

ANTIBACTERIAL ANTIPLAQUE ORAL COMPOSITION  
CONTAINING NOVEL STYRENE-PHOSPHONIC ACID  
COPOLYMER

This invention relates to styrenephosphonic  
5 polymers which are effective to enhance antiplaque  
effectiveness of an antibacterial antiplaque oral  
composition.

Dental plaque is a soft deposit which forms on teeth as  
opposed to calculus which is a hard calcified deposit on  
10 teeth. Unlike calculus, plaque may form on any part of the  
tooth surface, particularly including at the gingival  
margin. Hence, besides being unsightly, it is implicated in  
the occurrence of gingivitis.

Accordingly, it is highly desirable to include  
15 antimicrobial agents which have been known to reduce plaque  
in oral compositions. Frequently, cationic antibacterial  
agents have been suggested. Moreover, in U.S. Patent  
4,022,880 to Vinson et al, a compound providing zinc ions as  
an anticalculus agent is admixed with an antibacterial agent  
20 effective to retard the growth of plaque bacteria. A wide  
variety of antibacterial agents are described with the zinc  
compounds including cationic materials such as guanides and  
quaternary ammonium compounds as well as non-cationic  
compounds such as halogenated salicylanilides and  
25 halogenated hydroxydiphenyl ethers. The noncationic  
antibacterial antiplaque halogenated hydroxydiphenyl ether,  
Triclosan, has also been described in combination with zinc

citrate trihydrate in European Patent Publication 0161,899 to Saxton et al.

The cationic antibacterial materials such as chlorhexidine, benzthonium chloride and cetyl pyridinium chloride have been the subject of greatest investigation as antibacterial antiplaque agents. However, they are generally not effective when used with anionic materials. Noncationic antibacterial materials, on the other hand, can be compatible with anionic components in an oral composition.

However, oral compositions typically are mixtures of numerous components and even such typically neutral materials as humectants can affect performance of such compositions.

It is an advantage of this invention that an oral composition can be provided containing a substantially water-insoluble noncationic antibacterial agent and an antibacterial-enhancing agent including novel styrenephosphonic polymer which enhances the delivery of said antibacterial agent to, and retention thereof on, oral surfaces to inhibit plaque formation.

It is an advantage of this invention that said antibacterial-enhancing agents enhance the delivery and retention of the antibacterial agent on teeth and on soft oral tissues.

It is a further advantage of this invention that

the antiplaque oral composition is effective to reduce the occurrence of gingivitis.

Additional advantages of this invention will be apparent from consideration of the following specification.

According to the present invention there is provided a polymer selected from beta-styrene phosphonic acid homopolymer, and copolymers with vinylphosphonic acid.

These polymers are effective to enhance antiplaque effectiveness of oral compositions containing a substantially water-insoluble antibacterial antiplaque agent, for instance in amount of about 0.01-5% by weight, such as the halogenated diphenyl ethers, 2',4,4'-trichloro-2-hydroxy-diphenyl ether (Triclosan) (Registered Trade Mark) or 2,2'-dihydroxy-5,5'-dibromodiphenyl ether as well as halogenated salicylanilides, benzoic esters, halogenated carbanilides and phenolic compounds.

The antibacterial-enhancing agent (AEA) which enhances delivery of said antibacterial agent to, and retention thereof on, oral surfaces, is employed in amounts effective to achieve such enhancement preferably within the range in the oral composition of about 0.05% to about 4%, preferably about 0.1% to about 3%, more preferably about 0.5% to about 2.5% by weight.

Poly (beta styrene phosphonic acid) contains units of the formula:

