# PATENT SPECIFICATION

NO DRAWINGS

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**International Classification:—A61k.**


COMPLETE SPECIFICATION

## Oral Preparations

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with oral preparations that inhibit dental caries.

Within the last several decades the problem of inhibition of tooth decay has been extensively investigated by research workers in the field. It is recognized that there are numerous and complex variables associated with such biochemical phenomena which are of consideration in the etiology and control of dental caries. Among the myriad of factors of consideration have been the rate of acid formation and/or neutralization in the mouth; type of diet; character of enamel and saliva; presence of bacteria; and oral hygiene. It is generally accepted that the decalcification of tooth enamel characteristic of dental caries is caused to a large extent by the acids produced from the action of certain microorganisms, which are normally present in the mouth, e.g. in saliva, fermenting suitable carbohydrates in the mouth.

Dentifrice and like preparations used on the teeth and gums have been a partial aid in the cleaning of the teeth and mouth. From time to time the various proposals have been advanced relative to the development of "antiseptic" dentifrices and the like having allegedly the property of inhibition of tooth decay. Until recently, such claims were not substantiated by any factual evidence.

Within recent years it has been recognized that means for the prevention of tooth decay or at least its inhibition is a distinct possibility. The use of sodium fluoride by its addition to drinking water for a systemic effect or by topical application has received some degree of acceptance. Likewise, penicillin has been used experimently with some apparently desirable results, though this active ingredient may possess certain disadvantages such as sensitization of the patient, possibly rendering him susceptible to certain bacterial strains, etc.

Despite the extensive research relative to the theory of the cause, the nature and the inhibition of dental caries, it is recognized that the problem of reducing the incidence of caries by an effective dental preparation remains a challenging one. While a number of agents as indicated have been proposed as possibly preventing or neutralizing acid formation, either by the use of enzyme inhibitors or by direct bactericidal action on the microorganisms, the problem is rendered much more complex by the manner in which dentifrice preparations are conventionally used by the consumer. Thus, it is necessary for proper action that any effective substances should have a prolonged effect so that its introduction into the mouth once or twice a day will be sufficient to inhibit the degradation process during the day, if not for longer. In general, the proposed substances have been uniformly unsuccessful for any prolonged effect since their activity, if any, is generally persistent for only a short period of time, of the order of minutes. Thus, in addition to the need for the discovery of an effective agent, a primary difficulty is that some practicable means must be available whereby the inhibitor can be maintained at an effective concentration in the mouth at all times.

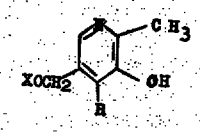
The problem is rendered even more complex by the necessity that the ingedient must possess certain requisite supplementary characteristics such as satisfactory properties from the viewpoint of oral toxicity, acute chronic toxicity, non-sensitization, and non-irritation to the mucous membranes, and perhaps an added beneficial effect on the oral epithelium.

The formulation and manufacture of dentifrice preparations, such as toothpastes, are

[*Price 3s. 6d.*]

highly varied in commence. The incorporation of an effective agent of the character indicated in such a preparation is usually beset with many difficulties peculiar to the agent. Thus, the other ingredients must be compatible with the active ingredient, which must be stable and active in the formulation; and considerations such as proper solubility characteristics, adequate concentration of solids, controlled foaming power, stability and homogeneity of the formulation at normal and reasonably adverse conditions, non-irritability, and a pleasant taste, are of prime concern also to the commercial practicality and acceptability of the product by the consumer.

In brief, the present invention provides an oral preparation as hereinafter defined containing as essential active ingredient a compound having the general formula



where R is a hydroxymethyl or aminomethyl group and X is a hydrogen atom, or R is a formyl group and X is a hydrogen atom or a phosphonyl group, or a salt or complex of such a compound.

The term 'oral preparation' is to be understood as meaning a dentifrice, mouth wash, chewing-gum or lozenge, but since it is highly desirable to have the active ingredient present in the oral cavity at all times or for extended periods, the preparations are preferably in the form of a lozenge which can be slowly dissolved in the mouth.

The term 'lozenge' is to be understood as meaning a solid mass containing a mucilaginous material such as gelatin, acacia or tragacanth, and at least one flavouring agent such as a sweetening agent, in addition to a compound as specified above.

Such lozenges can be in various shapes or forms such as flat, circular or rod-shaped.

The term 'dentifrice' is to be understood as meaning any of the conventional cleansing compounds such as pastes, creams, liquids and powders as well as compositions such as dental ointments and adhesives which are not necessarily considered cleansing compositions.

Compounds that can be used in the compositions of the invention include pyridoxine, pyridoxamine, codecarboxylase, pyridoxamine phosphate, vitamin $B_6$-borate complex, and pyridoxal, i.e., 2 - methyl - 3 - hydroxy - 4-formyl - 5 - hydroxymethyl pyridine and their salts such as the hydrochloride.

