/or a pharmaceutically acceptable salt thereof as an active ingredient, in particular, relates to a pharmaceutical composition for relieving pain in the oral cavity and/or the pharynx.

BACKGROUND

[0002]

Stomatitis is known as inflammation of the mucous membranes in and around the mouth (e.g., inside cheeks, gums, tongue, lips, palate, or the like). In severe cases of stomatitis, intense pain may interfere with brushing teeth, eating or drinking, and even speaking. Such severe stomatitis often occurs in patients who have undergone cancer treatment, such as anti-cancer drug therapy, radiation therapy, or the like, and the pain significantly impairs the patient's quality of life (QOL). It is also known that concurrent chemoradiotherapy to the head and neck region, etc. can cause severe oropharyngeal mucositis, which causes pain not only in the oral cavity but also in the pharynx, resulting in severe swallowing pain when swallowing food or drink.

[0003]

To relieve the intense pain caused by such stomatitis and/or pharyngitis, analgesics are taken orally, and when the pain is particularly severe, analgesics are used in combination with medical narcotics (such as morphine). However, since oral medications can affect the entire body, safer topical preparations are desired.

[0004]

As topical preparations that can be used to directly relieve pain caused by stomatitis or the like, Patent Document 1 discloses a drug preparation for mouth or pharynx, containing a local anesthetic (such as lidocaine) and a weak acid (such as citric acid or phosphoric acid), and Patent Document 2 discloses a jelly preparation containing phosphoric acid or a

pharmaceutically acceptable salt thereof and a local anesthetic drug. However, there is still a demand for topical pain relievers suitable for relieving oral and/or pharyngeal pain.

CITATION LIST

PATENT DOCUMENT

[0005]

Patent Document 1: JP-A-2005-015479

Patent Document 2: JP-A-2006-160607

SUMMARY

[0006]

An object of the present invention is to provide a topical pharmaceutical composition suitable for alleviating pain in the oral cavity and pharynx. In particular, an object of the present invention is to provide a topical pharmaceutical composition capable of stably maintaining an active ingredient.

[0007]

The inventors focused on a local anesthetic, Compound A (in particular, chloride of Compound A), and found that topical application of Compound A and/or its salt to the oral cavity or pharynx can not only alleviate oral or pharyngeal pain, but also improve oral hygiene due to its antimicrobial effect. Furthermore, since Compound A exhibits different properties from lidocaine, it was not possible to provide a stable preparation using the same approach as in Patent Documents 1 and 2, but through diligent study, the inventors also found ingredients that can keep Compound A and/or its salt stable.

[0008]

The present invention has the following features.

[1] A topical pharmaceutical composition for application to the oral cavity and/or pharynx, containing N,N-dimethyl-2-oxo-N-(2-oxo-2-(phenylamino)ethyl)-2-(phenylamino)ethan-1-aminium (hereinafter referred to as Compound A) and/or a pharmaceutically acceptable salt thereof as an active ingredient.

[2] The pharmaceutical composition according to [1], containing at least one selected from the group consisting of hydrochloric acid, lactic acid, tartaric acid, and a sugar alcohol having 4 or more carbon atoms.

[3] The pharmaceutical composition according to [1] or [2], containing at least one sugar alcohol having 4 or more carbon atoms.

[4] The pharmaceutical composition according to any one of [1] to [3], containing at least one acidic component selected from the group consisting of hydrochloric acid, lactic acid, and tartaric acid.

[5] The pharmaceutical composition according to any one of [1] to [4], containing:
at least one acidic component selected from the group consisting of hydrochloric acid, lactic acid, and tartaric acid, and

at least one basic component selected from the group consisting of sodium hydroxide, potassium hydroxide, diisopropanolamine, and sodium tartrate.

[6] The pharmaceutical composition according to any one of [2] to [4], wherein the at least one sugar alcohol is selected from the group consisting of xylitol, mannitol, and sorbitol.

[7] The pharmaceutical composition according to any one of [1] to [6], containing the chloride of Compound A as the active ingredient.

[8] The pharmaceutical composition according to any one of [1] to [7], having a pH of 3 to 7.

[9] The pharmaceutical composition according to any one of [1] to [8], further containing at least one selected from the group consisting of sucralose, sucrose, stevia extract, purified stevia extract, thaumatin, and acesulfame potassium.

[10] The pharmaceutical composition according to any one of [1] to [9], further containing at least one polyhydric alcohol selected from glycerin (glycerol) and propylene glycol.

[11] The pharmaceutical composition according to any one of [1] to [10], containing:
the chloride of Compound A,

at least one acidic component selected from the group consisting of hydrochloric acid, lactic acid, and tartaric acid, optionally at least one basic component selected from the group consisting of sodium hydroxide, potassium hydroxide, diisopropanolamine, and sodium tartrate

at least one sugar alcohol selected from the group consisting of xylitol, mannitol, and sorbitol,

at least one selected from the group consisting of sucralose, sucrose, stevia extract, purified stevia extract, thaumatin, and acesulfame potassium

at least one polyhydric alcohol selected from glycerin and propylene glycol,

0 to 5% by weight of additive(s), and

the balance being water.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009]

FIGS. 1A and 1B are graphs showing the effect of acidic or basic components on the hydrolysis of the chloride of Compound A. The lower the stability of Compound A, the higher the amount of hydrolysis product.