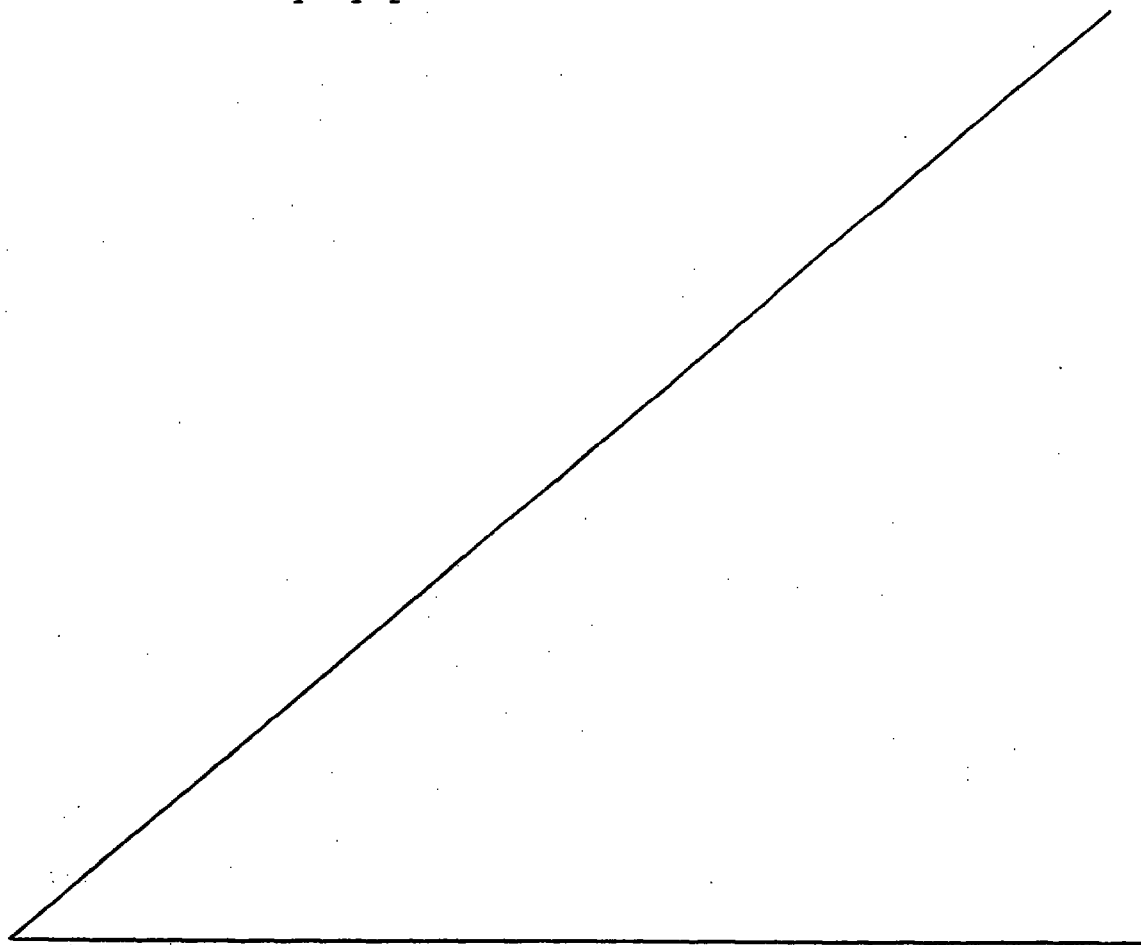


wherein Ph is phenyl, the phosphonic delivery-enhancing group and the phenyl retention-enhancing group being bonded on vicinal carbon atoms in the chain. A copolymer of beta styrene phosphonic acid with vinyl phosphonyl chloride can have the units of formula I alternating or in random association with the vinyl phosphonyl units.

These styrene phosphonic acid polymers and their copolymers generally have molecular weights in the range of 2,000 to 30,000, preferably 2,500 to 10,000. Such "inert" monomers do not significantly interfere with the intended function of any copolymer employed as an AEA herein.

The novel beta-styrene phosphonic acid polymers and copolymers may in general be prepared by heating the monomers or mixtures of monomers, preferably under nitrogen, in the presence of an effective amount, e.g. about 2.6-5% by weight of the monomers, of a radical initiator, e.g. AIBN, benzoyl peroxide, t-butyl hydroperoxide, persulfate or the like, neat or as

solutions in an inert solution such as acetonitrile, methylene chloride or 1,2-dichloromethane; at elevated temperatures, e.g. up to about 125°C or at solvent reflux, for periods of about 8 to 200 hours. The crude polymeric products after removal of any inert solvent, is mixed with water and the aqueous mixture adjusted to a pH of about 8-11, e.g. with aqueous sodium hydroxide. After filtration of any solid impurities, the filtrate solution is dialyzed against water (e.g. at 3500 Dalton cutoff), and the purified polymer isolated from the retentate solvent as by lyophilization.



The film forming property of the AEA and the enhanced delivery and retention of the antibacterial agent on tooth surfaces due to the AEA appears to make tooth surfaces unfavorable for bacterial accumulation particularly since the direct  
5 bacteriostatic action of the antibacterial agent controls bacterial growth. Therefore, through the combination of three modes of actions: 1) enhanced delivery, 2) long retention time on tooth surfaces, and 3) prevention of bacterial attachment to tooth surfaces the oral composition is made efficacious for  
10 reducing plaque. Similar antiplaque effectiveness is attained on soft oral tissue at or near the gum line.

In the oral preparation, an orally acceptable vehicle including a water-phase with humectant is present. The humectant is preferably glycerine and/or sorbitol. Significant  
15 amounts of polyethylene glycol, particularly of molecular weight of 600 or more, should be avoided since polyethylene glycol effectively inhibits the antibacterial activity of the noncationic antibacterial agent. For instance, polyethylene glycol (PEG) 600 when present with Triclosan in a weight ratio  
20 of 25 Triclosan:1 PEG 600 reduces the antibacterial activity of Triclosan by a factor of about 16 from that prevailing in the absence of the polyethylene glycol.

