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ORAL PROPHYLACTIC COMPOSITIONS COMPRISING A BETAINE DERIVATIVE

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The present invention relates to new and improved preparations for oral hygiene, and more particularly to compositions for restricting the formation of acids within the oral cavity.

The study of oral hygiene has gone forward rapidly within recent years, and there is now a considerable body of laboratory and theoretical support for the theory that the formation of acids within the oral cavity is largely responsible for tooth decay, which is one of the principal health problems encountered therein. The precise mechanism for acid formation has not yet been established, and the chemical system involved is so exceedingly complex that many measures which might be expected to be of benefit are in fact ineffective. For instance, the use of a simple alkaline wash neutralizes acids, but is effective to maintain alkaline conditions for only a short while. Similarly, the use of a neutral or alkaline buffer is also of short-term benefit. It is now believed that the production of acid arises through bacterial and/or enzymatic action, and that the inhibition thereof may require a treating agent which will not only overcome these factors, but which will persist within the mouth over an extended period of time.

It is therefore an object of my invention to provide an effective oral prophylactic agent.

Another object is to provide an inhibitor of acid formation in the oral cavity which will retain its effectiveness over an extended period of time.

A further object is to provide a tooth paste, a tooth powder, and a mouth wash having prolonged acid-inhibiting properties.

I have discovered that the formation of acid within the oral cavity is effectively inhibited for a period of 24 hours or more by treating the surfaces thereof with a minute quantity of a betaine derivative of a class to be defined hereinafter. These substances are effective for the desired purpose when employed in a concentration above about 200 parts per million in a suitable treating solution, or when incorporated into the buccal fluids in at least such concentration.

In one embodiment, my invention is a tooth paste of conventional formulation, suitable for packaging in collapsible tubes, containing between about 0.05 and about 5% by weight, preferably between about 0.1 and about 2% by weight, of a betaine derivative of the defined class.

In another embodiment, my invention is a tooth powder of conventional composition, to which has been added between about 0.05 and about 5% by weight, preferably between about 0.1 and about 2% by weight, of a betaine derivative of the defined class.

In another embodiment, my invention is a mouth wash, of conventional formulation, containing between about 0.02 and about 1% by weight, of a betaine derivative of the defined class.

The betaine derivatives employed in my invention belong to the class of C_{10}–C_{18} alkyl esters and the C_{10}–C_{18} alkylamides of the trimethylbetaines of the C_2 and C_3 aminoalkanoic acids. Thus, they have the following structural formula:

$$(CH_3)_3N^+—R—CO—Y$$

where R is C_1 or C_2 alkylene, and where Y is C_{10}–C_{18} alkoxy or C_{10}–C_{18} alkylamino, preferably n-alkoxy or n-alkylamino. The aminoalkanoic acids involved therein are glycine, alanine, or beta-alanine. Inasmuch as the betaine nitrogen is strongly cationic, the compound must also include an anion, preferably chloride or hydroxide, for electrical neutrality. The defined substances are by no means identical in effectiveness, but vary from species to species in their ratings with respect to the desired properties. I prefer to employ the glycine betaines, and my best results have been obtained with glycine betaine decyl ester chloride and glycine betaine tetradecylamide chloride. When used herein without qualification, the term "betaine" is intended to refer to the trimethylbetaine of glycine.

My new inhibitors for oral acid formation are useful in general in conjunction with preparations intended for application to the oral cavity, and may therefore be prepared in the form of tooth pastes or other creams, tooth powders, lozenges, liquid dentrifrices, mouth washes, and the like. The active substances of my invention owe their prophylactic effectiveness to the fact that they inhibit the growth of bacteria, they adhere to the mucin plaque and are thus maintained in effective contact with the dental surfaces, they do not dissolve calcium or permit it to be dissolved, and they do not permit the pH of the oral fluids to drop more than transiently below about 6.

