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DENTAL PREPARATIONS CONSISTING ESSENTIALLY OF A FLUORIDE COMPOUND AND A SARCOSIDE COMPOUND TO REDUCE THE FLUORIDE TOXICITY

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The present invention relates to a dental preparation comprising in combination a fluoride compound which releases fluoride ions in water and a higher aliphatic acyl amide of an amino carboxylic acid compound, as hereinafter described and claimed.

It has been found that improved dental preparations may be obtained by a combination of said fluoride compound and said higher aliphatic acyl amide of an amino carboxylic acid compound. The combination of these two ingredients, possesses a number of unusual and desirable characteristics and superior effects. A dental preparation containing these essential ingredients exhibits a prolonged and marked effect in the inhibition of acid produced from fermentable carbohydrates by the bacteria in the oral cavity and a superior anti-bacterial effect against the oral flora, in addition to exerting a marked reduction in the solubility of tooth enamel in acid solutions. There is achieved a simultaneous adsorption of the fluoride primarily upon the inorganic material or tooth structure and of the amide primarily upon the organic material such as dental plaque. The result is a dual protective function against the acid-producing bacteria combined with an increase in the resistance of the tooth enamel to acid, both properties being highly desirable for the proper care of the teeth. Such unitary result is unique with this specific combination, and not exhibited with the substitution of other materials such as sulfonated detersive compounds in place of the amides.

In addition to the above properties, it has been found that the addition of the amide compound to the fluoride compound affects the pharmacological activity of the mixture in a favorable and beneficial manner, and in a manner which is ordinarily not predictable from a consideration of the pharmacological or biological properties of the individual materials. More particularly, the pharmacological properties or toxicity of the soluble fluoride salts such as sodium fluoride is known. On the other hand, sodium N-lauroyl sarcoside and like amide compounds are relatively non-toxic. It has been found that the combination of the sodium fluoride and sodium N-lauroyl sarcoside is considerably less toxic than the mathematically derived potency of the mixture calculated from the results obtained by the use of the materials individually.

These results were obtained using standard testing methods known in the art. For example, groups of albino rats were administered orally sodium fluoride alone, sodium N-lauroyl sarcoside alone, and a combination of sodium fluoride and sodium lauroyl sarcoside in the ratio of 1:10 by weight. In this manner, toxicity data were obtained on animals using these three sample materials. It was found that the acute oral LD_{50} of the sodium fluoride when used alone was 195 milligrams per kilogram, the acute oral LD_{50} of the sodium N-lauroyl sarcoside was 1740 milligrams per kilogram, and the combination of these two ingredients, viz. the mixture of the fluoride and sarcoside materials, had an acute oral LD_{50} of 1390 milligrams per kilogram.

In order to determine if the mixture produced an additive, synergistic or antagonistic effect, the technique used by Finney in his second edition of Probit Analysis

was used. Based upon said analysis using the data obtained by use of the fluoride and sarcoside individually, it was found that the calculated value of the acute oral LD_{50} for the combination of the fluoride and the sarcoside materials was 1010 milligrams per kilogram. In contrast thereto, it was found that the actual LD_{50} for the combination was 1390 milligrams per kilogram. Therefore, a mixture of the two compounds is 37.5% less toxic than expected.

Similar results were obtained using a combination of stannous fluoride and sodium N-lauroyl sarcoside in a 1:5 ratio by weight. It was found that the actual acute oral LD_{50} of this mixture was 34.4% less toxic than expected as compared to the calculated oral LD_{50} for this combination as determined from the results obtained by the use of the ingredients separately in the same type of animal tests. It is apparent that, when either the sodium fluoride or stannous fluoride was combined with said sarcoside, the action of the two ingredients in each combination is antagonistic to a significant degree, resulting in a beneficial effect on the toxicity of the mixture.

Thus, the present invention relates to a dental preparation comprising said amide and fluoride in a ratio greater than 1:1 by weight, said mixture decreasing the solubility of tooth enamel in acid solution and inhibiting the formation of acid by the oral bacteria, said amide and fluoride compounds being antagonistic pharmacologically as to result in a beneficial effect on the toxicity of the mixture. Various preferred embodiments will be apparent in the following description.

