

SPECIFICATION

Aerosol compositions containing benzocaine

This invention relates to liquid anaesthetic compositions in aerosol containers. More specifically, this invention relates to liquid compositions of the anaesthetic benzocaine which form single phase mixtures in combination with solvent and hydrocarbon propellants, and which are single phase after exposure to low temperatures and with high concentrations of benzocaine.

Benzocaine, the ethyl ester of p-aminobenzoic acid, is a well known local anaesthetic which has been topically administered in the form of ointments, lotions, sprays, gels and as an impregnant in first aid pads. In order to enhance or prolong benzocaine's anaesthetic activity, various efforts have been made to increase the concentration of benzocaine in various solvents or to more effectively maintain the anaesthetic at its site of administration. Increasing the concentration of benzocaine, however, had to be balanced against the increasing probability of benzocaine precipitation, particularly at colder temperatures, thereby limiting their field of use. The goal of formulating highly concentrated benzocaine compositions characterized by cold temperature resistance is even greater in aerosol anaesthetic compositions wherein even small amounts of precipitate can clog valves and orifices, and wherein sufficient pressure must be maintained to both completely deliver all the benzocaine solution within the container and evenly distribute the benzocaine solution with desirable spray characteristics.

Many solvents have been disclosed for benzocaine. For example, U.S. Patent 2,187,597 discloses anaesthetic formulations containing up to five percent of the anaesthetic agent in a mixture of benzyl alcohol and ethyl chloride. Other formulations containing up to 10% benzocaine in mixtures with a procaine salt, water, water miscible poly-hydroxy aliphatic alcohols and their ethers have been disclosed in U.S. Patent 2,382,546. U.S. Patent 2,457,188 discloses benzocaine solutions containing at least 10% benzocaine at 20°C utilizing solvents selected from certain polyoxyalkylene glycols, aliphatic ethers of dihydric alcohols, aromatic ethers of aliphatic dihydric alcohols, carboxylic acid esters of aliphatic dihydric alcohols, and carboxylic acid esters of aromatic and aliphatic ethers of aliphatic dihydric alcohols. In U.S. Patent 2,682,182, benzocaine solutions containing up to 16% benzocaine at 0°C were disclosed in a mixture employing a major amount of propylene glycol and a polyoxyethylene (8—25) hexitan monolaurate.

Anaesthetic aerosol preparations containing at least 10% benzocaine in diesters of C_8 — C_{12} carboxylic acids and polyethylene glycols having a molecular weight of approximately 300—600, and a propellant system made from mixture of chlorofluorohydrocarbons have been disclosed in U.S. Patent 3,322,634. These aerosol formulations, however, are no longer acceptable because of certain atmospheric effects associated with chlorofluorohydrocarbons.

Benzocaine has also been employed in formulations containing certain other therapeutic ingredients, for example, as disclosed in U.S. Patent 3,808,319 wherein the solvent is volatile alcohol such as ethyl alcohol or isopropyl alcohol. Solvents of this type, however, are generally counterproductive to desirable anaesthetic properties because of their stinging nature to sensitive or wounded skin and the like. Compositions containing up to 15% benzocaine are further disclosed in U.S. Patent 4,052,513 in the form of oil in water emulsions.

This invention provides a liquid anaesthetic composition in an aerosol container comprising a single phase mixture of a propellant and a water washable base comprising benzocaine in a solvent wherein

(a) the weight percent of the benzocaine in the solvent is from 0.5% up to its maximum solubility in the solvent;

(b) the solvent is selected from at least one of polyoxyethylene sorbitan trioleate having an average of about 20 units of ethylene oxide in the polyoxyethylene chains, polyethylene glycol dilaurate wherein the polyethylene glycol has an average molecular weight of about 400 and polyethylene glycol monolaurate; and

(c) the propellant is selected from difluoroethane and at least one of n-butane, isobutane and n-propane;

with the proviso that the composition is a single phase mixture after exposure to temperatures of about -20°C when the benzocaine comprises about 20% of said base.

The liquid anaesthetic compositions in aerosol containers of the present invention comprise a single phase mixture of a water washable base of benzocaine in a solvent and a propellant. The weight percent of benzocaine in the solvent is from about 0.5% up to its maximum solubility in the solvent. For most effective anaesthetic properties, the benzocaine comprises at least 10% by weight of the base and preferred compositions contain about 20% by weight of benzocaine.

Solvents useful in this invention may be at least one of polyoxyethylene sorbitan trioleate having an average of about 20 units of ethylene oxide in the polyoxyethylene chain, polyethylene glycol monolaurate wherein the polyethylene glycol has an average molecular weight of about 200 to about 600 (e.g. about 400) and polyethylene glycol dilaurate wherein the polyethylene glycol has an average molecular weight of about 400. Although wider ranges of one solvent to another are acceptable, the solvent is preferably selected from two of the herein listed class of solvents in a ratio of 40:60 to each other, and most desirably in a ratio of 50:50.