The compositions employed in my invention were shown to be excellent inhibitors of acid formation in saliva by the following series of tests. Saliva from a number of subjects was collected by paraffin stimulation, pooled, and measured into ten-milliliter portions. To each portion were added 0.1 gram of glucose and 0.1 gram of powdered human tooth enamel. A series of test mixtures was prepared by adding test inhibitor to the saliva mixtures in a range of concentrations. An equal number of saliva mixtures were allowed to remain inhibitor-free as controls. The test mixtures and controls were sampled (2 milliliters) for calcium analysis, then shaken and incubated at a temperature of 37° C. for four hours, after which they were centrifuged and again sampled. For the calcium analysis, 3 milliliters of a 4% ammonium oxalate solution were added to each 2-milliliter analytical sample and the mixture was allowed to stand for 45 minutes. The mixture was then centrifuged for 30 minutes and the clear supernatant liquid was gently poured off. The centrifuge tube was allowed to drain for five minutes and the precipitate was washed with 5 milliliters of 2% ammonium hydroxide and recentrifuged. The washed calcium oxalate precipitate was dissolved in 2 milliliters of 1.0 N sulfuric acid, heated on a steam bath, and titrated with 0.01 N potassium permanganate. The amount of

calcium was calculated in terms of milligrams per 100 ml. of saliva. The relative calcium content of the control and test samples before and after incubation are a measure of the amount of acid formed by the saliva-glucose mixture under the test conditions, and conversely a measure of the acid-inhibiting power of the test inhibitor. The following are the results of the tests:

Inhibitor	Inhibitor Concentration in Saliva, mg./100 ml.	Calcium in Saliva, mg./100 ml.		
		Before Incubation	After Incubation	
			Control	Test
Betaine n-decyl ester chloride.	50	6.5	18.4	3.7
		6.0	18.2	3.5
	10	7.5	20.5	6.3
		7.0	20.6	6.8
	1	5.0	14.9	10.0
		4.8	14.5	10.2
Betaine n-dodecyl ester chloride.	50	6.5	18.4	6.1
		6.0	18.2	6.5
	10	7.0	20.5	20.0
		7.5	20.6	20.2
Betaine n-tetradecyl ester chlorde.	50	6.0	19.2	3.2
		6.2	19.3	3.3
	10	5.0	14.9	5.4
		4.8	14.5	5.6
	1	4.8	15.3	12.6
		4.3	15.4	13.1
Betaine n-decylamide chloride.	50	6.0	19.2	3.0
		6.2	19.3	3.2
	10	5.5	15.5	7.5
		6.2	15.8	7.2
	1	7.5	20.5	10.3
		7.0	20.6	10.5
Betaine n-tetradecylamide chloride.	50	6.0	19.2	5.3
		6.2	19.3	6.2
	10	7.5	20.5	4.5
		7.0	20.6	4.7
	1	5.0	14.9	9.1
		4.8	14.5	9.4
Betaine n-octadecyl ester chloride.	50	6.5	18.4	4.8
		6.0	18.2	5.1
	10	7.5	20.5	17.0
		7.0	20.6	17.8
Betaine n-hexadecylamide chloride.	10 ml. sat. soln.	6.5	18.4	7.2
		6.0	18.2	7.4
	1 ml. sat. soln.	7.5	20.5	11.0
		7.0	20.6	11.3
Betaine n-octadecylamide chloride.	10 ml. sat. soln.	6.0	19.2	4.8
		6.2	19.3	4.5
	1 ml. sat. soln.	5.0	14.9	5.0
		4.8	14.5	5.1

As a measure of the persistence of my new inhibitors on the dental surfaces, the following casein-adherence tests were carried out:

One gram of casein was placed in 50 ml. of a 0.25% water solution of the test material and shaken at room temperature for 10 minutes. The casein was allowed to settle, the test solution was decanted, and the casein was washed ten times by adding 50 ml. of water, shaking in a mechanical shaker for 5 minutes, and decanting. After the last wash, the suspension was filtered and the casein was dried for 30 minutes at 100° C., then stored in a desiccator until needed.