As described in my patent, U.S. Patent No. 2,689,170, issued September 14, 1954, the suitable amide compounds are the substantially saturated higher aliphatic acyl amides of a saturated aliphatic monoaminocarboxylic acid compound having 2 to 6 carbon atoms, the acyl group having about 12 to 16 carbon atoms. Optimum results are achieved with the dodecanoyl, tetradecanoyl, hexadecanoyl derivatives, with the preferred amides having the formula:

$$R{-}CO{-}\underset{\displaystyle R'}{\underset{|}{N}}{-}CH_2{-}COOX$$

wherein R—CO— is a saturated fatty acyl radical of about 12 to 16 carbon atoms, R' is hydrogen or a lower alkyl group and X is hydrogen or a cation which forms water-soluble salts. It is preferred particularly to employ the N-lauroyl, myristoyl and palmitoyl sarcosides and sodium N-lauroyl sarcoside has been used in commercial practice.

These compounds may be produced by the condensation of a higher fatty acylating substance with the suitable amino compound. The amino acid portion of these active ingredients is generally derived from the lower aliphatic saturated monoaminocarboxylic acids having about 2 to 6 carbons, usually the monocarboxylic acid derivatives.

Such amides of amino carboxylic acid compounds are to be employed generally in the form of their free acids or preferably as the water-soluble salts thereof. In general, the desired salts are the water-soluble carboxylate salts such as the alkali metal (e.g. sodium, potassium), ammonium, amine and alkylolamine (e.g. mono-, di-, triethanolamine). Further specific examples are sodium N-lauroyl sarcoside, potassium N-lauroyl sarcoside, sodium N-myristoyl sarcoside, sodium N-palmitoyl sarcoside, ethanolamine N-lauroyl sarcoside, N-lauroyl sarcosine, sodium N-lauroyl ananine, and sodium N-lauroyl glycide. For convenience herein, reference to "amino carboxylic acid compound," "sarcoside," "glycide," etc., refers to such compounds having a free carboxylic group or the water-soluble carboxylate salts.

These amides are utilized in pure or substantially pure

form. They should be substantially free from soap or similar higher fatty acid material which is formed in commercial methods of manufacture and which tends to neutralize or substantially reduce the special characteristics which are exhibited by these amide compounds. In usual practice, the amount of higher fatty acid material should be less than 15% by weight of the amide compound and insufficient to substantially adversely affect said amide, and preferably less than about 10% of said amide compound.

Any suitable fluoride compound may be used and such materials which inhibit the solubility of tooth enamel in acid solution are known in the art. Laboratory tests are known for evaluating the reduction in enamel solubility after exposure to the fluoride compound. In general, the compounds should release fluoride ions in water, though the fluoride compound may be of slight or limited solubility or fully water-soluble in solution. It is preferred to use the inorganic fluoride salts, such as the suitable alkali metal, alkaline earth metal and heavy metal salts. Suitable examples are sodium fluoride, potassium fluoride, ammonium fluoride, lead fluoride, a copper fluoride such as cuprous fluoride, zinc fluoride, a tin fluoride such as stannic fluoride, stannous fluoride, potassium stannous fluoride ($SnF_2 \cdot KF$), or stannous chlorofluoride; barium fluoride, sodium fluosilicate, ammonium fluosilicate, aluminum mono- and di-fluorophosphate, fluorinated sodium calcium pyrophosphate, and the like. Optimum results are achieved with the alkali metal and tin fluorides, such as sodium and stannous fluorides, and mixtures thereof.

The amide material and fluoride exert their beneficial effects in variable proportions depending up on the specific type of composition and presence of other ingredients. A simple mixture of these two essential components may be used as an active dental mixture either in solid form or as an aqueous solution, suspension or slurry by the consumer or in dental practice. The relative proportions, however, are significant in order to obtain optimum effects. The amount of the amide compound should be greater than the weight of the fluoride compound in the mixture, and accordingly the ratio of the amide to fluoride should be greater than 1:1 by weight. In the examples infra, the ratio varies from about 2:1 to about 30:1 which is the preferred range.

The amount of fluoride compound is dependent to some extent upon the type of fluoride compound, its solubility and type of dental composition, but should be an effective but non-toxic amount. As indicative thereof, a 2% aqueous solution of sodium fluoride has been used for topical application which is equivalent to about 1% fluoride ion in solution and to which the amide compound may be added in suitable proportion. It is considered that an amount of fluoride compound releasing a maximum of 0.1% fluoride ion in a 20% aqueous slurry of a tooth-paste or a toothpowder will be used generally. Any suitable minimum amount of fluoride will be used but it will be usual to employ an amount releasing a minimum of 0.0001% fluoride ions under the above-indicated conditions. In the case of a dentifrice composition, it is preferred that the amount of fluoride compound be up to about 2% by weight, and usually within the range of 0.05 to about 1% by weight.