The propellant system comprises difluoroethane and at least one of n-butane, isobutane and n-propane. In the preferred system which utilizes n-butane, the difluoroethane comprises about 35—70% by weight of the propellant system. In the most preferred embodiments each of the propellants in a two propellant system comprise about 50% of the total propellant.

5 Preferably, the water washable base of benzocaine in solvent and the propellant each comprise about 45% to about 55% by weight of the liquid anaesthetic composition, and in preferred embodiments, about 50%. 5

The compositions of this invention are further defined by the provision that the compositions form a single phase mixture following exposure to temperatures of about -20°C , when the benzocaine comprises about 20% of said water washable base. Illustratively, when the benzocaine content of the base is other than about 20% the above mentioned single phase characteristics of the compositions may be determined by adjusting the benzocaine content of the base to about 20% at the expense of the solvent, without altering the relative ratios of the solvents to each other if there is more than one solvent. In preferred embodiments, the composition is a single phase mixture (clear liquid solution) 10 when at about -20°C . Compositions having the preferred single phase characteristics at -20°C employ polyethylene glycol monolaurate, or mixtures of polyoxyethylene sorbitan trioleate with the polyethyleneglycol mono- or di-laurate as the solvent. 15

In formulating the composition of this invention, other ingredients such as anti-pruritic agents, anti-infectives, anti-fungal agents and anti-bacterial agents may be typically incorporated.

20 The following composition is an illustration of a preferred embodiment of this invention: 20

Water Washable Base

	Benzocaine	200.0 g	
	Menthol	5.0 g	
	Methylparaben	10.0 g	
25	Polyoxyethylene 20 Sorbitan Trioleate	392.5 g	25
	Polyethyleneglycol 400 Monolaurate	392.5 g	

The composition of the invention may be prepared by charging the solvent into a suitable container equipped with a stirrer, adding the benzocaine and/or other active ingredients and mixing until dissolution. The solution may be then filtered through a suitable screen and loaded into an aerosol container along with the propellants in a conventional manner. 30

A suitable container for the composition of this invention is a can having a "2P" rating as specified by the United States Department of Transportation. Among the valve systems which have been employed satisfactorily in any position are those similar to Seaquist NS-36 or NS-34 (Seaquist Valve Co., Cary, Ill.) or those similar to ARC-KN-37 (Ethyl Products Co., North Riverside, Ill.).

35 The invention is further illustrated by the following Examples 1 to 6, 10 to 16, 21 to 25, 27 to 34, 35 36 and 38 to 41. The compositions of these Examples form a single phase mixture at room temperature and/or at -20°C after exposure at -20°C . The other Examples below are included for reference.

Examples

40 The following bulk concentrates were prepared for further evaluation: 40

Bulk Concentrates				
	I	II	III	
Benzocaine	20%	20%	20%	
Menthol	0.5%	0.5%	0.5%	
45 Methylparaben	1.0%	1.0%	1.0%	45
Polyoxyethylene 20 Sorbitan Trioleate	78.5%	—	—	
PEG 400 Monolaurate	—	78.5%	—	
PEG 400 Dilaurate	—	—	78.5%	

Example No.	Bulk Concentrates			Propellants		Pressure psig @ 70°F	Physical Stability RT -20°C (for 1 day)
	I	II	III	difluoroethane	n-butane		
1.	25%	25%	—	25%	25%	57	OK*
2.	22.5%	22.5%	—	27.5%	27.5%	71**	OK
3.	27.5%	27.5%	—	22.5%	22.5%	71**	OK
4.	25%	—	25%	25%	25%	57	OK
5.	22.5%	—	22.5%	27.5%	27.5%	—	OK
6.	27.5%	—	27.5%	22.5%	22.5%	—	OK
7.	—	25%	25%	25%	25%	45	OK
8.	—	22.5%	22.5%	27.5%	27.5%	—	Wt. ppt. wt. ppt. @ RT
9.	—	27.5%	27.5%	22.5%	22.5%	—	Wt. ppt. wt. ppt. @ RT
10.	—	50%	—	35%	15%	—	Wt. ppt. OK @ RT
11.	—	50%	—	30%	20%	57	OK
12.	—	50%	—	25%	25%	56	OK
13.	—	50%	—	20%	30%	51	OK
14.	—	—	50%	35%	15%	—	OK
15.	—	—	50%	30%	20%	—	OK
16.	—	—	50%	25%	25%	—	OK
17.	—	—	50%	20%	30%	—	OK
18.	—	—	50%	15%	35%	43	OK
19.	—	—	50%	10%	40%	39	OK
20.	—	—	50%	5%	45%	31	OK
21.	25%	25%	—	35%	15%	63	OK
22.	10%	40%	—	30%	20%	60	OK
23.	25%	25%	—	30%	20%	58	OK
24.	25%	25%	—	25%	25%	57	OK
25.	25%	25%	—	20%	30%	52	OK
26.	25%	25%	—	15%	35%	—	Separation
27.	25%	25%	—	18%	32%	—	OK
28.	25%	—	25%	35%	15%	—	Ppt. OK @ RT

