ANTIPLAQUE/ANTIGINGIVITIS AGENTS

This invention relates to the use of non-antibacterial agents and oral compositions for promoting human oral hygiene, and especially to agents for treating, controlling or inhibiting both plaque and gingivitis, which latter is characterised by such symptoms as inflammation, bleeding, recession, and/or swelling of the gums. Types of gingivitis include a functional gingivitis, gingivitis marginal and cotton-roll gingivitis. Gingivitis leads to periodontitis.

The gums are seriously harmed by deposits of dental plaque, a combination of minerals and bacteria found in the mouth. The bacteria associated with plaque can secrete enzymes and endotoxins which can irritate the gums and cause an inflammatory gingivitis. As the gums become increasingly irritated by this process they have a tendency to bleed, lose their toughness and resiliency, and separate from the teeth, leaving periodontal pockets in which debris, secretions, more bacteria and toxins further accumulate. It is also possible for food to accumulate in these pockets, thereby providing nourishment for increased growth of bacteria and production of endotoxins and destructive enzymes.

Actinomyces viscosus, a gram positive rod, has been identified as implicated in the aetiology of gingivitis (Loeche et al., "Bacteriology of human experimental gingivitis: effects of plaque and

gingivitis sores," Infection and Immunity 21, 830-839 (1978)). This organism attaches to tooth surfaces to form the dental plaque.

A multitiude of materials have been previously proposed and employed for controlling plaque and gingivitis, but none has been entirely satisfactory. For example, some of such materials have been found to be unstable in the presence of the anionic surface active agents generally present in conventional oral preparations. A number of such materials such as the cationic quaternary ammonium agents exert an anti-bacterial function which undesirably tends to disrupt or destroy the normal microflora of the mouth and/or the digestive system.

U.S. Patent No. 3,429,963 issued February 25, 1969 to Leo Shedlovsky and assigned to Colgate-Palmolive Company, proposes, among a number of other water soluble polyelectrolytes, the use of polyvinyl phosphonic acid (VPA polymer) or salts thereof for complexing calcium and inhibiting oral calculus, but the sole *in vivo* test described therein involved the supplying of drinking water containing a hydrolysed copolymer of ethylene and maleic anhydride for *ad libitum* drinking by rats for a period of five days. This test is in the nature of a stoichiometric complexation of calcium and is unrelated to the threshold effect occurring in actual oral use involving treatment of dental surfaces 1 to 3 times substantially daily for at least 2 weeks or lifetime. When subjected to such an actual use test, polyvinyl phosphonic acid failed to significantly inhibit oral calculus.

U.S. Patent No. 4,342,857 issued August 3, 1982 to Abdul Gaffar, the inventor named in this application, discloses and claims antigingivitis compositions containing a vinyl phosphonic acid/vinyl phosphonyl fluoride copolymer, but a number of scientists, authorities and/or jurisdictions object to administration of fluorinated materials to humans.

This invention enables the provision of an antiplaque/antigingivitis agent which will not be subject to one or more of the above deficiencies and objections. Other objects and advantages will appear as the description proceeds.

The attainment of the above objects is made possible by the discovery that VPA polymer and its salts interfere with or inhibit the attachment of Actinomyces viscosus to saliva coated hydroxyapatite (HAP) beads. This is a reliable indication that the agent would interfere with the attachment of the organism to tooth surfaces, should reduce plaque, and hence reduce or inhibit gingivitis. Such antigingivitis activity has in fact been corroborated by an in vivo test on beagles as more fully discussed below.

The invention broadly provides a composition containing a dentally acceptable oral vehicle and an effective plaque- and gingivitis-inhibiting amount of polyvinyl phosphonic acid (as herein defined), or an orally acceptable salt thereof, for inhibiting human dental plaque and gingivitis, the polyvinyl phosphonic

acid having a molecular weight of about 6000 to about 10,700.

The invention also provides a method of industrially formulating a composition for inhibiting human dental plaque and gingivitis, the method comprising admixing polyvinyl phosphonic acid (as herein defined) having a molecular weight in the range 6000 to 10700, or an orally acceptable salt thereof, with a dentally acceptable oral vehicle, and the industrial use of such polyvinyl-phosphonic acid, or any orally acceptable salt thereof, for preparing medicaments for inhibiting human dental plaque and gingivitis.

