OSIM

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EXAMEN PENTRU CONSILIERI ÎN PROPRIETATE INDUSTRIALĂ

Brevete de invenţie

Sesiunea: MARTIE 2011

Proba practică 2

Domeniul tehnic de specialitate: **CHIMIE**

Redactarea unui răspuns la o notificare transmisă de OSIM

Sunteţi, în conformitate cu art. 39 din Legea 64/1991 privind brevetele de invenţie, republicată în Monitorul Oficial al României, Partea I, nr. 541 din 8 August 2007, reprezentantul autorizat în faţa OSIM al unui solicitant care a înregistrat la OSIM o cerere de brevet de invenţie nr. 2006-00301 (fictiv), în vederea obţinerii protecţiei prin brevet pentru o invenţie cu titlul "Pastă de dinţi antitartru".

Aveţi la dispoziţie următoarele:

1. Notificarea OSIM conţinând rezultatele examinării în fond a invenţiei revendicate din cererea de brevet privind îndeplinirea condiţiilor de brevetabilitate realizată pe baza analizei comparative cu materialele documentare relevante selectate din stadiul tehnicii (anexa I);

2. O copie a descrierii invenţiei şi revendicărilor aşa cum au fost depuse la OSIM de către solicitant (anexa II);

3. Documentele relevante din stadiul tehnicii, consemnate în notificare, faţă de care s-a efectuat analiza comparativă.

Vi se cere să redactaţi răspunsul la notificare (anexa I), exprimând punctul dvs. de vedere faţă de observaţiile din notificare, prin argumentaţie tehnică bazată pe descrierea invenţiei şi revendicări, în ansamblul lor, care să justifice îndeplinirea condiţiei de activitate inventivă, conform art. 12 din Legea 64/1991privind brevetele de invenţie.

De asemenea, vi se cere să redactaţi revendicarea independentă, cuprinzând soluţia tehnică care rezolvă problema invenţiei şi care să îndeplinească condiţia de activitate inventivă.

O.S.I.M.

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Anexa I:

Către,

Solicitantul CBI....

Notificare

Referitor la cererea de brevet nr. **2006-00301** din 30.08.2006 (fictiv) cu titlul **"Pastă de dinți antitartru"**

Vă aducem la cunoştință că, în urma examinării cererii de brevet de invenție sus-menționate în conformitate cu prevederile Legii 64/1991 privind brevetele de invenție, republicată în Monitorul Oficial al României, Partea I, nr. 541 din 8 August 2007 şi ale Regulamentului de aplicare al acesteia, rezultă că obiectul pentru care se solicită protecție prin brevet este o compoziție de pastă de dinți, cu efect antitartru constituită dintr-o combinație de săruri alcaline solubile în apă şi un purtător acceptabil farmaceutic (revendicarea independentă 1).

Obiectul invenției revendicate este un produs, el fiind dezvăluit în cererea de brevet în conformitate cu prevederile art.18, alin. 1 din Legea brevetelor şi ale art. 37 din Regulamentul de aplicare al acesteia.

Analiza comparativă a invenției din revendicarea 1 a avut la bază următoarele documente în temă selectate din stadiul tenicii:

-**WO 9414407**, notat în prezenta notificare cu **D1,** se consideră documentul cel mai apropiat de invenția revendicată;

-**EP-A-0469722**, notat în prezenta notificare cu **D2**.

D1 dezvăluie o compoziție antitartru în care agenții antitartru sunt unul sau mai mulți agenți selectați dintr-un grup care conține pirofosfat şi polifosfați liniari condensați. Exemplul XVI din descrierea D1 prezintă o compoziție antitartru care cuprinde o combinație de pirofosfat solubil în apă - pirofosfat tetrapotasic şi un polifosfat - tripolifosfat de sodiu. Compoziția poate fi utilizată ca pastă de dinți.

D2 se referă la o compoziție dentară care poate fi utilizată ca pastă de dinți conținând drept agent antibacterian triclosan, ambalată într-un recipient flexibil pe bază de polifluoretilenă sau policloruă de vinil, polimeri compatibili cu triclosanul. În descriere se precizează, la pag. 6 rd. 5-17, că în compoziție se pot adăuga agenți antitartru cum ar fi polifosfați sau pirofosfați în proporție de la 0,1 până la 3%, de preferat de la 1,5 până la 2,5%.