The treated casein was tested for acid-inhibiting properties in Snyder's medium, which is a well known dextrose-agar culture medium adjusted to pH 4.8–5.0 and containing brom cresol green as an indicator. This medium, when incubated with caries-active saliva, will ordinarily turn from green to yellow within 24 hours because of acid formation. The tests were carried out as follows. Into 10 ml. of liquefied Snyder's medium were placed 0.1 gram of the treated and dried casein and 0.2 ml. of caries-active saliva. The mixture was shaken and allowed to solidify, after which it was incubated for 48 to 72 hours at 37.5° C. A control tube of Snyder's medium, plus the saliva, plus 0.1 gram of washed, untreated casein was also incubated. The tubes were examined at 24, 48, and 72 hours. The results are reported in the following table, where a complete change in color is indicated by ++, a change around the casein only by +, a change above the casein mass by ±, and no change is considered negative.

Inhibitor	Color Change		
	24 hr.	48 hr.	72 hr.
Tetradecyl betaine amide	±	+	++
Betaine decyl ester chloride	−	±	+
Betaine tetradecyl ester chloride	+	++	++
Control	++	++	++

The actual inhibition of acid formation on tooth surfaces by the compositions of my invention was demonstrated by means of the seven-day plaque pH test of Fosdick et al., Journal of Dental Research, 32 (August 1953), pages 486–496. The tests were carried out at two levels, 0.1% and 0.5% by weight, the test inhibitor in each case being betaine decyl ester chloride. In each series of tests, a group of individuals brushed their teeth twice a day in the conventional manner with a toothpaste of conventional composition to which the test inhibitor had been added. Several hours after the teeth had been brushed, the pH of the dental plaque was measured. The mouth was then rinsed with a 50% glucose solution, and the pH measurements were repeated at the end of 5, 10, 15, and 20 minutes. The drop in pH in each case was a measure of the amount of acid formation, and conversely of the effectiveness of the inhibitor. The results are reported as average pH values for the test group before the use of the inhibited toothpaste had been started ("0 days of use") and at the end of 7 days. The results of three series of tests were as follows:

Inhibitor Conc'n	No. of Cases	Days of Use	Before Sucrose	After Sucrose			
				5 min.	10 min.	15 min.	20 min.
0.1 wt.-percent	8	0	5.8	5.7	5.2	5.5	5.8
		7	6.0	5.7	5.8	6.1	6.0
0.5 wt.-percent	8	0	6.5	6.0	5.6	5.6	5.7
		7	6.2	6.1	5.8	6.0	6.1
0.5 wt.-percent	16	0	6.0	5.5	5.25	5.4	5.8
		7	6.6	6.4	6.2	6.2	6.4

PREPARATION OF ADDITIVES

The betaine esters and amides employed in my invention are conveniently prepared by reacting an anhydrous betaine hydrochloride with thionyl chloride to produce the corresponding betaine acid chloride, then reacting the latter with an alcohol to yield an ester, or with an amine in the presence of a hydrogen chloride acceptor to yield an amide:

$$(CH_3)_3N{-}CH_2{-}COOH + SOCl_2 \longrightarrow (CH_3)_3N{-}CH_2{-}COOCl + SO_2 + HCl$$

$$(CH_3)_3N{-}CH_2{-}COCl + ROH \longrightarrow (CH_3)_3N{-}CH_2{-}COOR\,HC$$

$$(CH_3)_3N{-}CH_2{-}COCl + RNH_2 \longrightarrow (CH_3)_3N{-}CH_2{-}CONHR + HCl$$