It is common to incorporate various adjuvant materials in oral preparations. The final dentifrice formulation may contain such materials in suitable amounts provided they are compatible with the active ingredient and the essential properties of the dentifrice preparations of the present invention. 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 can be used as soluble saccharin, flavouring oils (e.g. oils of spearmint, peppermint, wintergreen), colouring or whitening agents, (e.g. titanium dioxide), preservatives (e.g. sodium benzoate), alcohol, or methanol, in addition to other added materials which are described in the present specification.

Any suitable essentially water-insoluble abrasives or polishing agents can be used in dentifrice preparations such as tooth powders, pastes, creams and liquids as an aid in general cleansing. Among such abrasives are calcium carbonate, dicalcium phosphate, tricalcium phosphate, aluminium hydroxide, insoluble sodium metaphosphate, bentonite, and suitable mixtures of these agents. In general, these materials will usually comprise the major proportion of the solid ingredients. The amount, which is variable with respect to the abrasive effects desired and the particular type of preparation, will usually be from 5 to 95% by weight of the total composition and more particularly from about 20 to 75% in a dental cream.

In the preparation of tooth powders, it is usually sufficient to mechanically admix the various solid ingredients, the abrasives constituting the major amount, e.g. at least about 70%. In dental cream formulations, the liquids and solids must necessarily be proportioned to attain a creamy mass of desired consistency. In general, the liquids will comprise chiefly such materials as water, glycerin, sorbitol, propylene gylcol, including suitable admixtures of them. There is included within the scope of the invention both water-free and humectant-free creams. It is advantageous to use a mixture of both water and a humectant such as glycerin or sorbitol, in view of good consistency attainable initially and upon storage, since the hygroscopicity and plasticizing action of the mixture prevent appreciable hardening of the cream and help to maintain proper solubilization effects and relationships.

For optimum effects, the active ingredient should be suitably dissolved or dispersed in the liquid phase or vehicle and the essentially water-insoluble abrasive maintained in suspension, the cream being gelled or set to maintain the mixture as stable as possible. The formation of a gel favourably affects the stability of the cream. Any suitable gelling agent or hydrophilic colloid having the necessary swelling and setting action can be used. The gelling agents are preferably the natural and synthetic gum and similar gum-like materials such as Irish moss, gum tragacanth, sodium alginate, gum karaya, pectin, sodium

carboxymethylcellulose, and starch, including materials such as tragacanth glycerite or glycerite of starch which are essentially mixtures of glycerin and the mucilaginous substance. The amounts of these gums will usually be up to about 10% by weight of the dental cream, and about 0.5—5% usually.

As an embodiment of the present invention, a commercially acceptable and substantially uniform homogeneous and stable dental cream having the essential property of inhibiting tooth decay may be prepared by suitable proportioning of the following ingredients within the specified ranges to produce a cream extrudible from a collapsible aluminium or lead tube or the like:

| | Percent |
|---|---|
| Active ingredient | 0.5— 5 |
| Water-insoluble abrasive | 20.0—75 |
| Liquid vehicle | 20.0—75 |
| Gelling agent | 0.0—15 |

Minor amounts of flavour or sweetener, such as soluble saccharin, will also be added usually. The liquid vehicle is preferably water, or a liquid humectant or excipient such as glycerin, sorbitol, etc. and suitable mixtures thereof, the total liquid content being usually in an amount from about 30—65% by weight of the total ingredients. Preferred creams of the present invention which yield optimum results have the proportions below, the amounts in parentheses being highly desirable in commercial practice.

| | Percent. |
|---|---|
| Active ingredient | 0.5— 4 ( 1— 3) |
| Water-insoluble abrasive, preferably containing insoluble phosphate | 30.0—65 (40—60) |
| Glycerine | 5.0—50 (10—40) |
| Water | 5.0—50 (10—40) |
| Gelling agent | 0.1— 4 (0.5–1.5) |

The pH of the dental cream is variable and may be slightly alkaline or acid as desired since the saliva is a buffered medium. The pH of a 20% aqueous slurry of the cream will be usually about 5 to about 10. It is preferred that it be substantially neutral, e.g. about 6—8, for optimum effects.

As previously indicated, mouth washes or rinses are also within the scope of the present invention. By mouthwash is meant a suitably flavoured liquid vehicle, preferably an aqueous alcoholic vehicle. While amounts of up to five per cent active ingredient can be used, it is desirable to use abuot 0.05 to about 2%, and preferably up to about 1% by weight. The alcohol concentration may vary depending on the mouth effect desired, such as about 5—70% alcohol, and preferably 5—40%. Liquid dentifrices are also included, such products usually containing larger amounts of active ingredients, e.g. 0.5—5% dissolved in an aqueous mucilaginous vehicle, optionally combined with small amounts of abrasive, alcohol, glycerine, and colouring and flavouring materials.