În urma examinării cererii de brevet şi a analizei comparative, bazată pe materialele relevante din stadiul tehnicii, luate în analiză în mod individual, apreciem că invenția din revendicarea independentă 1 *prezintă ca elemente de noutate natura elementelor asociate în compoziție, şi anume, ingredienții activi antitartru cu purtătorul acceptabil farmaceutic, precum şi rapoartele de asociere ale acestora în compoziția de pastă de dinți.* În consecință, considerăm că invenția revendicată îndeplineşte condiția de noutate în conformitate cu prevederile art. 10 din Legea 64/1991 privind brevetele de invenție.

Problema tehnică pe care o rezolvă invenția constă în stabilirea raportului optim între ingredienții activi antitatru şi între aceştia şi apă în compoziția de pastă de dinți, astfel încât să se obțină o eficiență antitartru cel puțin echivalentă cu cea a pastelor de dinți cunoscute şi o stabilitate îmbunătățită a pastei de dinți la depozitare.

Soluția de rezolvare a problemei tehnice din cererea de brevet 2006-00301, constă în obținerea unei compoziții de pastă de dinți care cuprinde 0,5% până la 2% pirofosfat alcalin solubil în apă şi 0,5% până la 3% polifosfat alcalin solubil în apă.

Analizând soluția *aşa cum este prezentată în revendicarea 1*, comparativ cu cele două documente selectate din stadiul tehnicii, apreciem că asocierea unei sări polifosfat solubilă în apă şi a unei sări pirofosfat solubilă în apă, reprezintă o soluție tehnică ce rezultă, în mod evident, pentru o persoană de specialitate în domeniu pentru rezolvarea problemei tehnice enunțate anterior. În consecință, *apreciem că invenția revendicată, reprezintă o combinație de caracteristici care rezultă în mod evident din stadiul tehnicii, fără să conducă la un efect tehnic neaşteptat.*

În concluzie, considerăm că invenția revendicată *nu îndeplineşte condiția de activitate inventivă* prevăzută la art. 12 din Legea 64/1991 privind brevetele de invenție, republicată în Monitorul Oficial al României, Partea I, nr. 541 din 8 August 2007.

Aşteptăm punctul dvs. de vedere față de considerațiile de mai sus în termen de 60 de zile de la data prezentei. În caz contrar cererea va fi soluționată pe baza documentelor existente la dosar şi a observațiilor din prezenta notificare.

Examinator

.....

Invenţia se referă la o compoziţie de pastă de dinţi cu efect antitartru, utilizată pentru igiena dentară.

Prezenţa compuşilor peroxidici în igiena orală este cunoscută ca fiind eficientă pentru albirea dinţilor, pentru tratarea gingivitelor, a periodontitelor şi în combaterea inflamaţiilor. Asemenea compoziţii de paste de dinţi se regăsesc în brevetele **US 4971782**, **4897258** şi **4837008**. Însă compuşii peroxidici nu au efect în combaterea tartrului.

Între numeroşii agenţi chimici descrişi în stadiul anterior al tehnicii ca fiind eficienţi ca agenţi antitartru sunt sărurile solubile în apă de polifosfat şi pirofosfat. Publicaţiile brevetelor **US 4923684** şi **4985236** descriu folosirea unui tripolifosfat de metal alcalin solubil în apă ca agent antitartru în compoziţiile de pastă de dinţi. Pentru a fi stabilă la depozitare, sarea de tripolifosfat trebuie încorporată în pasta de dinţi la o concentraţie de cel puţin 4% în greutate, pasta de dinţi având un *p*H alcalin, de exemplu un *p*H de 8 - 10. *La concentraţii mai mici de 4% în greutate, de exemplu, 3% în greutate, se arată că sarea de polifosfat este instabilă în compoziţia de pastă de dinţi.*

De asemenea, **US 4684518** dezvăluie că sărurile de pirofosfat de metal alcalin solubile în apă sunt eficiente ca agenţi anticalcul, atunci când sunt prezente în compoziţiile de pastă de dinţi la o concentraţie suficientă pentru a asigura cel puţin 1,5% anion pirofosfat.

Brevetul **US 5176900** descrie o compoziţie de pastă de dinţi care conţine o combinaţie anticalcul de sare tripolifosfat solubilă în apă, suficientă pentru a asigura 0,5 - 7,5% anion P_3O_{10} şi o sare ortofosfat solubilă în apă în proporţie suficientă pentru a asigura 0,2 - 5% anion ortofosfat, combinaţia fiind stabilă la înmagazinare la un *p*H sub 8.

Problema tehnică pe care o rezolvă invenţia constă în stabilirea raportului optim între ingredienţii activi antitatru şi între aceştia şi apă în compoziţia de pastă de dinţi astfel încât să se obţină o eficienţă antitartru cel puţin echivalentă cu cea a pastelor de dinţi cunoscute şi o stabilitate îmbunătăţită a pastei de dinţi la depozitare.

