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AMYL NITRITE INHALANT COMPOSITION

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This invention relates to medicament compositions containing amyl nitrite, and to their preparation and use. In particular, this invention relates to self-propelling medicament compositions containing amyl nitrite and adaptable to dispersion in aerosol form, and to their preparation and use.

The use of amyl nitrite as a vasodilator in the treatment of angina pectoris is well known in the art. Treatment using this drug is commonly by inhalation, and the drug is usually marketed in sealed breakable ampoules or pearls. When chest pain occurs, a patient employing the drug breaks the ampoule wrapped in a handkerchief and inhales the fumes of the drug.

This method of treatment suffers from a number of disadvantages. First, it is almost imposible properly to dose a patient with the drug by this technique, since the amount of drug inhaled will vary greatly with the manner of inhalation, such as the depth of breathing and the distance at which the source of the drug is held from the nose and mouth. Also, to insure that an adequate dosage of the drug is delivered to the patient, the ampoules must contain wastefully large amounts of the drug, usually 200–300 mg., which amount far exceeds the required dose. Further, the drug has a characteristic and offensive odor which may make its use in public inconvenient and embarrassing. Also, the inconvenience of packaging, merchandising, and carrying breakable ampoules is self-evident. Further, amyl nitrite vapors are inflammable, and inhalation of the vapors involves some risk.

However, the most important impediments to the medicinal use of amyl nitrite are its characteristic unpleasant taste and odor, which commonly cause nausea, vomiting, and headaches in many patients who ingest the drug. These side effects of the drug have heretofore hindered its use, even though the problems of inconvenient administration of the drug can be overcome by dispensing it in aerosol form, for example.

According to the present invention, it has been discovered that the disagreeable taste and odor of amyl nitrite can be effectively masked to reduce or eliminate the disagreeable side effects often caused by the drug. Although the masking agent may be combined with amyl nitrite for administration by conventional inhalation or other means, the greatest significance of the discovery is that it makes possible the practical administration of amyl nitrite by aerosol inhalation.

The masking agent of the invention is a critical combination of perfuming and flavoring agents. In particular, the disagreeable taste and odor of amyl nitrite are effectively masked with ionones. Many ionone isomers, including the alpha-, beta-, gamma-, and delta- etc. isomers, are known to the art and can be employed either alone or in mixtures containing two or more components in all proportions. Similarly, the isomeric methyl and allyl ionones can be employed, either alone, in admixture in all proportions with one another, or in admixture in all proportions with any and all of the unsubstituted ionone isomers.

These ionones have been used in the prior art in perfumery, and, in combination with sweetening agents, in small amounts as flavoring agents in hard candies, cough syrups and other artificially flavored materials. The ionones, undiluted, have a bitter and disagreeable taste, however, and because of this property the prior art has not heretofore employed them in the relatively large amounts in which they are used in the present invention, where they are not combined with sweeteners.

In the masking agent of the invention, these ionone materials are critically employed in combination with the so-called "C–14," "C–16," and "C–18" aldehydes, also known in the perfuming art. As known in the art, these various "aldehydes" are compounds, not necessarily aldehydes, which have common characteristic properties useful in flavoring and perfuming. The C–14 or "peach" aldehydes, for example, include gamma-undecalactone, delta-undecalactone, gamma-decalactone, and alpha-substituted gamma butyrolactones in which the substituents may be aliphatic, such as allyl, propyl, heptyl, and octyl, or aromatic, such as phenyl, benzyl, and citronellyl. Those skilled in the art recognize that these "C–14" materials may contain more or fewer than 14 carbon atoms.

Similarly, the C–16 or "strawberry" aldehydes include materials such as ethyl-phenyl-glycidate and ethyl-methyl-phenl-glycidate.

The C–18 or "coconut" aldehydes include octalactone, gamma-nonyllactone, gamma-substituted gamma-butyrolactones such as gamma-caprylolactone, gamma-n-amyl butyrolactone, and 8-methyl-1,4-octanolide.

These perfuming agents, together with other optional perfuming agents of a wide variety, are critically combined with a flavoring agent aiding the masking of the taste and odor of amyl nitrite and additionally masking the often disagreeable taste of the perfuming agents principally employed to mask the drug. As flavoring agents, agents from the so-called mint series are critically present, but can be used in combination with numerous other flavoring agents, preferably those from the so-called spice series, but also including fruit flavors, anise flavors (licorice, anethol, etc.), root extracts, and/or wintergreen, and the like.

The masking agent according to the present invention critically contains between about 7.5 and about 22.5 percent by weight, based on the total masking agent composition, preferably about 10–20 percent by weight, of ionone and/or methyl ionone and/or allyl ionone isomers. These materials are critically combined with between about 0.5 and about 2.5 percent by weight, preferably about 1 to about 2 percent by weight, of the so-called C–14 to C–18 aldehydes, alone or in combination. The composition also critically contains between about 45 and about 70 percent by weight of a flavoring agent from the mint series, preferably about 50 to 65 percent by weight of such a flavoring agent. In addition, other perfuming agents, well known to those skilled in the art, may be present in amounts of up to 8 percent by weight, suitably from about 6 to about 8 percent by weight, or 6.5 to 7.5 percent by weight of the composition. Also, other flavoring agents well known to those skilled in the art may be present in amounts of up to 30 percent by weight, suitably from 10 to 30 percent by weight, or 12 to 25 percent by weight of the composition.