PREPARATION OF BETAINE ACID CHLORIDE

The reaction is carried out in a glass-lined reaction vessel, equipped with a jacket for heating and cooling, an agitator, a reflux condenser protected against ingress of atmospheric moisture, and suitable temperature-measuring means. Into the vessel are charged 8 moles (1232 parts by weight) of oven-dried (105° C.), pulverized glycine betaine hydrochloride and 9.5 moles (1140 parts) of thionyl chloride. The mixture is stirred and heated slowly. When the internal temperature reaches 68° C., a copious evolution of SO_2 and HCl takes place, and the mass becomes pasty. By the end of the first 20 minutes of heating and stirring, the mixture is ordinarily quite fluid. If it is not, then an additional mole or

slightly more (120 to 160 parts) of $SOCl_2$ should be added. The temperature is maintained at 68–70° C. for 1.5 hours.

The betaine acid chloride is extremely unstable to moisture, and should be carefully protected during further treatment. The following isolation technique is suitable. At the end of the heating period, a sufficient volume of hot (80° C.) toluene is added to the reaction vessel to cover the melt with a ½ to 2-inch layer. The entire hot mixture is then run into a stirred, enclosed crystallizer of conventional design, and the melt is stirred slowly but continuously until the entire mass has crystallized. The toluene protects the betaine acid chloride during this operation from any moisture in the overlying atmosphere and simultaneously removes the excess thionyl chloride, while the stirring prevents the betaine acid chloride from setting into a solid mass, which could not be pulverized without exposure to air and consequent reversion to betaine hydrochloride. The toluene is decanted, fresh toluene is added, the mixture is heated sufficiently to melt the mass, and the melt is allowed to cool with stirring as described above. This washing process with toluene is repeated a third time to assure the complete removal of thionyl chloride. The final slurry of crystals and toluene is spun in a closed centrifuge, and the crystals are dried in a vacuum oven at 50° C.

Other methods for preparing and isolating betaine acid chlorides are described in U.S. Patents 2,359,863 and 2,429,171, British Patents 589,232 and 590,727, and elsewhere in the art.

PREPARATION OF BETAINE ESTERS

Into the glass-lined reaction vessel, described above, are charged 500 parts by weight of ethylene chloride and 0.5 mole of the desired alcohol. Additional solvent is added if required for complete solution of the alcohol. Betaine acid chloride (0.6 mole) is then quickly added, and an exothermic reaction starts immediately. After the reaction has subsided, the mixture is heated to reflux temperature and refluxed overnight. The copiously escaping HCl fumes are led off through the reflux condenser to recovery. The reaction product is filtered hot. The filtration solids are betaine hydrochloride which, after being dried, can be recycled for the preparation of betaine acid chloride. The filtrate is decolorized with charcoal, then crystallized at reduced temperature. The crystals are filtered off, the mother liquor is concentrated, and a second crop of crystals is obtained. The combined crystals are recrystallized twice from ethylene chloride.

Purified esters of glycine betaine chloride, prepared as described above, were found to have the following properties:

Ester	N Analysis		Cl Analysis		Softening Pt., °C.	Melting Pt., °C.
	Theo., percent	Found percent	Theo., percent	Found percent		
n-Decyl	4.77	5.02	12.11	11.65	-------	88–9
n-Dodecyl	4.33	4.45	11.05	10.85	84–5	159
n-Tetradecyl	4.00	4.22	10.17	9.57	99	148–9
n-Hexadecyl	3.70	3.82	9.41	9.11	80–1	130
n-Octadecyl	3.45	3.60	8.75	8.93	83	140–1

PREPARATION OF BETAINE AMIDES

Into the glass-lined reaction vessel, described above, are charged 0.3 mole of the appropriate amine (depending upon the amide to be prepared), 0.31 mole of dimethylaniline or other hydrogen chloride acceptor, and a sufficient quantity of ethylene chloride to effect complete solution thereof (e.g., about 1250 parts by weight of the solvent are required in producing the n-dodecyl and n-tetradecyl amides). The solution is warmed to 50° C., and 0.31 mole of betaine acid chloride is quickly added. The temperature is raised carefully to about 70–75° C., at which point the reaction starts and vigorous boiling occurs. Cooling is applied as required to control the reaction during the initial period, after which the mixture is refluxed for 2.5 hours. The completed reaction product is filtered hot to separate the solid phase, which is largely betaine hydrochloride and dimethylaniline hydrochloride.