FIG. 2 is a graph showing the effect of sugar alcohols (sorbitol or xylitol) on the hydrolysis of the chloride of Compound A.

FIG. 3 is a graph showing the effect of sugar alcohols (mannitol or erythritol) on the hydrolysis of the chloride of Compound A.

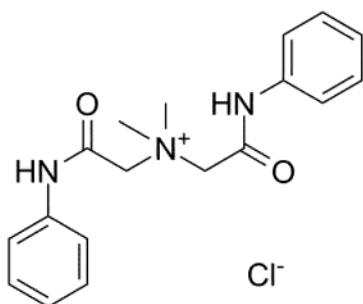
DETAILED DESCRIPTION

[0010]

The composition of the present invention is a pharmaceutical composition. Examples of the pharmaceutical composition include compositions that fall under the categories of pharmaceuticals for medical use, pharmaceuticals requiring guidance, OTC (over-the-counter) pharmaceuticals, or quasi-pharmaceutical products according to "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices".

[0011]

The composition of the present invention contains at least one selected from Compound A and pharmaceutically acceptable salts thereof as an active ingredient. In particular, a composition containing the chloride of Compound A represented by the following structural formula as an active ingredient is preferred.



[0012]

The content of Compound A and/or its salt is preferably from 0.1 to 5% by weight, more preferably from 0.5 to 2.5% by weight, and especially preferably from 1 to 2% by weight.

As used herein, the content of each component contained in the composition of the present invention means a percentage of the weight of each component when the total weight of the composition is 100.

[0013]

Compound A and its salt have local anesthetic effect. Furthermore, Compound A and its salt were found to have antimicrobial activity against several bacteria and fungi. Patients with oral or pharyngeal pain due to stomatitis, pharyngitis or the like are more likely to have poor oral hygiene because the pain makes it difficult for them to brush their teeth or gargle thoroughly. As a result, cases have been reported where pathogens multiply and enter the trachea with saliva, causing pneumonia. There have also been reports of cases in which the pathogens enter the blood vessels from the ulcerated areas of stomatitis, spreading through the blood vessels throughout the body, and causing high fever. Therefore, a composition containing Compound A/salt thereof, which has antimicrobial activity in addition to local anesthetic effect, is highly suitable for topical application to the oral cavity and pharynx of the above patient because the composition can relieve pain and also prevent diseases caused by the bacteria. Thus, the composition of the present invention is particularly suitable for relieving pain due to stomatitis and/or pharyngitis caused by cancer treatment using anticancer drugs or radiation, and is suitable for relieving pain due to oropharyngeal mucositis caused by concurrent chemoradiotherapy of the head and neck, etc.

[0014]

Further, since the composition of the present invention has a local anesthetic effect, it can be used as a local composition for anesthetizing the oral cavity, pharynx, and/or nasal cavity, etc., when performing gastroscopy or the like.

[0015]

For pharmaceutical compositions, it is important to maintain an active ingredient stable in the composition (i.e., to inhibit decomposition of an active ingredient) in order to prevent a decrease in medicinal efficacy during storage. The inventors found that adding citric acid or phosphoric acid, etc., which are widely used as pH adjusters, to compositions containing Compound A and/or its salt accelerates the hydrolysis of Compound A and its salt, making it difficult to keep the active ingredient stable. On the other hand, the inventors have found that some acidic and basic components are less likely to accelerate the hydrolysis of Compound A and its salt. This phenomenon was not observed with lidocaine and its salt, which are typical drugs used as local anesthetics, and the fact that the rate of hydrolysis differs greatly depending

on the type of acidic/basic component to be added is considered to be unique to Compound A and its salt.

[0016]

More specifically, the measurement of the degradation products (hydrolysates) resulting from the hydrolysis of Compound A or its salt showed that when hydrochloric acid (HCl), lactic acid, tartaric acid, sodium hydroxide, potassium hydroxide, diisopropanolamine, or sodium tartrate hydrate was added, the degradation products were small in amount (i.e., Compound A and its salt were stable). In contrast, when other acidic or basic components such as citric acid, phosphoric acid, sodium dihydrogen phosphate, sodium hydrogen carbonate (sodium bicarbonate), or sodium acetate were added, the amount of degradation products was significantly higher. Therefore, when adjusting the pH of the composition of the present invention, it is preferable to select an ingredient that is unlikely to accelerate the decomposition of Compound A and its salt. For example, it is preferable to adjust pH by using only at least one or more acidic components selected from hydrochloric acid (HCl), lactic acid and tartaric acid or by using at least one or more acidic components selected from hydrochloric acid (HCl), lactic acid, and tartaric acid in combination with at least one or more basic components selected from sodium hydroxide, potassium hydroxide, diisopropanolamine, and sodium tartrate (including hydrates).