The VPA polymer of this invention has a number average molecular weight (obtained from viscosity or light scattering measurements) of from 6,000 to 10,700, and may be prepared in known manner by polymerizing vinyl phosphonyl dichloride under substantially anhydrous conditions in the presence of a free radical catalyst, and then mixing the resulting polymer with water to convert the vinyl phosphonyl dichloride units in the polymer hydrolytically to VPA units. The resulting polymer is in free acid form and may desirably be converted to salt form by treatment with any orally acceptable cation-providing base such as an alkali metal (e.g. sodium or potassium), ammonium or C_{1-18} mono-, di- and tri-substituted ammonium, (e.g. alkanol substituted ammonium, such as mono-, di- and tri-ethanolammonium or organic amine) -contaning base.

It will be understood that the mono- and di- salt forms of the polymer are the equivalent of the free acid form and that the term "water soluble" applicable to all such forms is inclusive of readily water dispersible forms thereof in the usual use concentrations.

It will also be understood that the VPA polymer may also contain minor proportions, i.e. less than 50 wt. %, preferably less than about 10 wt. %, more preferably less than about 5 wt. %, most preferably less than about 2 wt. %, of units derived from other non-fluorinated ethylenically unsaturated monomers which, in type and amount, are non-toxic and do not interefere with the desired water soluble and antigingivitis activities of the polymer. Other such monomers may, for example, include olefins or alkenes such as ethylene, propylene, isopropylene, butylene and isobutylene, vinyl lower alkyl ethers such as vinyl methyl, ethyl and isobutyl ethers, alpha, beta unsaturated carboxylic acids and their lower alkyl and substituted lower alkyl esters such as acrylic, methacrylic, aconitic, maleic and fumaric acids and their methyl, ethyl, isobutyl and dimethylaminoethyl esters, allyl alcohol and acetate, vinyl and vinylidene halides, vinyl lower alkanoic acid esters such as vinyl acetate and butyrate, acrylamide and methacrylamide and N-lower alkyl and N,N-dilower alkyl substituted derivatives thereof, and the like.

The term "alkyl" as used herein refers to a radical preferably having from 1 to 4 carbon atoms,

and cognate terms should be construed accordingly.

The concentration of the VPA polymeric anti-gingivitis agent in oral compositions can range widely, typically upwards of 0.01% by weight with no upper limit except as dictated by cost or incompatibility with the vehicle. Generally, concentrations of from 0.01% to 10.0%, preferably from 0.1% to 8.0%, more preferably from 0.5% to 5.0% by weight are used. Oral compositions which in the ordinary course of use could be accidentally ingested preferably contain concentrations in the lower portions of the foregoing ranges.

In certain highly preferred forms of the invention, the oral composition may be substantially liquid such as mouthwash or rinse. Such preparations generally contain a humectant and the vehicle is typically a water-alcohol mixture. Generally, the ratio of water to alcohol is in the range of from 1:1 to 20:1 preferably from 3:1 to 20:1 and most preferably about 17.3, by weight. The total amount of water-alcohol mixture in this type of preparation is typically in the range of from 70 to 99.9% by weight of the preparation. The pH of such liquid and other preparations of the invention is generally in the range of from 4.5 to 9 and typically from 5.5 to 8. The pH is preferably in the range of from 6 to 8.0. It is noteworthy that the compositions of the invention may be applied orally at a lower pH without substantially decalcifying dental enamel.

Such liquid oral preparations may also contain a surface active agent and/or a fluorine-providing compound.

In certain other desirable forms of this invention, the oral composition may be substantially solid or pasty in character, such as toothpowder, a dental tablet, a toothpaste or dental cream. The vehicle of such solid or pasty oral preparations contains polishing material. Examples of polishing materials water water-insoluble sodium metaphosphate, potassium metaphosphate,tricalcium phosphate, calcium pyrophosphate, magnesium orthophosphate, trimagnesium phosphate, calcium carbonate, alumina, hydrated alumina, aluminium silicate, zirconium silicates, silica, bentonite, and mixtures thereof. Preferred polishing materials include crystalline silica having particle sizes of up to 5 microns, a mean particle size of up to 1.1 microns, and a surface area of up to 50,000 cm^2/gm, silica gel, complex amorphous alkali metal aluminosilicate, hydrated alumina and dicalcium phosphate.