Invenţia are drept obiect o compoziţie de pastă de dinţi antitartru care cuprinde 0,5 până la 3% polifosfat alcalin solubil în apă şi 0,5% până la 2% pirofosfat alcalin solubil în apă.

Polifosfatul alcalin solubil în apă este tripofosfat de sodiu.

Pirofosfatul de metal alcalin este pirofosfat de sodiu.

Purtătorul acceptabil farmaceutic preferat este în proporţie de 40% până la 70% în compoziţie, având un conţinut maxim de apă de 5% până la 8%.

Pasta de dinți conține 0,25%-5% compuşi peroxidici. De preferat, compusul peroxidic este peroxidul de calciu.

Pasta de dinți conține 10-2000 ppm ioni florură. De preferat, compusul fluorurat este monofluorfosfat de sodiu.

Pasta de dinți conține 8-15% compus bicarbonat. De preferat, compusul bicarbonat este bicarbonatul de sodiu.

Compoziția de pastă de dinți antitartru prezintă următoarele avantaje:

-eficiență foarte bună antitartru;

-stabilitate mare la depozitare fără modificări ale concentrației şi proprietăților ingredienților activi;

-prezintă bune proprietăți antibacteriene.

S-a constatat că folosind o combinație de săruri alcaline solubile în apă de pirofosfat şi polifosfat, *în anumite proporții*, în prezența unui purtător acceptabil farmaceutic *adecvat*, având un conținut limitat de apă şi a altor ingredienți activi folosiți în mod obişnuit pentru igiena dentară şi a cavității bucale, se asigură concentrația necesară de ioni de agenți antitartru în compoziție, la concentrații mai mici ale agenților antitartru decât cele din stadiul tehnicii, astfel încât prin *efectul antitartru cumulat* al acestora se înregistrează un efect antitartru cel puțin echivalent cu al compozițiilor cunoscute.

De asemenea, s-a constatat că, atunci când cantitatea de apă prezentă în pasta de dinți este menținută *la o concentrație de mai puțin de 8% în greutate şi, de preferință, 5 până la 8%*, concentrația ionului liber de pirofosfat ca şi orice concentrație de ioni liberi de fluorură încorporați în pasta de dinți se mențin pe perioada depozitării, în principal, la nivelurile inițiale de încorporare, în ciuda prezenței în pasta de dinți a ingredienților reactivi, cum ar fi compuşii peroxid şi bicarbonat, ca şi cationii de metal polivalent, cum ar fi ionul de calciu, care în mod normal este incompatibil cu fluorura si sărurile de pirofosfat, solubile în apă, întrucât aceşti cationi polivalenți interacționează, în mod normal, pentru a forma săruri insolubile în apă care nu sunt active în mediul apos al cavității bucale. Prin urmare, stabilitatea la depozitare este îmbunătățită.

Sărurile de pirofosfat cu eficacitate antitartru care pot fi folosite în prezenta invenție includ săruri solubile în apă, cum ar fi săruri de pirofosfat de metal dialcalin sau tetra-alcalin, cum ar fi $Na_4P_2O_7$ (TSPP), $K_4P_2O_7$, $Na_2K_2P_2O_7$, $Na_2H_2P_2O_7$ şi $K_2H_2P_2O_7$. Sărurile de pirofosfat sunt încorporate în compoziția pastei de dinți din prezenta invenție la

o concentrație de aproximativ 0,5 până la aproximativ 2% în greutate şi, de preferință, 1,5 până la aproximativ 2% în greutate.

Sărurile de polifosfat includ tripolifosfați de metal alcalin solubili în apă, cum ar fi tripolifosfat de sodiu (STPP) şi tripolifosfat de potasiu. Sărurile de polifosfat sunt încorporate în compoziția pastei de dinți din prezenta invenție la o concentrație de aproximativ 1 până la aproximativ 3% în greutate şi, de preferință, aproximativ 2 până la aproximativ 3% în greutate.

Purtătorul folosit pentru a prepara compoziția de pastă de dinți din prezenta invenție poate fi în mod substanțial anhidru sau poate conține cantități limitate de apă. Acesta nu este limitat în mod specific şi poate fi selectat din grupul constituit din: glicerină, sorbitol, polietilen glicol sau orice amestec corespunzător al acestora. Cantitatea de apă care poate fi inclusă *în purtător este limitată la cel mult 9% în greutate. În cantități mai mari apa poate influența negativ stabilitatea compoziției de pastă de dinți.*

Purtătorul reprezintă, în general de la aproximativ 40 până la aproximativ 70% în greutate din compoziția pastei de dinți, de preferință aproximativ 50% în greutate din compoziția pastei de dinți. Glicerina este preferată ca purtător pentru compoziția conform invenției.