Many flavoring agents in the so-called mint series are known to the flavoring chemist. This series includes spearmint oil, USP, peppermint oil, USP, terpeneless peppermint, terpeneless spearmint, menthol, synthetic menthols, and others.

As additional flavoring agents may be mentioned substances in the so-called spice series such as cassia, USP, clove bud oil, USP, eugenol, nutmeg oil, cinnamic aldehyde, methyl cinnamic aldehyde, as well as other flavoring agents such as vanillin, ethyl vanillin, heliotropin, methyl salicylate, sweet birch oil, and various esters of aromatic alcohols and/or acids such as methyl anthranilate, or other esters of anthranilic, benzoic, salicylic, and

cinnamic acids, or benzyl, and cinnamyl alcohols, and the like. Additional flavoring agents may be found in the fruit flavors, such as orange, lemon, lime, the anise flavors, the root extracts, wintergreen, and others.

As additional perfuming agents useful in the compositions of the invention may be mentioned materials such as iso-eugenol, benzyl acetate, linalool, geranyl acetate, rose oil, and the like.

The above listing of perfuming and flavoring agents, including materials in the mint series, spice series, and others, is not intended to be exhaustive. Numerous other flavoring and perfuming agents are known to those skilled in the art and are comprised within the scope of the present invention. Specific reference is made to "Synthetic Food Adjuncts," by Morris B. Jacobs, D. Van Nostrand, New York (1947), and "Perfume and Flavor Materials of Natural Origin," by Steffan Arctander, published by the author, Elizabeth, New Jersey (1960), where numerous materials known to the art and suitable for use in the invention are discussed.

To prepare a masked amyl nitrite composition, the pre-compounded masking agent, prepared by thorough mixing of the flavoring and perfuming ingredients, is suitably combined with amyl nitrite in amounts of from about 0.5 to about 4 percent by weight of amyl nitrite, preferably in amounts of from 1 to 3 percent by weight of amyl nitrite. The final composition, with an aerosol propellant, suitably contains a minimum of about 0.1 perent by weight of masking agent.

In preparing an aerosol composition, the masking agent and amyl nitrite are dissolved in a non-toxic volatile liquefied propellant. Suitable non-toxic volatile propellants are known in the art, and are discussed in Patent 2,868,691 for example. These materials are generally fluorinated or fluorochlorinated lower saturated aliphatic hydrocarbons, suitably halogenated alkanes containing one to four carbon atoms, preferably one or two carbon atoms, and at least one fluorine atom. In general, any of the materials disclosed in the earlier mentioned patent can be employed according to the present invention, including propellants such as dichlorodifluoromethane ("Freon 12"), dichlorotetrafluoroethane ("Freon 114"), trichloromonofluoromethane ("Freon 11"), and octafluorocyclobutane ("Freon C-318"). These propellants, or suitable mixtures thereof, will produce a propellant vapor pressure between about 25 and about 60 pounds per square inch at room temperatures (20–25° C.). Suitable mixtures of the propellants can be employed to give a preferred vapor pressure between about 35 and about 40 pounds per square inch at these temperatures. The best propellant compositions contain about 60 percent by weight of "Freon 12," blended with "Freon 114." However, this mixture or other specific mixtures are not critical to the invention and any non-toxic liquid volatile propellant, such as those earlier described herein, may be employed.

The products of the invention are conveniently used in aerosol containers having a metered valve which dispenses a controlled quantity of the self-propelling aerosol composition as a single dose. These containers are well known in the art, and may be made of any material, such as glass, plastic, or metal, adequate to contain the pressures generated by the volatile propellant materials therein. Conventionally, these metered containers have an internal well of predetermined volume which is filled with the self-propelling composition. On activation of the aerosol valve, only this predetermined volume of self-propelling composition is dispersed as an aerosol, and the internal well is refilled.

When used in such a metered valve container, the relative proportion of amyl nitrite (and masking agent) to volatile propellant may vary with the dose of pure amyl nitrite to be dispensed and the size of the metered dose delivered by the valve. Dosage rates of pure amyl nitrite will vary between about 1 milligram and about 25 milligrams, generally between about 5–10 milligrams, and the quantity of propellant combined therewith will be chosen to deliver this amount of pure amyl nitrite on activation of a metered valve of chosen size. For example, in metered aerosol dispensers having a so-called "50 milligram valve," that is, a valve which will dispense 50 milligrams of a liquid of unit density each time it is activated, amyl nitrite is usually combined with a propellant in amounts of between about 5 and about 20 percent, suitably about 10 percent by weight, based on the total composition. In such a combination containing 10 percent by weight of amyl nitrite, about 0.5 to 0.4 percent by weight of masking agent, usually between about 0.1 and 0.3 percent by weight, is present, the balance being the volatile propellant mixture.

A better understanding of the invention and of its many advantages will be had by referring to the following specific examples, given by way of illustration.