[0017]

The pH of the composition of the present invention is preferably from 3 to 7, more preferably from 3 to 6, and particularly preferably from 4.5 to 5.5. Thus, since the pH of the composition of the present invention is preferably on the acidic side, the pH of the composition is preferably adjusted using at least one of acidic components selected from hydrochloric acid (HCl), lactic acid, tartaric acid, and monosodium fumarate (more preferably, an acidic component(s) selected from hydrochloric acid, lactic acid, and tartaric acid, especially preferably, hydrochloric acid). When a basic component is used in addition to the above acidic component(s), the basic component(s) is/are preferably selected from sodium hydroxide, potassium hydroxide, diisopropanolamine, sodium tartrate (including hydrate), and disodium succinate (including hydrate) (more preferably, the basic component(s) selected from sodium hydroxide, potassium hydroxide, diisopropanolamine, and sodium tartrate, especially preferably, sodium hydroxide and/or potassium hydroxide). In particular, the use of hydrochloric acid is preferred, and the use of hydrochloric acid and sodium hydroxide together is more preferred. As used herein, hydrochloric acid means an aqueous solution of hydrogen chloride (HCl), and the

concentration of hydrogen chloride is not particularly limited; for example, concentrated hydrochloric acid (containing 35 to 38 w/v% hydrogen chloride) or dilute hydrochloric acid (containing 9.5 to 10.5 w/v% hydrogen chloride) can be used.

[0018]

When one or more of the above acidic/basic components are used, the total concentration of the acidic/basic component(s) in the composition is preferably from 0.001 to 1% by weight, more preferably from 0.005 to 0.1% by weight, and especially preferably from 0.008 to 0.05% by weight.

[0019]

In addition, the present inventors found that sugar alcohols inhibit the hydrolysis of Compound A and its salt. Therefore, the composition of the present invention preferably contains a sugar alcohol. Examples of the sugar alcohol include sugar alcohols with 4 to 12 carbon atoms such as erythritol, xylitol, sorbitol, mannitol, maltitol, and reduced palatinose. Sugar alcohols with 4 to 6 carbon atoms (erythritol [C4], xylitol [C5], sorbitol [C6], or mannitol [C6]) are preferred, sugar alcohols with 5 or 6 carbon atoms are more preferred, and sugar alcohols with 6 carbon atoms are especially preferred. In particular, sorbitol (D-sorbitol) and mannitol have a high inhibitory effect on the hydrolysis of Compound A. Therefore, it is preferred that the composition of the present invention contains sorbitol and/or mannitol (especially sorbitol).

[0020]

The total content of the sugar alcohol(s) in the composition of the present invention is preferably from 0.4 to 20% by weight, more preferably from 1 to 15% by weight, especially preferably from 2 to 10% by weight, and further preferably from 3 to 7% by weight.

[0021]

Since Compound A and its salt have a strong bitterness, the composition of the present invention may further contain a sweetener other than the sugar alcohols to reduce the bitterness. Among sweeteners, saccharin sodium hydrate and dipotassium glycyrrhizate were found to decrease the solubility of the active ingredient (Compound A and/or its salt) in the composition. Therefore, when using a sweetener, it is particularly desirable to select a sweetener that does not reduce the solubility of the active ingredient, even in situations where the active ingredient is expected to be prone to precipitation (e.g., when the composition is stored at a low temperature).

[0022]

It is preferred that the composition of the present invention contains a sweetener selected from the group consisting of sucralose, sucrose, stevia extract, purified stevia extract, thaumatin, and acesulfame potassium, and it is more preferred to contain a sweetener selected from the group consisting of sucralose, stevia extract, purified stevia extract, and thaumatin, and it is especially preferred to contain sucralose and purified stevia extract. As used herein, the stevia extract means one containing a total of 80.0% or more by weight of four steviol glycosides (stevioside, rebaudioside A, rebaudioside C, and dulcoside A) obtained by extraction from stevia leaves. As used herein, the purified stevia extract means one obtained by extracting stevia leaves with water and then purifying, containing a total of 90.0 to 96.0% by weight of 5 steviol glycosides (stevioside, rebaudioside A, rebaudioside C, dulcoside A, and rubusoside), as described in Japanese Pharmaceutical Excipients 2018. The total content of the sweetener(s) in the composition is preferably from 0.01 to 3% by weight, more preferably from 0.05 to 2% by weight, especially preferably from 0.1 to 1% by weight, and further preferably from 0.2 to 0.6% by weight.

[0023]

The composition of the present invention preferably contains a polyhydric alcohol selected from glycerin (including concentrated glycerin) and propylene glycol, especially preferably contains glycerin. As used herein, the polyhydric alcohols do not include sugar alcohols having 4 or more carbon atoms. The total content of the polyhydric alcohol(s) in the composition is preferably from 2 to 30% by weight, more preferably from 3 to 20% by weight, and especially preferably from 5 to 15% by weight.

[0024]

The composition of the present invention preferably contains water (preferably purified water). The water content of the composition is preferably 50% or more by weight, more preferably 60% or more by weight, particularly preferably from 70 to 95% by weight, and further preferably from 80 to 90% by weight.

[0025]

The composition of the present invention may or may not contain an additive (such as a preservative and a thickener) other than the above ingredients. The content of the additive(s) in the composition is preferably from 0 to 5% by weight, more preferably from 0 to 3% by weight, and especially preferably from 0 to 1% by weight.