Alumina, particularly the hydrated alumina sold by Alcoa as C-333, which has an alumina content of 64.9% by weight, a silica content of 0.008%, a ferric oxide content of 0.003%, and a moisture content of 0.037%, at 110°C., and which has a specific gravity of 2.42 and a particle size such that 100% of the particles are less than 50 microns and 84% of the particles are less than 20 microns, is particularly desirable.

When visually clear gels are employed, a plishing agent of colloidal silica, such as those sold under the trade mark SYLOID as Syloid 72 and Syloid 74 or under the trade mark SANTOCEL as Santocel 100 and alkali metal aluminosilicate complexes are particularly useful, since they have refractive indices close to the refractive indices of gelling agent-liquid (including water and/or humectant) systems commonly used in dentifrices.

Many of the so-called "insoluble" polishing materials are anionic in character and also include small amounts of soluble material. Thus, insoluble sodium metaphosphate may be formed in any suitable manner, as illustrated by Thorpe's Dictionary of Applied Chemistry, Volume 9, fourth Edition, pp. 510-511. The forms of insoluble sodium metaphosphate known as Madrell's salt and Kurrol's salt are further eamples of suitable materials. These metaphosphate salts exhibit a minute solubility in water, and therefore are commonly referred to as insoluble metaphosphates. There is present therein a minor amount of soluble phosphate material as impurities, usually a few percent such as up to 4% by weight. The amount of soluble phosphate material, which is believed to include a soluble sodium trimetaphosphate in the case of insoluble metaphosphate, may be reduced by washing with water if desired. The insoluble alkali metal metaphosphate is typically employed in powder form of a particle size such that no more than about 1% of the material is larger than 37 microns.

The polishing material is generally present in amounts ranging from 10 to about 99% by weight of the oral preparation. Preferably, it is present in amounts ranging from 10 to 75% in toothpaste, and from 70 to 99% in toothpowder.

In the preparation of toothpowders, it is usually sufficient to admix mechanically, e.g. by milling, the various solid ingredients in appropriate quantities and particle sizes.

In pasty oral preparations the above-defined combination of the antigingivitis agent and polishing material should be compatible with the other components of the preparation. Thus, in a toothpaste, the liquid vehicle may comprise water and humectant typically in an amount ranging from about 10 to about 90% by weight of the preparation. Glycerine, soribtol, or polyethylene glycol may also be present as humectants or binders. Particularly advantageous liquid ingredients are polyethylene glycol and polypropylene glycol. Also advantageous are liquid mixtures of water, glycerine and sorbitol.

In clear gels where the refractive index is an important consideration, from 3 to 30% by weight of water, 0 to 80% by weight of glycerine, and from 20 to 28% by weight of sorbitol is preferably employed. A gelling agent, such as natural or synthetic gums or gum like materials, typically Irish moss, sodium carboxymethylcellulose, methyl cellulose, hydroxyethyl cellulose, gum tragacanth, polyvinylpyrrolidone, starch and preferably hydroxypropyl methyl cellulose and the

Carbopols (Carbopol is a Registered Trade Mark) (e.g. 934,940 and 941), is usually present in toothpaste in an amount of up to 10% by weight, preferably in the range of from 0.5 to 5%. In a toothpaste or gel, the liquids and solids are proportioned to form a creamy or gelled mass which is extrudable from a pressurised container or from a collapsible, e.g. aluminium or lead, tube.

The solid or pasty oral preparation which typically has a pH measured on a 20% slurry of about 4.5 to 9, generally about 5.5 to about 8 and preferably about 6 to about 8.0 may also contain a surface active agent and/or a fluorine-providing compound.

It will be understood that, as is conventional, the oral preparations are to be sold or otherwise distributed in suitable labelled packages. Thus a jaw of mouthrinse will have a label describing it, in substance, as a mouthrinse or mouthwash and having directions for its use; and a toothpaste will usually be in a collapsible tube, typically aluminium or lined lead, or other squeeze dispenser for metering out the contents, having a label describing it, in substance, as a toothpaste or dental cream.