Example

The following masking agents were prepared by mixing the enumerated ingredients in the amounts indicated.

(I)

	Parts by weight
A. Ionones: α-β methyl ionone	2000
B. Mint flavors:	
Spearmint oil, USP	2000
Peppermint oil, USP	5000
Menthol	2000
C. C–14—C–18 aldehydes: C–14 aldehyde	150
D. Other flavoring agents:	
Cassia, USP	1000
Eugenol	500
Vanillin	500
Heliotropin	500
Methyl anthranilate	100
E. Other perfuming agents:	
Benzyl acetate	500
Rose oil	500

(II)

A. Ionones:	
α-β ionone	1000
α-β methyl ionone	1500
B. C–14—C–18 aldehydes:	
C–14 aldehyde	100
C–18 aldehyde	50
C. Mint flavors:	
Spearmint oil, USP	3000
Peppermint oil, USP	2000
Terpeneless spearmint	1000
Menthol	3000
D. Other flavoring agents:	
Cassia, USP	500
Clovebud oil, USP	500
Nutmeg oil	500
Vanillin	200
Ethyl vanillin	200
Heliotropin	400
E. Other perfuming agents:	
Benzyl acetate	400
Linalool	100
Geranyl acetate	100
Rose oil	400

(III)

A. Ionones:	
α-β ionone	600
α-β methyl ionone	1500
B. C–14—C–18 aldehydes: C–14 aldehyde	150
C. Mint flavors:	
Peppermint oil, USP	3000
Terpeneless peppermint	1000
Menthol	2000
D. Other flavoring agents:	
Cassia, USP	500

Cinnamic aldehyde	300
Vanillin	500
Heliotropin	400
Methyl salicylate	500
Sweet birch oil	100
Methyl anthranilate	50
E. Other perfuming agents:	
Benzyl acetate	400
Rose oil	400

These masking agents were used to compound aerosol compositions with amyl nitrite as follows.

(IV)

Ingredients:	Parts by weight
Masking agent	0.25
Amyl nitrite	9.75
"Freon 12"	54
"Freon 114"	36
	100

(V)

Ingredients:	Parts by weight
Masking agent	0.30
Amyl nitrite	14.70
"Freon 12"	60
"Freon 114"	15
"Freon 11"	10
	100

(VI)

Ingredients:	Parts by weight
Masking agent	0.20
Amyl nitrite	6.80
"Freon 12"	53
"Freon 114"	30
"Freon C-318"	10
	100

Although specific embodiments have been shown and described, it is to be understood that they are illustrative, and are not to be construed as limiting on the scope and spirit of the invention.

What is claimed is:

1. A composition suitable for inhalation therapy consisting of amyl nitrite and a masking agent comprising a blend of (A) a member selected from the group consisting of ionone, methyl ionone, and allyl ionone isomers, (B) a perfuming agent selected from the group consisting of the C–14, C–16, and C–18 aldehydes, and (C) a flavoring agent of the mint series.

2. A composition as in claim 1 wherein said masking agent is present in an amount of at least 0.5 percent by weight of amyl nitrite.

3. A composition as in claim 1 in a non-toxic liquefied propellant.

4. A composition as in claim 1 wherein additional flavoring and perfuming agents are present.

5. A composition as in claim 4 wherein said propellant comprises 60 percent by weight of dichlorodifluoromethane, the balance being dichlorotetrafluoroethane.

6. In a composition adaptable to use in inhalation therapy in aerosol form and comprising amyl nitrite in a non-toxic liquefied propellant, a masking agent combined in said composition and consisting essentially of a blend of:

(A) between about 7.5 and 22.5 percent by weight of a member selected from the group consisting of ionone, methyl ionone, and allyl ionone isomers;

(B) between about 0.5 percent to about 2.5 percent by weight of a perfuming agent selected from the group consisting of the C–14, C–16, and C–18 aldehydes;

(C) between about 45 percent and about 75 percent of a flavoring agent of the mint series;

(D) up to about 8 percent by weight of other optional perfuming agents; and

(E) up to about 30 percent by weight of other optional flavoring agents, all percentages being based on the weight of the blend.

7. A composition as in claim 6 wherein said masking agent is present in an amount of at least 0.5 percent by weight of amyl nitrite.

8. The method of masking the disagreeable taste and odor of amyl nitrite which comprises combining therewith from about 0.5 to about 4 percent, by weight of amyl nitrite, of a masking agent comprising a blend of (A) a member selected from the group consisting of ionone, methyl ionone, and allyl ionone isomers, (B) a perfuming agent selected from the group consisting of the C–14, C–16, and C–18 aldehydes, and C a flavoring agent of the mint series.

9. The method as in claim 8 wherein said amyl nitrite and masking agent are dispersed in a non-toxic liquefied propellant.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,106,511 October 8, 1963

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It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 6, line 3, for the claim reference numeral "4" read -- 6 --; same column 6, lines 35 and 36, for "C a flavoring agent" read -- (C) a flavoring agent --.

Signed and sealed this 12th day of May 1964.

(SEAL)
Attest:
ERNEST W. SWIDER

Attesting Officer

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Commissioner of Patents