[0026]

Examples of the preservative include, but are not particularly limited to, thymol, dibutylhydroxytoluene, citric acid hydrate, boric acid, parahydroxybenzoic acid, parahydroxybenzoate (methyl parahydroxybenzoate, ethyl parahydroxybenzoate, propyl parahydroxybenzoate, butyl parahydroxybenzoate), sodium benzoate, phenoxyethanol, chlorobutanol, chlorocresol, benzyl alcohol, salicylic acid, disodium edetate hydrate, tetrasodium edetate, sodium dehydroacetate, sorbic acid, potassium sorbate, benzethonium chloride, benzalkonium chloride, or dried sodium sulfite, etc., and one can be used alone or two or more can be used. Since Compound A and its salt exhibit antimicrobial activity against bacteria and fungi, the composition of the present invention may be free of a preservative.

[0027]

Examples of the thickener include, but are not particularly limited to, sodium alginate, gelatin, carboxy vinyl polymer, sodium polyacrylate, methylcellulose, glyceryl monooleate, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, sodium carboxymethylcellulose, polyvinyl alcohol, or xanthan gum, etc., and one can be used alone or two or more can be used. The composition of the present invention may be free of such a thickener.

[0028]

The composition of the present invention is preferably a topical preparation applied, in particular, to mucous membranes of lumens such as the oral cavity, pharynx, and nasal cavity. The dosage form is preferably a form such as a liquid preparation (including a liquid, an elixir, a suspension, an emulsion, a limonade, a syrup, a lotion, etc.), a gel preparation (including a jelly), or a spray preparation, which is easy to contact with the luminal mucosa. For example, the composition may be a spray for the oral and/or pharyngeal mucosa, an oral rinse or a mouthwash. It is also preferable that the composition is not washed out by gargling or the like after being applied to the mucosa of the oral cavity or pharynx. For example, a patient with stomatitis or pharyngitis may apply the composition to the oral cavity before eating or drinking, and eat or drink as is. Since the composition has antimicrobial effect in addition to local anesthetic effect, it is expected that, by using the composition without washing, the oral cavity will be kept hygienic by antimicrobial effect in addition to pain relief by anesthetic effect.

[0029]

Preferred examples of the composition of the present invention include liquid compositions. The liquid compositions have a low viscosity, the viscosity of which is usually 3000 mPa·s or less, preferably 2000 mPa·s or less, more preferably 500 mPa·s or less, and most

preferably 300 mPa·s or less. The liquid compositions may be free of a thickener. In the present invention, the viscosity means a viscosity after 60 seconds from the start of rotation with a cone-plate viscometer (Modular Compact Rheometer) at a measuring temperature of 25°C, cone plate No. 50-1, and a rotational speed of 5 rpm.

[0030]

The liquid composition may be contained in a spray container with a nozzle (a container capable of discharging or spraying the liquid composition within the container by means of a pump without the use of propellant) and may be discharged or sprayed into the oral cavity through a discharge hole at the tip of the nozzle. For example, as the spray container with a nozzle, a container including a container body and a discharger mounted on the upper part thereof can be used, in which the discharger has a nozzle extending in a horizontal direction, and the container can discharge or spray the liquid composition within the container body from a discharge hole at the tip of the nozzle by pushing down the top of the discharger toward the container body. By using such a container, it is possible to hit the affected area with the liquid composition. When the liquid composition is discharged or sprayed toward the back of the throat, the liquid composition flows from the oral cavity to the hypopharyngeal region due to its fluidity, thereby capable of relieving pain not only in the oral cavity but also in the pharyngeal region.

[0031]

Preferred examples of the composition of the present invention include a pharmaceutical composition containing:

- Compound A and/or a pharmaceutically acceptable salt thereof (in particular, chloride of Compound A);
- at least one acidic component selected from the group consisting of dilute hydrochloric acid, lactic acid, and tartaric acid (especially dilute hydrochloric acid), optionally at least one basic component selected from the group consisting of sodium hydroxide, potassium hydroxide, diisopropanolamine, and sodium tartrate;
- at least one sugar alcohol having 5 or 6 carbon atoms (more preferably a sugar alcohol selected from the group consisting of xylitol, sorbitol, and mannitol, especially sorbitol);
- at least one sweetener selected from the group consisting of sucralose, sucrose, stevia extract, purified stevia extract, thaumatin, and acesulfame potassium (especially sucralose and/or purified stevia extract);
- at least one polyhydric alcohol (especially glycerin);

- optionally at least one additive; and
- the balance being water (especially purified water).

The composition is particularly preferably a composition for pain relief or local anesthesia applied to the oral cavity, pharynx and/or nasal cavity, in particular for pain relief in the oral cavity and/or pharynx. The pH of the composition is preferably from 3 to 7 (more preferably from 3 to 6, especially from 4.5 to 5.5).

[0032]

Among the above preferred examples, the composition in which,

- the content of Compound A and/or its pharmaceutically acceptable salt is from 0.1 to 3% by weight (more preferably from 0.5 to 2.5% by weight, especially from 1 to 2% by weight),
 - the total content of the at least one acidic component and the optional at least one basic component is from 0.001 to 1% by weight (more preferably from 0.005 to 0.1% by weight, especially preferably from 0.008 to 0.05% by weight),
 - the content of the at least one sugar alcohol is from 0.4 to 20% by weight (more preferably from 1 to 15% by weight, especially from 2 to 10% by weight, or from 3 to 7% by weight),
 - the content of the at least one sweetener is from 0.01 to 3% by weight (more preferably from 0.05 to 2% by weight, especially preferably from 0.1 to 1% by weight, further preferably from 0.2 to 0.6% by weight),
 - the content of the at least one polyhydric alcohol is from 2 to 30% by weight (more preferably from 3 to 20% by weight, especially from 5 to 15% by weight), and
 - the content of the additive(s) is from 0 to 5% by weight (more preferably from 0 to 3% by weight, especially from 0 to 1% by weight),
- is especially preferred.