Compuşii peroxidici pot fi folosiți ca ingredienți activi pentru albire în compoziția pastei de dinți din invenție şi pot fi prezenți într-o concentrație de 0,25 până la 5% în greutate şi, de preferință, 0,5 până la 2% în greutate. Compuşii peroxidici corespunzători pentru folosirea în invenție includ peroxizi metalici, cum ar fi peroxid de calciu, peroxid de magneziu şi peroxid de zinc.

Florurile se adaugă în compozițiile de pastă de dinți datorită efectului acestora de a combate cariile dentare. Florurile utilizate sunt caracterizate prin posibilitatea de a elibera ioni de fluorură în apă şi pot fi selectate dintre fluorură de sodiu, fluorură de potasiu, monofluorfosfat de sodiu şi fluor silicat de sodiu. Florurile preferate sunt fluorura de sodiu şi monofosfatul de sodiu. Este de preferat să se folosească o fluorură solubilă în apă cu un conținut de 10 - 2000 ppm de ion fluorură.

Compuşii de bicarbonat sunt incluşi la concentrații de 5% până la 20% în greutate pentru a se sigura un pH al compoziției de 8 până la 10. Este preferat bicarbonatul de sodiu.

Pentru o bună dispersare a compoziției de pastă de dinți în cavitatea bucală atunci când este aplicată, dar şi pentru a îmbunătăți proprietățile de detergent şi de spumare ale pastei de dinți, se folosesc agenți de suprafață. Aceştia pot fi selectați dintre: lauril sulfat

de sodiu (SLS), lauril sulfoacetat de sodiu, sulfonat de monogliceridă de nucă de cocos, sarcozinat de N-lauroil de sodiu; sarea de sodiu a monosulfat monogliceridei acizilor graşi de ulei hidrogenat de nucă de cocos.

Agentul activ de suprafață este inclus în purtătorul pastei de dinți din invenție într-o concentrație de 0,5 pană la 3% în greutate, de preferință 1 până la 2% în greutate.

Agenții de lustruire preferați pentru compoziția de pastă de dinți conform invenției sunt materiale silicoase, cum ar fi silice, cu dimensiuni ale particulei de până la 10 μ şi o suprafață specifică foarte mare, adică de la 150 la 170 m^2/g. Preferat pentru compoziția conform invenției este un precipitat de silice amorf hidratat, cum ar fi Sorbosil AC-35, Zeodent 115.

Agentul de lustruire poate fi adăugat în compoziția pastei de dinți din invenție într-o concentrație de aproximativ 10 până la aproximativ 30% în greutate.

Agenții de îngroşare folosiți în compoziție pot fi anorganici sau organici. Cei anorganici pot include silice afumată (Cab-o-sil) sau silice de îngroşare (Sylox 15). Cei organici pot fi gume naturale sau sintetice, coloizi care sunt recomandați mai ales dacă conținutul de apă al compoziției este de până la 9% în greutate. Exemplele de astfel de substanțe de îngroşare includ muşchi irlandez, gumă de xantan şi sodiu carboximetil celuloză, amidon, polivinilpirolidonă, hidroxietilpropil-celuloză, hidroxibutil metil celuloză, hidroxipropil metil celuloză şi hidroxietil celuloză.

Agenții de îngroşare pot fi încorporați în compozițiile din prezenta invenție la o concentrație de 0,05 până la 2% în greutate.

Coloranți, cum ar fi pigmenții, pot fi folosiți în compoziția conform invenției. Pigmenții includ pigmenți anorganici insolubili în apă, netoxici, cum ar fi dioxid de titan şi oxid de crom pentru verde. Pigmenții au o mărime a particulei variind de la 5 -1000 μ, de preferință 250 - 500 μ şi sunt prezenți în concentrație de 0,5 până la 3% în greutate.

În compoziția pastei de dinți din prezenta invenție poate fi de asemenea încorporat orice material de aromatizare sau îndulcire. Exemple de constituenți corespunzători de aromatizare sunt uleiuri aromatizante, adică, uleiuri de izmă, mentă piperată, perişor, dafin american, salvie, cuişoare, eucalipt, scorțişoară, lămâie şi portocală şi metil salicilat. Agenți corespunzători de îndulcire includ sucroză, lactoză, maltoză, sorbitol, xilitol, ciclamat de sodiu, perilartină şi zaharină de sodiu. În mod corespunzător, agenții de aromatizare şi îndulcire pot cuprinde împreună de la 0,01% până la 5% sau mai mult din preparat.