The lozenges or troches are prepared by mixing fine particles of the active material with saccharin and mucilage. They can also have a base of gelatine and water and be flavoured with non-sugar flavouring agents. The active ingredient can be used up to 5% but a range of 0.05 to about 2% is preferable. In a similar manner, a chewing gum can be prepared by the addition of a gum base for the mucilage such as chicle or other natural gum or combinations as, for example, Jelutong gum, catiau gum, hangkang gum, lechicasti gum, pendari gum or ester gum. Suitable filling and flavouring ingredients can be added.

The addition of other antimetabolites in various concentrations to the composition are also useful, for example, pantoyltaurine, which interferes with the growth and acid formation of L. acidophilus, and bis betapantoylaminoethyl disulphide, which interferes with pantothenic acid metabolism. The useful concentrations would vary from 1 to 50 mg. per unit dose depending on the various factors. The addition of about 0.5% of papain to chewing gum will help digest protein matter around teeth.

The following examples are given for the purpose of illustration:

EXAMPLE 1

A quantity of lozenges were prepared each having the following composition:

| | |
|---|---|
| Pyridoxine Hydrochloride | 0.0250 Gm. |
| Sodium citrate | 0.0125 Gm. |
| Saccharin | 0.0025 Gm. |
| Magnesium Stearate | 0.0050 Gm. |
| Methocel | 0.0125 Gm. |
| Cherry selva | 0.0082 Gm. |
| Polyethylene glycol 4000 | 0.2222 Gm. |
| Calcium lactate | 0.2222 Gm. |
| Acacia | 0.0555 Gm. |
| | 0.5656 Gm. |

The polyethylene glycol is melted and mixed with distilled water. Acacia was mixed with enough 95% ethanol to form a damp mass. The acacia was then added to the mixture of polyethylene glycol and water while agitating. The calcium lactate is then added and the mixture blended until smooth, after which the mixture is cooled and granulated. The granules are dried at 35°C. for 48 hours and then regranulated. The pyridoxine hydrochloride, sodium citrate, saccharin, magnesium stearate, cherry selva and methocel were blended together. This blend was then mixed

with the dried granules and the composition blended for two hours. The composition was then formed into lozenges.

EXAMPLE 2

A dental ointment of vitamin $B_6$ containing the following ingredients was prepared as described below:

| | Gram |
|---|---|
| Vitamin $B_6$ | 0.050 |
| White Wax | 0.049 |
| White Petrolatum | 0.901 |
| | 1.000 |

The white wax and white petrolatum were weighed into a container. The container was placed on a steam bath and all contents melted. The vitamin $B_6$ was added and the ointment allowed to cool with stirring until it had congealed. The cool ointment was passed through a roller mill and samples were removed from the roller mill at intervals to assure uniform distribution of vitamin $B_6$. The product was then packaged.

A small quantity of ointment was placed between glass slides and viewed through a strong light contained no crystal aggregates visible to the eye.

EXAMPLE 3

A dental ointment of pyridoxal hydrochloride containing the following ingredients was prepared as follows:

| | Gram |
|---|---|
| Pyridoxal hydrochloride | 0.005 |
| White wax | 0.054 |
| White petroleum | 0.941 |
| | 1.000 |

This formulation was prepared in the same manner as that described in Example 2.

EXAMPLE 4

A flavoured dental ointment of pyridoxamine dihydrochloride containing the following ingredients was prepared as described below:

| | Gram |
|---|---|
| Pyridoxamine dihydrchloride | 0.025 |
| White wax | 0.049 |
| White petrolatum | 0.918 |
| Oil of Peppermint | 0.008 |
| | 1.000 |

The white wax and white petrolatum were melted and stirred until the temperature reached 50°C. The pyridoxamine dihydrochloride and oil of peppermint were then added and the ointment allowed to cool with stirring until it had congealed. The congealed mixture was then milled to form a uniform ointment.

EXAMPLE 5

A dental paste of codecarboxylase containing the following ingredients was prepared as described below:

| | Percent |
|---|---|
| Codecarboxylase | 1.00 |
| Carboxymethylcellulose | 0.86 |
| Glycerin | 10.00 |
| Propylene glycol | 20.00 |
| Water | 13.20 |
| Methyl *para*-hydroxybenzoate | 0.10 |
| Saccharin solution (50%) | 0.20 |
| Oil of spearmint | 0.24 |
| Non-ionic surface-active agent | 2.50 |
| Mineral oil | 0.90 |
| Dicalcium phosphate | 51.00 |

The glycerine and propylene glycol were mixed together and about one-fifth of this solution was added to the carboxymethylcellulose and mixed to form a slurry. The methyl *para*-hydroxy-benzoate was dissolved in the water with the aid of heat and then added to the slurry and mixed well to form a gel. The remainder of the glycerine-propylene glycol solution was thoroughly incorporated into the gel. The saccharin solution, oil of spearmint, mineral oil and the non-ionic surface-active agent were added to the gel and thoroughly mixed. The powdered dicalcium phosphate codecarboxylase were mixed and incorporated into the gel in small amounts until it had all been added. The above mixture was then milled to form a smooth, white toothpaste.