[0033]

More preferred examples of the composition of the present invention include a pharmaceutical composition containing;

- 0.1 to 3% by weight (more preferably from 0.5 to 2.5% by weight, especially from 1 to 2% by weight) of the chloride of Compound A,
- 0.001 to 1% by weight (more preferably from 0.005 to 0.1% by weight, especially preferably from 0.008 to 0.05% by weight) of dilute hydrochloric acid, and optionally sodium hydroxide (especially dilute hydrochloric acid and sodium hydroxide),
- 0.4 to 20% by weight (more preferably from 1 to 15% by weight, especially from 2 to 10% by weight, or from 3 to 7% by weight) of sorbitol and/or xylitol (especially sorbitol),

- 0.01 to 3% by weight (more preferably from 0.05 to 2% by weight, especially preferably from 0.1 to 1% by weight, and further preferably from 0.2 to 0.6% by weight) of sucralose and/or purified stevia extract (especially sucralose and purified stevia extract)
- 2 to 30% by weight (more preferably from 3 to 20% by weight, especially from 5 to 15% by weight) of glycerin,
- 0 to 5% by weight (more preferably from 0 to 3% by weight, especially from 0 to 1% by weight) of the additive(s), and
- the balance being water (especially purified water).

The composition is preferably a composition for the relief of oral and/or pharyngeal pain. The pH of the composition is preferably from 3 to 7 (more preferably from 3 to 6, especially from 4.5 to 5.5).

[0034]

The composition may be provided in the form of a concentrated liquid which, when diluted with water at the time of use (e.g., when diluted from 2 to 10 times or from 2 to 5 times), will have the concentration described above.

[0035]

The present invention will be described in more detail by the following examples, but the present invention is not intended to be limited by the examples.

[0036]

[Example 1]

Aqueous solutions were prepared by dissolving 0.2% by weight of an acidic component in purified water, to which sodium hydroxide was added to adjust the pH to 6, or by dissolving 0.2% by weight of a basic component in purified water, to which hydrochloric acid was added to adjust the pH to 6. The chloride of Compound A was added to the aqueous solutions to reach 10 mg/10 ml. The aqueous solutions were then stored at 60°C for 2 weeks, and the amount of hydrolysis product resulting from hydrolysis of the chloride of Compound A was determined by high-performance liquid chromatography (HPLC). The percentage of hydrolysis product was determined by dividing the amount (weight) of hydrolysis product by the added weight of chloride of Compound A and multiplying by 100. Hydrochloric acid, citric acid, phosphoric acid, lactic acid, tartaric acid, or sodium dihydrogen phosphate was used as the acidic component, and sodium hydroxide, sodium citrate, sodium hydrogen carbonate, sodium hydrogen phosphate hydrate, or trisodium phosphate was used as the basic component.

[0037]

The results are shown in Figure 1A. As shown in Figure 1A, the amount of hydrolysate varied greatly depending on the type of acid/basic component added. Specifically, citric acid, phosphoric acid, sodium dihydrogen phosphate, or sodium hydrogen carbonate greatly accelerated hydrolysis of the chloride of Compound A (2% or more hydrolysate was produced), and sodium citrate, sodium hydrogen phosphate hydrate, or trisodium phosphate also accelerated hydrolysis of the chloride of Compound A (1% or more hydrolysate was produced). In contrast, when hydrochloric acid, lactic acid, tartaric acid, or sodium hydroxide is added, the amount of hydrolysis product is less, indicating that hydrolysis of the chloride of Compound A is unlikely to occur. On the other hand, for lidocaine hydrochloride, which has the same local anesthetic effect as Compound A, there was no event that the rate of hydrolysis differed significantly depending on the type of pH adjuster used.

[0038]

[Example 2]

Aqueous solutions were prepared by dissolving 0.2% by weight of a basic component (sodium hydroxide, potassium hydroxide, sodium acetate, sodium tartrate hydrate ($C_4H_4Na_2O_6 \cdot 2H_2O$), or diisopropanolamine) in purified water, to which hydrochloric acid was added to adjust the pH to 6. The chloride of Compound A was added to the aqueous solutions to reach 10 mg/10 ml. The aqueous solutions were then stored at 60°C for 2 weeks, as in Example 1, and the amount of hydrolysis product resulting from hydrolysis of the chloride of Compound A was determined by HPLC.

[0039]

The results are shown in Figure 1B. As shown in from Figure 1B, the amount of hydrolysate of Compound A was lower when sodium hydroxide, potassium hydroxide, sodium tartrate hydrate, and diisopropanolamine were used, but higher when sodium acetate was used.

[0040]

From the results of Examples 1 and 2, it was found that among the acidic/basic components used for pH control, there are those that are likely to cause degradation of Compound A and those that are unlikely to do so. In addition, the effect of pH of the composition on the stability of the chloride of Compound A was examined, and the range of pH 3-7 was more favorable, pH 3-6 was more favorable, and pH about 5 was most favorable.