The amide material may be present in any suitable proportion. In general, it will be a minor amount of a dentifrice composition, such as at least about 0.05%, and preferably from about 0.1 to about 10% by weight of the composition. In the case of dentifrices such as dental creams, it is usual to use about 0.5 to about 5% by weight of the amide.

This combination of ingredients may be utilized in any preparations designed for application to the oral cavity which are referred to herein as dental preparations. Such dental preparations include suitable toothpastes or dental creams, tooth powders, liquid dentifrices, mouth washes or rinses, lozenges, tablets, chewing gum, dental floss and the like.

Any suitable water-insoluble polishing agent may be admixed with this novel combination in the preparation of the dentifrice compositions such as tooth powders, pastes, cream and the like. It is understood, of course, that the polishing material will be selected so as to be compatible with the fluoride compound. Such fluoride-compatible polishing agents and mixtures are known. There is a relatively large number of polishing materials known in the art, including for example, calcium phosphates such as dicalcium phosphate, aluminum hydroxide or alumina, magnesium carbonate, bentonite, including suitable mixtures thereof. Among the typical polishing agents are the insoluble polyphosphates. The insoluble polyphosphates may be considered as derived from the ortho-phosphates by dehydration or elimination of bound water (other than any water of hydration) from the molecule by heating at suitable temperatures, and have been referred to as condensed or molecularly-dehydrated phosphates. These insoluble polyphosphates are preferably the alkaline earth salts (e.g. calcium) of the polyphosphoric acids, such as pyrophosphoric, polymetaphosphoric, triphosphoric acids and the like. Further examples of suitable materials are calcium pyrophosphate, sodium calcium pyrophosphate, calcium polymetaphosphate, magnesium pyrophosphate, calcium tri-phosphate, and the like. As indicated, mixed salts containing calcium and other metal cations may be used also. In general, these polishing agents will comprise a major proportion by weight of the solid ingredients. The polishing agent content in a dentifrice is variable, but will generally be from about 20% to about 99% by weight of the total composition. In the case of a dental cream such polishing agents will generally be about 20–75% whereas in tooth powders the polishing agents will usually be in greater proportion such as about 70–95% by weight.

In the preparation of tooth powders, it is usually sufficient to mechanically admix the various solid ingredients.

In dental cream formulations, the liquids and solids should necessarily be proportioned to form a creamy mass of desired consistency which is extrudible from a collapsible tube. In general, the liquids in the dental cream will comprise chiefly water, glycerine, sorbital, propylene glycol or the like, including suitable mixtures thereof. It is advantageous usually to use a mixture of both water and a humectant or binder such as glycerin or sorbital. The total liquid content will generally be about 20–75% by weight of the formulation. It is preferred to use also a gelling agent in dental creams such as the natural and synthetic gums and gum-like materials, e.g., Irish Moss, gum tragacanth, sodium carboxymethylcellulose, polyvinylpyrrolidone, starch and the like, usually in an amount up to about 10% and preferably about 0.5–5% by weight of the formulation.

Other types of dental preparations will be formulated in known manner also.

Various other adjuvant materials may be incorporated in such dental preparations. Added materials in the formulation which do not substantially adversely affect the properties and characteristics may be suitably selected and used in proper amount depending upon the particular type of preparation. Such materials may be used as soluble saccharin, flavoring oils (e.g. oils of spearmint, peppermint, wintergreen), coloring or whitening agents (e.g. titanium dioxide), preservative (e.g. sodium benzoate), emulsifying agents, silicones, alcohols, menthol, chlorophyll compounds (e.g. sodium copper chlorophyllin), and the like. There may be added various ammoniated ingredients such as urea, diammonium phosphate and mixtures thereof which are designed to release ammonia in the mouth. Typical formulations include dentifrices containing 3% of urea and 5% diammonium phosphate, or 10–25% urea with 5% diammonium phosphate. Anti-

biotics such as penicillin, tetracycline and tyrothrycin may be added also.

The pH of the final formulations of the present invention is variable and, therefore, the products may have any suitable pH value in solution compatible with the stability of the materials. Where reference is made to pH values it has reference to the pH as determined on a liquid product per se, and in the case of a dental cream or powder or similar product as determined on a 20% aqueous slurry or mixture of said cream or powder. Thus it is generally desired that the pH of the product under the testing conditions indicated be within the range from about 5 up to about 10, and preferably from about 5.5 to 9 with optimum desired effects at a substantially neutral pH value in solution, e.g. about 6 to 8.