Example No.	Bulk Concentrates			Propellants		Pressure psig @ 70°F	Physical Stability	
	I	II	III	difluoroethane	n-butane		RT	-20°C (for 1 day)
29.	10%	—	40%	30%	20%	—	OK	Ppt.
30.	25%	—	25%	30%	20%	60	OK	OK @ RT
31.	25%	—	25%	25%	25%	57	OK	OK
32.	25%	—	25%	20%	30%	50	OK	Wt. ppt.
33.	—	25%	25%	35%	15%	—	OK	OK @ RT
34.	—	25%	25%	30%	20%	—	OK	Wt. ppt.
35.	—	25%	25%	25%	25%	45	OK	OK @ RT
36.	—	25%	25%	20%	30%	50	OK	Wt. ppt.
37.	—	25%	25%	15%	35%	45	OK	OK @ RT
38.	25%	25%	—	25%	25%	57	OK	Wt. ppt. @ RT
39.	20%	30%	—	25%	25%	79**	OK	Wt. ppt.
40.	30%	20%	—	25%	25%	78**	OK	OK @ RT
41.	25%	—	25%	25%	25%	57	OK	Wt. ppt.
42.	20%	—	30%	25%	25%	—	OK	OK
43.	30%	—	20%	25%	25%	—	OK	Ppt.
44.	—	25%	25%	25%	25%	45	OK	ppt. @ RT
45.	—	20%	30%	25%	25%	—	OK	Wt. ppt.
46.	—	30%	20%	25%	25%	—	OK	Wt. ppt. @ RT

*One phase system, clear solution

**Measured at RT

ppt.=precipitate

wt. ppt.=white precipitate

Claims

1. A liquid anaesthetic composition in an aerosol container comprising a single phase mixture of a propellant and a water washable base comprising benzocaine in a solvent wherein.
- (a) the weight percent of the benzocaine in the solvent is from 0.5% up to its maximum solubility in the solvent;
- (b) the solvent is selected from at least one of polyoxyethylene sorbitan trioleate having an average of about 20 units of ethylene oxide in the polyoxyethylene chains, polyethylene glycol dilaurate wherein the polyethylene glycol has an average molecular weight of about 400 and polyethylene glycol monolaurate; and
- (c) the propellant is selected from difluoroethane and at least one of n-butane, isobutane and n-propane;
- with the proviso that the composition is a single phase mixture after exposure to temperatures of about -20°C when the benzocaine comprises about 20% of said base.
2. A composition as claimed in Claim 1 when the propellant comprises about 35% to about 70% by weight of difluoroethane.
3. A composition as claimed in Claim 1 or 2 wherein the propellant comprises about 50% by weight of difluoroethane and about 50% by weight of n-butane, isobutane or n-propane.
4. A composition as claimed in any one of Claims 1 to 3 wherein the solvent comprises polyoxyethylene sorbitan trioleate having an average of about 20 units of ethylene oxide in the polyoxyethylene chains and one of polyethylene glycol monolaurate and polyethylene glycol dilaurate wherein the polyethylene glycol has an average molecular weight of about 400.
5. A composition as claimed in any one of Claims 1 to 4 wherein the benzocaine comprises at least 10% by weight of the base.
6. A composition as claimed in any one of Claims 1 to 5 wherein the benzocaine comprises about 20% by weight of the base.
7. A composition as claimed in any one of Claims 1 to 6 wherein the base and propellant each comprise about 45% to about 55% of the composition.
8. A composition as claimed in any one of Claims 1 to 7 which comprises at least 10% benzocaine in the base; the solvent comprises polyoxyethylene sorbitan trioleate having an average of about 20 units of ethylene oxide in the polyoxyethylene chains and polyethylene glycol monolaurate wherein the polyethylene glycol has an average molecular weight of about 400; and the propellant comprises difluoroethane and n-butane.
9. A composition as claimed in any one of Claims 1 to 8 wherein the polyoxyethylene sorbitan trioleate comprises about 40% to about 60% of the solvent; the difluoroethane comprises about 35% to about 70% of the propellant; and the propellant comprises about 45% to about 55% of the composition.
10. A liquid anaesthetic composition in an aerosol container comprising a single phase mixture of a propellant and a water washable base comprising benzocaine in a solvent, wherein the base comprises by weight about 20% benzocaine, about 40% polyoxyethylene sorbitan trioleate having an average of about 20 units of ethylene oxide in the polyoxyethylene chains and about 40% polyethylene glycol monolaurate, the polyethylene glycol having an average molecular weight of about 400; the propellant comprises about 50:50 by weight mixture of difluoroethane and n-butane; and wherein each of the base and propellant comprise about 50% of the composition.
11. A liquid anaesthetic composition substantially as hereinbefore described with reference to any one of Examples 1 to 6, 10 to 16, 21 to 25, 27 to 34, 36 and 38 to 41.