[0041]

[Example 3]

The effect of sweeteners on the stability of the chloride of Compound A was examined. Sugar alcohols having 4 or more carbon atoms (D-sorbitol, xylitol, mannitol), sucralose, purified stevia extract, saccharin Na hydrate, acesulfame potassium, or dipotassium glycyrrhizate were used as sweeteners. Aqueous solutions were prepared by adding each sweetener to a pH 8 buffer solution including boric acid, citric acid hydrate and trisodium phosphate dodecahydrate at concentrations shown in Table 1, and then to which the chloride of Compound A was added to reach 10 mg/10 ml.

[0042]

The aqueous solutions were then stored at 60°C for 2 weeks as in Example 1, and the amount of hydrolysis product resulting from hydrolysis of the chloride of Compound A was determined by HPLC. The results are shown in Table 1.

[Table 1]

Table 1-1

Sweetener	Buffer solution alone	D-Sorbitol	D-Sorbitol	Xylitol	Mannitol
Concentration of sweetener (wt.%)	0	3.5%	5%	5%	5%
Preparation Possibility	possible	possible	possible	possible	possible
Amount of carboxylic acid form (initial)	0.62	0.04	0.03	0.04	0.03
Amount of carboxylic acid form (after 60°C/2 weeks)	18.62	4.03	3.16	3.89	3.82

Table 1-2

Sweetener	Sucralose	Purified stevia extract	Saccharin Na hydrate	Acesulfame K	Di-K Glycyrrhizinate
Concentration of sweetener (wt.%)	5%	5%	5%	5%	5%
Preparation Possibility	possible	possible	impossible (undissolved)	impossible (undissolved)	possible

Amount of carboxylic acid form (initial)	0.53	0.24	-	-	0.08
Amount of carboxylic acid form (after 60°C/2 weeks)	13.01	14.16	-	-	10.75

[0043]

As shown in Table 1-1, the addition of sugar alcohols having 4 or more carbon atoms greatly reduced the amount of carboxylic acid forms after 2 weeks at 60°C, compared to the buffer solution alone. In contrast, as shown in Table 1-2, the addition of sucralose, purified stevia extract and dipotassium glycyrrhizate reduced the amount of carboxylic acid forms compared to the buffer solution alone, but the degree of reduction was smaller than when sugar alcohols having 4 or more carbon atoms were added. When saccharin sodium hydrate and acesulfame potassium were added to the buffer solution, Compound A did not dissolve, making preparation of the formulation impossible. The pH after 2 weeks at 60°C was in the range of about 5.5-6.5 and there was no significant difference between the addition of sugar alcohol and the addition of other sweeteners.

[0044]

These results indicate that sugar alcohols having 4 or more carbon atoms are useful for improving the stability of Compound A (inhibiting the degradation of Compound A).

[0045]

[Example 4]

The compositions shown in Table 2 (pH about 4.5-5.5) were prepared to test the effect of the type and concentration of sugar alcohols on the stability of the chloride of Compound A. D-sorbitol, xylitol, erythritol, or mannitol was used as the sugar alcohol. The stability of the chloride of Compound A was tested by measuring the amount of hydrolysis product resulting from the hydrolysis of the chloride of Compound A, as in Example 1, after the prepared composition had been stored at 50°C for 2 weeks.

Table 2

Component	Concentration (wt.%)
Chloride of Compound A	1.0
Sugar alcohol	0-10

Dilute hydrochloric acid	trace amount (0.05 or less)
Sodium hydroxide	trace amount (0.05 or less)
Purified water	Amount that adds up to 100

[0046]

The results are shown in Figures 2 and 3. As shown in Figures 2 and 3, the decomposition of the chloride of Compound A was inhibited by the addition of sugar alcohols having 4 or more carbon atoms. The degradation inhibition effect of each sugar alcohol tended to increase as the amount of added sugar alcohol increased, but the degree of degradation inhibition varied depending on the type of sugar alcohol. The degradation inhibition effect was higher for D-sorbitol, mannitol, xylitol, and erythritol, in that order.

[0047]

[Example 5]

Since the solubility of the chloride of Compound A decreased by the addition of specific sweeteners, the compatibility of the chloride of Compound A with sweeteners was examined. More specifically, an aqueous solution of 0.2% by weight was prepared for each sweetener and the chloride of Compound A was gradually added while stirring the aqueous solution until an insoluble compound was found. The stirring was then stopped and the aqueous solution was allowed to stand overnight. The aqueous solution was filtered through a filter and the concentration of chloride of Compound A dissolved in the solution was determined by HPLC. The results are shown in Table 3.

[0048]

Table 3

Solvent			Solubility (w/w %)	pH
Purified water			4% or more	
Aqueous sweetener solution (0.2%)	Non-ionic sweetener	Sucralose	4% or more	6.37
		Purified stevia extract	4% or more	6.21
		Thaumatococcus	4% or more	3.89
	Ionic sweetener	Saccharin sodium hydrate	1-2%	5.65
		Acesulfame potassium	2-4%	6.14
		dipotassium glycyrrhizate	< 0.1%	5.31

[0049]

As shown in Table 3, the solubility of chloride of Compound A did not decrease with non-ionic sweeteners, but a tendency to decrease with ionic sweeteners was observed. In contrast, no such events were observed with lidocaine hydrochloride. As the concentration of ionic sweetener was increased, the solubility of the chloride of Compound A decreased further. Therefore, it is preferable to use a nonionic sweetener under circumstances where the chloride of Compound A is expected to precipitate easily, for example, when the room temperature is low.