EXAMPLE 6

A chewing gum can be prepared having the following composition.

| | Gram |
|---|---|
| Vitamin $B_6$ | 1.00 |
| Chicle | 30.30 |
| Corn syrup | 24.20 |
| Saccharin | 45.30 |

The chicle is heated until it is of syrupy consistency and washed with 3—4% aqueous hydrochloric acid, dilute aqueous sodium bicarbonate solution and water in turn. The corn syrup is then added to the gum base and a mixture of the saccharin and vitamin $B_6$ incorporated and the entire mass mixed well, allowed to cool and formed into 1 gm. units of desired shape.

EXAMPLE 7

A coated chewing gum can be prepared having the following amounts of Vitamin $B_6$ and papain per gm. unit of chewing gum.

| | |
|---|---|
| Vitamin $B_6$ | 1.6 mg. |
| Papain | 8.0 mg. |

Gum centres are prepared as described in the preceding example with the exception that no Vitamin $B_6$ is added prior to the formation of the 1 gm. units. The gum centres are coated with pharmaceutical glaze to retain moisture. A sugar subcoat is then applied followed by the Vitamin $B_6$ and papain mixed in a dusting powder comprising magnesium carbonate to a concentration of 1.6 mg. of Vitamin $B_6$ and 8 mg. of papain per gum unit. The gum units are then coated with a sugar coating and polished.

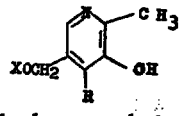
EXAMPLE 8

A tooth powder of papain and pyridoxine hydrochloride was prepared by thoroughly mixing the following ingredients in the proportions described below.

| | |
|---|---|
| Calcium phosphate, Dibasic | 0.6530 g. |
| Titanium Dioxide | 0.1000 g. |
| Sodium Citrate | 0.1000 g. |
| Citric Acid | 0.0200 g. |
| Saccharin | 0.0005 g. |
| Sodium Saccharin | 0.0005 g. |
| Spearmint Flavour | 0.0400 g. |
| Menthol Flavour | 0.0120 g. |
| Pyridoxine HCl | 0.0010 g. |
| Papain | 0.0050 g. |
| Pluronic F—68 | 0.0200 g. |
| Saponin | 0.0010 g. |
| Vanillin | 0.0010 g. |
| Cinnamon Flavour | 0.0130 g. |
| Birch Flavour | 0.0130 g. |
| Wintergreen Flavour | 0.0200 g. |
| | 1.0000 g. |

WHAT WE CLAIM IS:—

1. An oral preparation as hereinbefore defined containing as essential active ingredient a compound having the general formula



where R is a hydroxymethyl or aminomethyl group and X is a hydrogen atom or R is a formyl group and X is a hydrogen atom or a phosphonyl group, or a salt or complex of such a compound.

2. A preparation as claimed in Claim 1, in the form of a lozenge.

3. A preparation as claimed in Claim 2, in which the essential active ingredient is pyridoxine.

4. A preparation as claimed in Claim 1, in the form of a dental ointment.

5. A preparation as claimed in Claim 1, in the form of a chewing-gum.

6. A preparation as claimed in Claims 4 or 5 in which the essential active ingredient is vitamin $B_6$.

7. A preparation as claimed in Claim 1, in the form of a toothpaste.

8. A preparation as claimed in Claim 7 in which the essential active ingredient is codecarboxylase.

9. A preparation as claimed in Claim 1, in the form of a toothpowder.

10. A preparation as claimed in Claim 9, in which the essential active ingredient is pyridoxine hydrochloride.

11. A preparation as claimed in any preceding claim, containing from 0.50 to 5 weight per cent of the essential active ingredient.

12. A preparation as claimed in Claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

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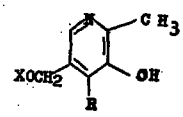
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| Papain | 0.0050 g. |
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| Saponin | 0.0010 g. |
| Vanillin | 0.0010 g. |
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8. A preparation as claimed in Claim 7 in which the essential active ingredient is codecarboxylase.

9. A preparation as claimed in Claim 1, in the form of a toothpowder.

10. A preparation as claimed in Claim 9, in which the essential active ingredient is pyridoxine hydrochloride.

11. A preparation as claimed in any preceding claim, containing from 0.50 to 5 weight per cent of the essential active ingredient.

12. A preparation as claimed in Claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

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