The oral compositions of this invention may contain a non-soap synthetic sufficiently water soluble organic anionic or nonionic surfactant in concentrations generally ranging from from 0.05 to 10, preferably from 0.5 to 5, weight percent, to promote wetting, detersive and foaming properties. U.S. Patent No. 4,041,149 discloses such suitable anionic surfactants in column 4, lines 31-38, and such suitable

nonionic surfactants in column 8, lines 30-68 and column 9.

In certain forms of this invention a fluorine-providing compound is present in the oral preparation. These compounds may be slightly soluble in water or may be fully water-soluble. They are characterised by their ability to release fluoride ions in water and by substantial freedom from reaction with other components of the oral preparaton. Among these materials are inorganic fluoride salts, such as soluble alkali metal, alkaline earth metal and heavy metal salts, for example, sodium fluoride, potassium fluoride, ammonium fluoride, Ca fluoride, a copper fluoride such as cuprous fluoride, zinc fluoride, a tin fluoride such as stannic fluoride or stannous chlorofluoride, barium fluoride, sodium fluorosilicate, ammonium fluorosilicate,
sodium fluorozirconate, sodium monofluorophosphate, aluminium mono- and di-fluorophosphate, and fluorinated sodium calcium pyrophosphate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate and mixtures of them, are preferred.

The amount of the fluorine-providing compounds is dependent to some extent upon the type of compound, it solubility, and the type of oral preparation, but it must be a non-toxic amount. In a solid oral preparation, such as toothpaste or toothpowder, an amount of such compound which releases a maximum of about 1% by weight of the preparation is considered

satisfactory. Any suitable minimum amount of such compound may be used, but it is preferable to employ sufficient compound to release from 0.005 to 1% and preferably about 0.1% of fluoride ion. Typically, in the cases of alkali metal fluorides and stannous fluoride, this component is present in an amount up to about 2% by weight, based on the weight of the preparation, and preferably in the range of from 0.05 to 1%. In the case of sodium mono-fluorophosphate, the compound may be present in an amount up to 7.6% by weight, more typically about 0.76%.

In a liquid oral preparation such as a mouthwash, the fluorine-providing compound is typically present in an amount sufficient to release up to 0.13%, preferably from 0.0013 to 0.1% and most preferably about 0.0013% or 0.013% by weight, of fluoride.

Various other materials may be incorporated in the oral preparations of this invention, subject to the above. Examples are whitening agents, preservatives, silicones, chlorophyll compounds, and ammoniated material such as urea, diammonium phosphate, and mixtures thereof. These adjuvants, where present, are incorporated in the preparations in amounts which do not substantially adversely affect the properties and characteristics desired.

Any suitable flavouring or sweetening material may also be employed, also subject to the above. Examples of suitable flavouring constituents are flavouring oils, e.g. oils of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus,

marjoram, cinnamon, lemon and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, sorbitol, sodium cyclamate, perillartine, APM (aspartylphenylalanine, methyl ester) and saccharin. Suitably, flavouring and sweetening agents may together constitute from 0.1 to 5% or more the preparation.

In the practice of this invention an oral composition according to this invention such as mouthwash or toothpaste containing the antigingivitis agent in an orally acceptable vehicle may be prepared by unifying the components in conventional manner, and applied to the gingiva and teeth regularly, substantially daily, e.g. from about 1 to 3 times daily or possibly every second or third day, at a pH of from 4.5 to 9, generally from 5.5. to 8.5, preferably from 6 to 8, preferably for at least two weeks up to eight weeks or more, or ideally for a lifetime.

In the case of chewing gum and other products, the VPA active ingredients can be incorporated in any suitable manner during the usual manufacture of the product. For example, they can be incorporated in a warm gum base with stirring to distribute the same uniformly therein. They can also be added to the exterior or outer surfaces of a gum base in order to coat the base. The usual gum bases can be used, representive materials being jelutone, rubber latex and vinylite resins, in addition to other usual materials such as plasticizers or softeners, sugar or other suitable carbohydrates such as glucose, sorbitol, etc.

The following examples are further illustrative of the nature of this invention but it is understood that the invention is not limited to them. All amounts and proportions referred to herein and in the appended claims are by weight, and temperatures are in degrees celcius unless otherwise indicated. The VPA polymer employed in these examples had a molecular weight (M.W.) of about 10,700 and is employed in the form of the disodium salt.