[0050]

[Example 6]

The compositions shown in Table 4 (pH about 5) were prepared and tested for the antibacterial effect of the compositions against three bacteria: *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Table 4

Component	Concentration (wt.%)		
	Comparative composition	0.1% composition	0.8% composition
Chloride of Compound A	-	0.1	0.8
Sweetener	7.2	7.2	7.2
pH adjuster (acidic component and basic component)	0.1 or less	0.1 or less	0.1 or less
polyhydric alcohol	11	11	11
Purified water	Amount that adds up to 100	Amount that adds up to 100	Amount that adds up to 100

[0051]

As shown in Table 5, a composition in which the concentration of the chloride of Compound A was increased to 2% (pH about 5) was prepared, and its effects on the three bacteria described above and two fungi (*Candida* [*Candida albicans*] and *Aspergillus* [*Aspergillus brasiliensis*]) were tested.

Table 5

Component	Concentration (wt.%)
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Chloride of Compound A	2.0
Sweetener	3.9
pH adjuster (acidic component and basic component)	0.1 or less
polyhydric alcohol	10
Purified water	Amount that adds up to 100

[0052]

[Test Procedure]

The test strains used were *Staphylococcus aureus* (NBRC13276), *Pseudomonas aeruginosa* (NBRC13275), *Escherichia coli* (NBRC3972), *Candida albicans* (NBRC1594) and *Aspergillus brasiliensis* (NBRC9455). *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* were cultured on SCDA (Soybean Casein Digest Agar) plate medium at 30-35°C for 18-24 hours. *Candida albicans* was cultured on NSDA (Sabouraud Dextrose Agar) plate medium at 20-25°C for 48 hours. *Aspergillus brasiliensis* was cultured on NSDA (Sabouraud Dextrose Agar) plate medium at 20-25°C for 6-10 days. The sterility of the pre-culture medium was confirmed by the presence or absence of bacterial growth after cultivation under the same conditions using one each of SCDA and NSDA plate medium.

Test microbial solutions were prepared by suspending the cultured microbes in physiological saline and centrifuging to obtain about 10^8 CFU per 1 mL, and for *Aspergillus brasiliensis*, a solution was prepared by suspending the spores in physiological saline supplemented with 0.05% polysorbate 80 and centrifuging to obtain about 10^8 CFU per 1 mL, and these were used as the respective test microbial solutions. Mixed samples were prepared by placing 20 mL of each composition in a sterile glass container and then adding 0.1 mL of each test microbial solution. The mixed samples were light-shielded and stored at 20-25°C for 28 days.

On each measurement day (0, 14, and 28 days later), 1 mL was collected from each mixed sample. Each mixed sample was added to 9 mL of Soybean Casein Digest Medium supplemented with Lecithin and Polysorbate 80 and stirred well to prepare a diluted sample solution. Ten-fold serial dilutions of this solution were repeated with peptone saline buffer as necessary to prepare each diluted mixture sample. 1 mL of each diluted mixture sample was dispensed to each of two Petri dishes and mixed and diluted with SCDLPA (Soybean Casein Digest Agar supplemented with Lecithin and Polysorbate 80) for bacteria or NSDLPA

(Sabouraud Dextrose Agar supplemented with Lecithin and Polysorbate 80) for fungi. After 5 days of cultivation at 30-35°C for SCDLPA and 20-25°C for NSDLPA, the number of emerging colonies (CFU: colony-forming unit) was counted.

[0053]

Table 6 shows the number of viable bacteria per mL on days 0, 14 and 28 after using the compositions shown in Table 4.

Table 6

Tested Microbe	Storage days	Comparative composition	0.1% composition	0.8% composition
<i>Escherichia coli</i> (<i>E. coli</i>)	inoculum count	5.0×10^5	5.0×10^5	5.0×10^5
	Day 0	5.6×10^5	4.1×10^5	7.8×10^4
	Day 14	1.1×10^4	< 10	< 10
	Day 28	7.1×10^2	< 10	< 10
<i>Pseudomonas aeruginosa</i> (<i>P. Aeruginosa</i>)	inoculum count	4.3×10^5	4.3×10^5	4.3×10^5
	Day 0	3.8×10^5	2.9×10^5	8.5×10^4
	Day 14	1.3×10^3	< 10	< 10
	Day 28	40	< 10	< 10
<i>Staphylococcus aureus</i> (<i>S. Aureus</i>)	inoculum count	3.9×10^5	3.9×10^5	3.9×10^5
	Day 0	4.7×10^5	3.7×10^5	2.2×10^5
	Day 14	< 10	< 10	< 10
	Day 28	< 10	< 10	< 10

[0054]

As shown in Table 6, the compositions containing the chloride of Compound A showed significantly higher antimicrobial efficacy against each bacterium from day 0, compared to the comparative composition without the chloride of Compound A. The 0.8% composition showed higher antimicrobial efficacy than the 0.1% composition.