The filtered product is cooled to crystallize the amide therefrom. After filtration the mother liquor is concentrated to one-fourth its volume and is cooled to obtain a second crop. The combined crystals are recrystallized three times from ethylene chloride.

Amides having the following properties were obtained from glycine betaine chloride:

Amide	N Analysis		Cl Analysis		Softening Pt., ° C.	Melting Pt., ° C.
	Theo., Percent	Found, Percent	Theo., Percent	Found, Percent		
n-Decyl	9.57	9.43	12.14	12.33	126–8	180–1
n-Dodecyl	8.74	8.54	11.08	10.92	135–6	186–6
n-Tetradecyl	8.04	7.89	10.19	10.31	125–6	183–5
n-Hexadecyl	7.44	7.34	9.43	10.01	115–8	194–5
n-Octadecyl	6.93	6.71	8.78	8.58	125–30	187–9

My new inhibitor compounds can satisfactorily be incorporated in any of the conventional preparations for oral and dental use without substantial modification thereof. Suitable formulas are disclosed, for example, by Bennett (The Chemical Formulary, New York: Van Nostrand, 1933, vol. I, pp. 388–391), by the National Formulary, and by numerous other standard references. The following specific examples are presented to illustrate and clarify the invention, and not by way of limitation. All quantities are expressed in terms of parts by weight unless otherwise noted.

Example I.—Dental cream

The following illustrates a suitable dental cream incorporating one of my new inhibitors:

	Parts
Betaine decyl ester chloride	0.5
Dicalcium phosphate dihydrate	35
Calcium carbonate	12
Glycerol	30
Irish moss	1
Saccharin	0.25
Flavoring oils	1
Preservative	Q.S.
Water	15

The glycerol, Irish moss, saccharin, flavoring oils, preservative, and water are mixed, gelled by kneading and heating to around 175° F., and blended to a smooth mass. The betaine ester is then added, followed by the calcium salts, and the preparation is completed in a conventional manner by cooling, milling, deaerating, straining, and filling into tubes. A cream of this type is highly effective for the purpose of reducing the formation of acidic substances in the oral cavity.

Numerous modifications of the foregoing formula will be apparent to those skilled in the art. The dicalcium phosphate and the calcium carbonate are replaceable mutually or by other abrasive materials such as insoluble sodium phosphate, aluminum phosphate, iron phosphate, diatomaceous earth, or the like. The glycerol can be replaced wholly or in part by sorbitol, propylene glycol, polyethylene glycols, or the like. The Irish moss functions as a gelling agent, and can be replaced or supplemented with gum tragacanth, sodium carboxymethylcellulose, starch phosphate, sodium alginate, and the like. The saccharin can be replaced by sugar or other sweetening agent. When such modifications are made, it is ordinarily desirable to adjust the relative

quantities of the ingredients to obtain a smooth, stable cream of the desired characteristics.

Example II.—Dental cream

	Parts
Betaine tetradecylamide chloride	1
Calcium sulfate	82
Calcium chloride	1.5
Powdered neutral white soap	15
Gum tragacanth	2
Glycerol	41
Saccharin	0.2
Flavor	2
Water	37

Example III.—Tooth powder

Betaine lauryl ester chloride	1
Hard soap, powdered	5
Calcium carbonate, precipitated	95
Saccharin	0.2
Flavor	1.5

Example IV.—Tooth powder

Betaine dodecylamide chloride	2
Dicalcium phosphate dihydrate	75
Calcium carbonate	25
Saccharin	0.2
Flavor	2

Example V.—Liquid dentifrice

Betaine decyl ester chloride	2
Sodium carboxymethylcellulose	4
Flavor	0.5
Water	93.5

Example VI.—Mouth wash

Betaine tetradecylamide chloride	0.2
Saccharin	0.02
Flavor	0.2
Ethyl alcohol	10
Water	90

While I have described my invention with reference to certain specific embodiments thereof, it is to be understood that such examples are offered solely by way of illustration and not with any intent to limit the invention to less than the broad scope thereof otherwise disclosed herein. Furthermore, numerous modifications and equivalents of the invention will be apparent from the foregoing description to those skilled in the art.