EXAMPLE 1

Adsorption of Sodium Polyvinyl Phosphonate to Dental Enamel:

The adsorption of the polymer to enamel surfaces was measured in vitro. Human extracted, non-carious and non-filled molar teeth were cleaned by pumicing. They were then polished with a rubber cup and polishing agent. They were mounted onto a rubber stopper via a nichrome wire which was tied through a hole in the roots. A sodium salt of polymer solutions at pH 7.0 were dispensed in polyethylene tubes. The teeth were submerged in the solution at 37°C for 1 hour under a continuous agitation. Special care was taken to avoid the contact of solution with roots of the teeth. After one hour incubation, the teeth were removed and the solutions were analysed for the amount of polymer left in the solution. The adsorption was calculated by a dfference between amount initially added minus the amount left after exposing to teeth.

The concentration of the polymer in the solution was assessed by turbidimetric measurements using 5M

$CaCl_2$ solution at pH 4.5. 1 ml of $CaCl_2$ was added to 1 ml of the polymer solution. The turbidity of resulting colloidal suspension at 500 nanometers proved to be proportional to the polymer concentration ranging from 1 to 8 mg/ml. A calibration curve was carried out with the known amount of the polymer.

TABLE 1

Results:

Conc. of POly-Na_2VPA (mg/ml)	Amt. Left After Tooth Immersion (mg/ml)	Amt. Adsorbed to Teeth (mg/ml)
2	0.4	1.6
3	0.7	2.3
4	1.1	2.9
5	1.6	3.4
6	2.4	3.6
7	3.3	3.7

The data indicated a significant adsorption of the VPA polymer to enamel surfaces.

EXAMPLE II

Effect of Polymer on the Adsorption of Actinomyces Viscous T14 on Saliva Coated Hydroxyapatite (HAP) Beads:

80 mgs of HAP beads were pre-coated with human saliva (blood type A) for 12 hours. The beads were washed and pretreated with the solution of the polymer at pH 7.0 for 5 minutes. The treated beads were washed with a buffer consisting of 0.05 M KCl 1 mM PO_4, 1 mM $CaCl_2$ and 0.1 mM $MgCl_2$ at pH 6.0. This buffer simulates saliva inorganic constituents.

For the adsorption studies the mixture (1.0 ml) contained 5×10^7 ^3H thymidine labelled bacteria

(Actinomyces viscosus), 30 mg saliva coated beads (S HAP) and the buffer. The mixture was continuously shaken at room temperature for 2 hours. The beads were allowed to settle for one minute and the supernatant which contained unadsorbed cells was removed. The radioactivity was measured via liquid scintillation counts. Portions of known H^3 labelled cells were counted in a similar manner so that counts per minute may be related to bacterial cell member. Control bacterial suspensions were incubated with S-HAP beads.

TABLE II

Results:

Effects of Pre-treating Saliva Coated HAP Beads with Polyvinyl Phosphonate on Adsorption of Bacteria.

	A. Viscosus LY7	
S-HAP Treatment	Cells Absorbed (X 10^7) per 20 mg S-HAP	% Relative to Buffer
Buffered KCl	3.88 ± 0.04	100
1% Na_2VPA Polymer	1.23 ± 0.05	32
0.1% Na_2VPA Polymer	3.54 ± 0.16	91
0.01% Na_2 VPA	3.55 ± 0.09	92

The results show that a pre-treatment of S HAP with 1% polyvinyl phosphonate was significantly effective in inhibiting bacterial attachment.

EXAMPLE III

This study in 20 beagle dogs evaluated the effect of a placebo and a rinse containing 1% sodium salt of

polyvinyl phosphonic acid on plaque/gingivitis for 4 weeks. The dogs were given complete prophylaxis to remove soft and hard dental deposits. A disclosing solution was used to insure the complete removal of dental deposits. The beagles were kept on a soft diet for 4 weeks. Group I (10 dogs) were then treated with the placebo rinse, while Group II was treated with the rinse containing the polymer. The treatment was done 1/day/5 days per week by applying 5-6 mg of the rinse on all dentition. The study was double blind. Neither the evaluator nor the people involved in the treatments knew the assignments of rinses in the respective groups. The plaque and gingivitis was assessed via Loe and Silness index (Acta Odontologica Scandinavica; 21:551-555 (1963).