[0055]

Table 7 shows the number of viable microbes per mL on days 0, 14 and 28 after using the compositions shown in Table 5.

Table 7

Tested Microbe		Storage days	2% composition
Bacterium	<i>Escherichia coli</i> (<i>E. coli</i>)	inoculum count	5.8×10^5
		Day 0	1.3×10^2
		Day 14	< 10
		Day 28	< 10
	<i>Pseudomonas aeruginosa</i> (<i>P. Aeruginosa</i>)	inoculum count	3.2×10^5
		Day 0	1.6×10^2
		Day 14	< 10
		Day 28	< 10
	<i>Staphylococcus aureus</i> (<i>S. Aureus</i>)	inoculum count	3.5×10^5
		Day 0	3.5×10^4
		Day 14	< 10
		Day 28	< 10
Fungus	<i>Candida</i> (<i>C. Albicans</i>)	inoculum count	4.9×10^5
		Day 0	3.2×10^5
		Day 14	< 10
		Day 28	< 10
	<i>Aspergillus</i> (<i>A. Brasiliensis</i>)	inoculum count	4.5×10^5
		Day 0	3.3×10^5
		Day 14	2.3×10^2
		Day 28	1.1×10^2

[0056]

As shown in Table 7, when the 2% composition was added to bacteria, the number of viable bacteria on day 0 was more than an order of magnitude lower than the number of inoculum bacteria, indicating high antibacterial activity. For fungi, a decrease in the number of viable fungi was also observed from day 0 relative to the number of inoculum fungi.

[0057]

The composition of the present invention can relieve pain when applied to the oral cavity of patients suffering from severe stomatitis or pharyngitis caused by anticancer drugs or radiation therapy, etc. In addition to its pain-relieving effect, the composition also exhibits

antimicrobial effect against bacteria and fungi in the mouth. Therefore, when applied to patients who are unable to perform oral care such as brushing their teeth adequately due to pain, and whose oral hygiene is deteriorating, it is expected to improve the oral environment and help prevent diseases brought about by microbes.

[0058]

[Example 8]

An example formulation of the composition of the present invention is set forth below. The composition shown in the table is a liquid composition and can be used for the relief of oral and/or pharyngeal pain, for example by spraying it into the mouth using a spray container with a nozzle.

Table 8

Component	Concentration (wt.%)
Chloride of Compound A	0.1-2
D-Sorbitol	3-5
Sucralose	0.1-0.3
Purified stevia extract	0.1-0.3
Dilute hydrochloric acid	0.05 or less
Sodium hydroxide	0.05 or less (adjusted to pH 5)
Glycerin	5-15
Purified water	Amount that adds up to 100

Claims

1. A topical pharmaceutical composition for application to the oral cavity and/or pharynx, containing N,N-dimethyl-2-oxo-N-(2-oxo-2-(phenylamino)ethyl)-2-(phenylamino)ethan-1-aminium (hereinafter referred to as Compound A) and/or a pharmaceutically acceptable salt thereof as an active ingredient.
2. The pharmaceutical composition according to claim 1, containing at least one selected from the group consisting of hydrochloric acid, lactic acid, tartaric acid, and a sugar alcohol having 4 or more carbon atoms.
3. The pharmaceutical composition according to claim 1, containing at least one sugar alcohol having 4 or more carbon atoms.
4. The pharmaceutical composition according to claim 1 or 3, containing at least one acidic component selected from the group consisting of hydrochloric acid, lactic acid, and tartaric acid.
5. The pharmaceutical composition according to claim 1 or 3, containing:
at least one acidic component selected from the group consisting of hydrochloric acid, lactic acid, and tartaric acid, and
at least one basic component selected from the group consisting of sodium hydroxide, potassium hydroxide, diisopropanolamine, and sodium tartrate.
6. The pharmaceutical composition according to claim 2 or 3, wherein the at least one sugar alcohol is selected from the group consisting of xylitol, mannitol, and sorbitol.
7. The pharmaceutical composition according to any one of claims 1 to 6, containing the chloride of Compound A as the active ingredient.
8. The pharmaceutical composition according to any one of claims 1 to 7, having a pH of 3 to 7.

9. The pharmaceutical composition according to any one of claims 1 to 8, further containing at least one selected from the group consisting of sucralose, sucrose, stevia extract, purified stevia extract, thaumatin, and acesulfame potassium.

10. The pharmaceutical composition according to any one of claims 1 to 9, further containing at least one polyhydric alcohol selected from glycerin and propylene glycol.

11. The pharmaceutical composition according to claim 1, containing:
the chloride of Compound A,
at least one acidic component selected from the group consisting of hydrochloric acid, lactic acid, and tartaric acid, optionally at least one basic component selected from the group consisting of sodium hydroxide, potassium hydroxide, diisopropanolamine, and sodium tartrate
at least one sugar alcohol selected from the group consisting of xylitol, mannitol, and sorbitol,
at least one selected from the group consisting of sucralose, sucrose, stevia extract, purified stevia extract, thaumatin, and acesulfame potassium
at least one polyhydric alcohol selected from glycerin and propylene glycol,
0 to 5% by weight of additive(s), and
the balance being water.