In accordance with the foregoing description, I claim as my invention:

1. An oral prophylactic composition containing, as an inhibitor for acid formation within the oral cavity, a substance selected from the group consisting of the C_{10}–C_{18} alkyl esters and the C_{10}–C_{18} alkylamides of the trimethylbetaines of the C_2 and C_3 aminoalkanoic acids.

2. An oral prophylactic composition containing, as an inhibitor for acid formation within the oral cavity, a substance selected from the group consisting of the C_{10}–C_{18} alkyl esters and C_{10}–C_{18} alkylamides of betaine.

3. A dental preparation containing a proportion of a C_{10}–C_{18} alkyl ester of betaine effective to inhibit acid formation within the oral cavity.

4. The composition of claim 3 wherein said ester is betaine decyl ester chloride.

5. A dental preparation containing a proportion of a C_{10}–C_{18} alkylamide of betaine effective to inhibit acid formation within the oral cavity.

6. The composition of claim 5 wherein said amide is betaine tetradecylamide chloride.

7. A dental cream containing between about 0.05 and about 5% by weight of a substance selected from the group consisting of the C_{10}–C_{18} alkyl esters and the C_{10}–C_{18} alkylamides of the trimethylbetaines of the C_2 and C_3 aminoalkanoic acids.

8. A dental cream containing between about 0.1 and about 2% by weight of a C_{10}–C_{18} alkyl ester of betaine.

9. A dental cream containing between about 0.1 and about 2% by weight of betaine decyl ester chloride.

10. A dental cream containing between about 0.1 and about 2% by weight of a C_{10}–C_{18} alkylamide of betaine.

11. A dental cream containing between about 0.1 and about 2% by weight of betaine tetradecylamide chloride.

12. A tooth powder containing a substance selected from the group consisting of the C_{10}–C_{18} alkyl esters and the C_{10}–C_{18} alkylamides of the trimethylbetaines of the C_2 and C_3 aminoalkanoic acids in a proportion effective to inhibit the formation of acid within the oral cavity.

13. A liquid dentifrice containing a substance selected from the group consisting of the C_{10}–C_{18} alkyl esters and the C_{10}–C_{18} alkylamides of the trimethylbetaines of the C_2 and C_3 aminoalkanoic acids in a proportion effective to inhibit the formation of acid within the oral cavity.

14. A mouth wash containing a substance selected from the group consisting of the C_{10}–C_{18} alkyl esters and the C_{10}–C_{18} alkylamides of the trimethylbetaines of the C_2 and C_3 aminoalkanoic acids in a proportion effective to inhibit the formation of acid within the oral cavity.

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UNITED STATES PATENT OFFICE

Certificate of Correction

Patent No. 2,888,383 May 26, 1959

Harold J. Byrne

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

Column 3, line 25, in the table, first column thereof, third item, for the portion reading "chlorde" read —chloride—; column 4, lines 56 and 57, the formula should appear as shown below instead of as in the patent:

$$(CH_3)_2N-\underset{Cl}{CH}-COCl+ROH \longrightarrow (CH_3)_2N-\underset{Cl}{CH_2}-COOR+HCl$$

Signed and sealed this 19th day of January 1960.

[SEAL]

Attest:
KARL H. AXLINE,
Attesting Officer.

ROBERT C. WATSON,
Commissioner of Patents.