TABLE III

Results: Mouth Rinse	N	Group	Plaque Index/Tooth - 4 Wks Post Treatment
Placebo	10	I	0.99 ± 0.23
1% Na_2 VPA Polymer	10	II	0.68 ± 0.23

Mouth Rinse	% Change	Gingival Index 4 Wks Post Treatment	% Change
Placebo	---	0.91 ± 0.10	---
1% Na_2 VPA Polymer	-31	0.73 ± 0.29	-20

Compared to the placebo rinse, the polyvinyl phosphonate rinse significantly reduced plaque/gingivitis for four weeks.

The following examples of oral (mouthwash and toothpaste) formulations arefurther illustrative of this invention.

EXAMPLE IV

	Wt. Percent
Glycerin	10.0
Ethanol	10.0
Pluronic (Registered Trade Mark) F108*	3.8
Na Saccharin	0.03
Polyvinyl phosphonate	1.0
Flavour	0.22
Water to make	100.00

* BASF-Wyandotte block polymer nonionic surfactant containing about 20 wt. % polyoxypropylene chain of about 3250 M.W. and about 80 wt. % polyoxyethylene.

EXAMPLE V

	Wt. Percent
Glycerin	25.0
Carobxymethyl Cellulose	1.3
Sodium Benzoate	0.5
Na Saccharin	0.2
Silica	30.0
Sodium Lauryl Sulphate	1.5
Polyvinyl Phosphonate	3.0
Water to make	100.0

This invention has been disclosed with respect to preferred embodiments and it will be understood that modifications and variations apparent to those skilled in the art are to be included within the invention as defined in the claims.

CLAIMS

1. A composition containing a dentally acceptable oral vehicle and in an amount effective for inhibiting (a) attachment to tooth surfaces of Actinomyces viscosus, (b) dental plaque- and (c) gingivitis, polyvinyl phosphonic acid (as herein defined), having a molecular weight of about 6000 to about 10,700 or an orally acceptable salt thereof.

2. A composition according to Claim 1 containing from 0.01% to 10% by weight of the polyvinyl phosphonic acid or salt thereof.

3. A composition according to Claim 1 or Claim 2, containing from 0.5% to 5% by weight of the polyvinyl phosphonic acid or salt thereof.

4. A composition according to any one of Claims 1 to 3, which is a mouthwash having a pH of from 4.5 to 9 and including an aqueous-alcohol vehicle.

5. A composition according to any one of Claims 1 to 3, which is a toothpaste having a pH of from 4.5 to 9, including a liquid vehicle, a gelling agent and a dentally acceptable polishing agent.

6. A composition containing a dentally acceptable oral vehicle and in an amount effective for inhibiting (a) attachment to tooth surfaces of Actinomyces viscosus, (b) dental plaque- and (c) gingivitis, in the range of from 0.01% to 10% by weight, polyvinyl phosphonic acid (as herein defined) having a molecular weight of from 6,000 to 10,700 or an orally acceptable salt thereof.

7. A composition containing a dentally acceptable oral vehicle and in an amount effective for inhibiting (a) attachment to tooth surfaces of Actinomyces viscosus, (b) dental plaque- and (c) polyvinyl phosphonic acid (as herein defined) having a molecular weight of from 6,000 to 10,700, or an orally acceptable salt thereof, for use in medical or veterinary treatment or diagnosis.

8. A composition substantially as herein described with reference to any one of the Examples for inhibiting human dental plaque and gingivitis.

9. A method of industrially formulating a composition for inhibiting human dental plaque and gingivitis, the method comprising admixing polyvinyl phosphonic acid (as herein described) having a molecular weight in the range 6,000 to 10,700, or an orally acceptable salt thereof, with a dentally acceptable oral vehicle.

10. The industrial use of polyvinyl phosphonic acid (as herein defined) having a molecular weight in the range of 6,000 to 10,700 or an orally acceptable salt thereof, for preparing medicaments for inhibiting attachment of Actinomyces viscosus to teeth and/or gingivitis.