Materials which substantially dissolve the antibacterial agent, to permit its delivery to the soft oral  
25 tissues at or near the gum line, may be employed to dissolve the antibacterial agent in saliva. Typical solubilizing materials include the humectant polyols such as propylene

glycol, dipropylene glycol and hexylene glycol, cellosolves such as methyl cellosolve and ethyl cellosolve, vegetable oils and waxes containing at least about 12 carbon atoms in a straight chain such as olive oil, castor oil, and petrolatum esters such as amyl acetate, ethyl acetate, glyceryl tristearate and benzyl benzoate. Propylene glycol is preferred. As used herein, "propylene glycol" includes 1,2-propylene glycol and 1,3-propylene glycol.

The pH of oral preparation is generally in the range of about 4.5 to about 9 or 10 and preferably about 6.5 to about 7.5. It is noteworthy that the compositions may be applied orally at a pH below 5 without substantially decalcifying or otherwise damaging dental enamel. The pH can be controlled with acid (e.g. citric acid or benzoic acid) or base (e.g. sodium hydroxide) or buffered (as with sodium citrate, benzoate, carbonate, or bicarbonate, disodium hydrogen phosphate, sodium dihydrogen phosphate, etc.).

The oral preparation may be substantially liquid such as a mouthwash or may be a dentifrice containing a dentally acceptable polishing agent. The oral dentifrice composition typically contains a natural or synthetic thickener or gelling agent.

The oral composition may also contain a source of fluoride ions, or fluorine-providing component, as anti-caries agent.

It will be understood that, as is conventional, oral preparations are to be sold or otherwise distributed in

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suitable labelled packages. Thus a dentifrice gel will usually be in a collapsible tube, typically aluminum, lined lead or plastic, or other squeeze, pump or pressurized dispenser for metering out the contents, having a label describing it, in substance, as a dentifrice gel or the like.

Organic surface-active agents are used in oral compositions to achieve increased prophylactic action, assist in achieving thorough and complete dispersion of the antiplaque antibacterial agent throughout the oral cavity, and render the compositions more cosmetically acceptable. The organic surface-active material is preferably anionic, nonionic or ampholytic in nature, and it is preferred to employ as the surface-active agent a deterative material which imparts to the composition deterative and foaming properties.

Various other materials may be incorporated in the oral preparations such as whitening agents, preservatives, silicones, chlorophyll compounds and/or 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. Significant amounts of zinc, magnesium and other metal salts and materials which are generally soluble and which would complex with active components of the instant invention are to be avoided.

Any suitable flavoring or sweetening material may also be employed.

The oral composition is preferably applied regularly to dental enamel and soft oral tissues, particularly at or near the gum line, such as every day or every second or third day or preferably from 1 to 3 times daily, at a pH of about 4.5 to about 9, generally about 5.5 to about 8, preferably about 6.5 to 7.5, for at least 2 weeks up to 8 weeks or more up to lifetime.

The AEA and the antibacterial agent can be incorporated in lozenges, or in chewing gum or other products, e.g. by stirring into a warm gum base or coating the outer surface of a gum base, illustrative of which may be mentioned jelutong, rubber latex, vinylite resins, etc., desirably with conventional plasticizers or softeners, sugar or other sweeteners or carbohydrates such as glucose, sorbitol and the like.

The following Examples are further illustrative of the nature of the present invention, but it is understood that the invention is not limited thereto. All amounts and proportions are by weight, unless otherwise indicated.

#### EXAMPLE A

##### 20 Poly (beta-styrenephosphonic acid)

A mixture of 18.1 g. (0.1 M) of beta-styrenephosphonic acid and 0.82 g. (0.005 M) of azobisisobutyronitrile (AIBN) in 300 ml. of anhydrous acetonitrile is stirred under reflux under dry nitrogen for 96 hrs. The mixture is cooled and the crude product precipitate is isolated, filtered, washed with acetonitrile, and air dried.

The crude product is dissolved in aqueous sodium hydroxide (to pH

11) and dialyzed against water at 3000 Dalton cutoff. The retentate solution is reduced to 100 ml., in vacuo, and freeze-dried to yield the purified product polymer as a white powdery solid in 0.91 g. yield. Infrared spectrum: 1610, 1550, 745  $\text{cm}^{-1}$  (aryl, 5 adjacent H); 1240, 1020, 950  $\text{cm}^{-1}$  (phosphonate). Proton nmr ( $\text{D}_2\text{O}$ ): tr, 6.4 ppm. (H on carbon bearing phosphonate); m, 7.3 ppm (aryl and benzylic protons); area ratio 1 to 6. Phosphorus nmr ( $\text{D}_2\text{O}$ ): m, 6.2 ppm. (alkyl phosphonate).