The following specific examples are further illustrative of the nature of the present invention, but it is to be understood that the invention is not limited thereto. The compositions are prepared in the usual manner and all amounts of the various ingredients are by weight unless otherwise specified.

EXAMPLE I

Dental Cream

	Percent
Sodium N-lauroyl sarcoside	2.0
Sodium fluoride	0.2
Calcium pyrophosphate	50.8
Glycerine	30.4
Water	14.2
Irish moss gum	0.7
Soluble saccharin	0.2
Sodium benzoate	0.5
Flavor	1.0
	100.0

EXAMPLE II

Dental Cream

Sodium N-lauroyl sarcoside	2.0
Sodium fluoride	0.2
Sodium calcium pyrophosphate	48.4
Sodium carboxymethylcellulose	0.6
Glycerine	30.4
Water	16.8
Soluble saccharin	0.2
Sodium benzoate	0.5
Flavor	0.9
	100.0

EXAMPLE III

Dental Cream

Sodium N-lauroyl sarcoside	2.0
Sodium fluoride	0.1
Alumina	38.0
Silica gel	10.0
Glycerine	24.0
Water	22.9
Sodium carboxymethylcellulose	0.4
Soluble saccharin	0.2
Sodium benzoate	0.5
Titanium dioxide	1.0
Flavor	0.9
	100.0

EXAMPLE IV

Tooth Powder

Sodium N-lauroyl sarcoside	4.1
Stannous fluoride	0.2
Dicalcium phosphate dihydrate	86.0
Magnesium silicate	7.0
Soluble saccharin	0.2
Flavor	2.5
	100.0

EXAMPLE V

Mouth Wash

Sodium N-lauroyl sarcoside	0.1
Sodium fluoride	0.05
Ethyl alcohol	10.0
Flavor	0.15
Soluble saccharin	0.01
Water	Balance

EXAMPLE VI

Chewing Gum

Sodium N-lauroyl sarcoside	0.5
Sodium fluoride	0.1
Gum base, e.g. chicle	20.0
Sucrose	60.0
Corn syrup	18.4
Flavor	1.0
	100.0

EXAMPLE VII

Liquid Dentifrice

Potassium N-lauroyl sarcoside	6.0
Stannous chlorofluoride	0.2
Ethyl alcohol	10.0
Sodium carboxymethylcellulose	2.0
Flavor	0.5
Distilled water	Balance

The present application is a continuation-in-part of copending application S.N. 467,623, filed November 8, 1954, now abandoned, which is a continuation-in-part of application S.N. 454,633, filed September 7, 1954, now abandoned, said application S.N. 454,633 being a division of application S.N. 271,864, filed February 15, 1952, now U.S. Patent No. 2,689,170, issued September 14, 1954.

Although the present invention has been described with reference to particular embodiments and examples, it will be apparent to those skilled in the art that variations and modifications of this invention can be made and that equivalents can be substituted therefor without departing from the principles and true spirit of the invention.

Having thus described the invention what is claimed is:

1. A dental preparation consisting essentially of a fluoride compound selected from the group consisting of alkali metal fluorides and stannous fluorides, and a sarcoside compound selected from the group consisting of saturated higher fatty acid sarcosine and water-soluble salts thereof having about 12 to 16 carbon atoms in the acyl group and less than 15% by weight based on said sarcoside of higher fatty acid material, the amount of said higher fatty acid material being insufficient to substantially adversely affect said sarcoside, the ratio of said sarcoside compound to fluoride compound being about 2:1 to 30:1 by weight, said sarcoside being non-toxic and modifying the toxicity of the fluoride to produce a reduced toxicity effect.

2. A dental preparation consisting essentially of a fluoride compound selected from the group consisting of alkali metal fluorides and stannous fluorides, a water-soluble salt of N-lauroyl sarcosine having less than 10% by weight of higher fatty acid material based on said sarcosine compound, the ratio of said sarcosine compound to fluoride being from about 2:1 to 30:1 by weight, and water-insoluble polishing agent in an amount from about 20 to 99% by weight of the preparation, said sarcosine compound being non-toxic and modifying the toxicity of the fluoride to produce a reduced toxicity effect.

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