#### EXAMPLE B

##### 10 Copoly (beta-styrenephosphonic acid/vinylphosphonic acid)

A mixture of 10.68 g. (0.058 M) of beta-styrenephosphonic acid, 6.0 ml. (8.4 g., 0.058 M) of vinylphosphonyl dichloride, and 0.5 g. of AIBN is heated, with stirring, under an anhydrous nitrogen atmosphere intermittently for a few hours, then overnight at 80-90°C. The material is transferred to a beaker with 60-70 ml. of water. A crystalline precipitate forms as the warm solution cools. The mixture is filtered, the aqueous filtrate is diluted to 125 ml. with water, and the resulting solution is dialyzed vs. water at 3500 Dalton cutoff. The retentate solution is evaporated in vacuo to give 0.600 g. purified acid form of the copolymer. Proton nmr ( $\text{D}_2\text{O}$ ) shows <sup>two broad</sup> ~~te read~~ regions at 1.0-2.8 (alkyl, 11H) and 6.9-7.5 ppm (aryl, 5H). These data indicate a ratio of beta-styrenephosphonic acid to vinylphosphonic acid of 1:3 in the copolymer. Phosphorus nmr ( $\text{D}_2\text{O}$ ) shows two main phosphorus signals centered at about 23.4 and 29.2 ppm. respectively.

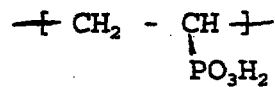
This invention has been described with respect to certain preferred embodiments and it will be understood that modifications and variations thereto obvious to those skilled in art are to be included within the scope of the appended Claims.

Attention is directed to our granted GB Patent No. 2227660, which claims an oral composition comprising an effective antiplaque amount of a substantially water insoluble noncationic antibacterial agent, 0.005-4% by weight of antibacterial enhancing agent which enhances delivery of said antibacterial agent to, and retention on, oral surfaces and an orally acceptable vehicle effective to enable the said antibacterial agent to dissolve in saliva in effective antiplaque amount, the said oral composition being free of polyphosphate anticalculus agent.

Attention is also directed to our granted GB Patent No. 2257362, which claims an oral composition comprising an orally acceptable vehicle, an effective anti-plaque amount of a substantially water-insoluble non-cationic anti-bacterial agent and an antibacterial-enhancing agent which has an average molecular weight of 1000 to 1,000,000, and contains at least one delivery enhancing functional group and at least one organic retention enhancing group, the said agent contained in the said groups being free from or substantially free from water soluble alkali metal or ammonium synthetic anionic linear polymer polycarboxylate salt having a molecular weight of 1000 to 1,000,000, the said oral composition being free of polyphosphate anti-calculus agent.

Attention is also directed to our granted GB Patent No. 2259856, which claims an oral composition comprising an effective antiplaque amount of a substantially water insoluble non-cationic antibacterial agent, 0.005 to 4% by weight of any

antibacterial-enhancing agent which enhances the delivery of the said antibacterial agent to oral surfaces, and an orally acceptable vehicle effective to enable the said antibacterial agent to dissolve in saliva in an effective antiplaque amount, the said oral composition being free of polyphosphate anticalculus agent, the antibacterial enhancing agent being a poly(vinyl phosphonic acid) containing units of the formula



the composition having a pH in the range 4.5-10.

No claim is made to any subject matter claimed in these three patents.



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CLAIMS

1. A polymer selected from beta-styrenephosphonic acid homopolymer and copolymers with vinylphosphonic acid.

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2. Beta-styrene phosphonic acid homopolymer.

3. Beta-styrene phosphonic acid/vinyl phosphonic acid copolymer.

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4. A polymer as claimed in any one of Claims 1 to 3 in which the said polymer has a molecular weight of about 2,000-10,000.

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5. A polymer as claimed in Claim 1 substantially as specifically described herein with reference to the examples.

6. A method of preparing a polymer as claimed in Claim 1 comprising polymerizing the monomer or mixture of monomers at elevated temperatures in the presence of a radical initiator, mixing the crude polymeric product with water, adjusting the resulting solution to a pH of about 8-11, dialyzing the solution against water and isolating the purified polymer therefrom.

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7. A method as claimed in Claim 6 in which the said purified polymer has a molecular weight of about 2,000-10,000.

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8. A method as claimed in Claim 6 substantially as specifically described herein with reference to the accompanying examples.



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9. A polymer as claimed in Claim 1 wherever made  
by a method as claimed in Claim 6, 7 or 8.

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