Pentru a prepara compoziția de pastă de dinți din prezenta invenție, umectanții-glicerina şi polietilen glicolul şi îndulcitorul, se dispersează într-un malaxor până când amestecul devine o fază de gel omogenă. În faza de gel se adaugă un colorant, agenții anticalcul şi agenții fluorură anticarii. Ingredienții se amestecă până când se obține o fază omogenă. Apoi se adaugă agentul de îngroşare, agentul de lustruire, ingredienții reactivi, cum ar fi peroxid, săruri de bicarbonat, aromatizantul şi agentul activ de suprafață. Amestecarea se realizează cu viteză mare sub vid de aproximativ 20 - 100 mm Hg. Produsul care rezultă este o pastă omogenă, semi-solidă, care poate fi extrudată.

Se prezintă în continuare două exemple nelimitative de realizare a invenției.

Exemplul 1. Pentru a demonstra eficacitatea anticalcul a compoziției din prezenta invenție, o compoziție de pastă de dinți din prezenta invenție numită "Compoziția A" se prepară, conținând 2% $Na_4P_2O_7$ şi 3% tripolifosfat de sodiu, urmând procedeul descris mai sus cu ingredientele din tabelul 1 de mai jos.

Tabelul 1

Compoziția A	
Ingrediente	
Glicerina	25,00%
PEG 600	3,00
Propilen glicol	17,94
Zaharină de Na	0,50
Xantan	0,20
Carboximetil Celuloză	0,20
Monofluorofosfat de sodiu (MFP)	0,76
$Na4P_2O_7$ (TSPP)	2,00*
Tripolifosfat de sodiu (STPP)	3,00
TiO_2	0,50
Silice precipitată hidratată amorfă	21,00
Colorant FD&C verde # 3 (1%)	0,20

Silice de îngroşare (Silox 15)	2,50
$NaHCO_3$	12,00
CaO_2	0,50
Aromă	1,0
Lauril sulfat de sodiu [SLS]	1,70
Apă	6,00
Na_2CO_3	2,00

* 2% $Na_4P_2O_7$ asigură 1,3% ion $P_2O_7^{-4}$

Pentru a determina dacă prezența combinației de TSPP şi STPP la nivelurile de concentrație prezente în Compoziția A (2% $Na_4P_2O_7$ şi 3% tripolifosfat de sodiu) asigură o eficacitate anticalcul acceptabilă, testarea *in vitro* a compoziției A are loc conform următoarei proceduri:

Compoziția A se diluează cu apă şi este centrifugată pentru a obține un supernatant care se diluează de 20 ori cu apă şi apoi se suspendă granule de hidroxiapatită (68 m^2/g) în supernatantul diluat pe timpul nopții la 37□C. Granulele tratate se separă apoi din supernatant şi se adaugă la o soluție de creştere a cristalului care conține 1,06 mmoli $CaCl_2$ şi 0,63 mmoli KH_2PO_4 şi 150 mmoli NaCl.

Se înregistrează *p*H-ul soluției de creştere a cristalelor de hidroxiapatită în funcție de timp. *O scădere a pH-ului reprezintă indiciul unei creşteri a cristalului de hidroxiapatită (adică tartrul).*

Rezultatele testului *in vitro* înregistrate în tabelul 2 de mai jos. Pentru comparație, testul se repetă, cu excepția faptului că pastele de dinți testate includ o pastă de dinți antitartru care se găseşte în comerț, numită "Pastă de dinți comercială I", şi o a doua pastă de dinți comercială care nu are calități antitartru, numită "Pastă de dinți comercială II", comercializată de diferiți producători, ca şi o pastă de dinți martor cu o compoziție identică cu Compoziția A, cu excepția faptului că nu sunt incluse TSPP şi STPP.

Rezultatele obținute cu pastele de dinți comerciale şi martor sunt, de asemenea, înregistrate în tabelul 2 de mai jos.

Tabelul 2

	*p*H		
Pasta de dinți	0 min	15 min	30 min
Compoziția A	7,38	7,25	7,22
Pastă de dinți comercială I	7,37	7,07	7,04
Pastă de dinți comercială II	7,38	6,48	6,40
Control	7,38	6,88	6,81

Rezultatele din tabelul 2 indică faptul că Compoziția A prezintă o cădere a *p*H-ului mult mai redusă decât căderea de *p*H înregistrată pentru pastele de dinți comerciale anticalcul sau de pasta de dinți martor, indicând faptul că Compoziția A asigură o eficacitate antitartru mai mare decât pastele de dinți comerciale.

Exemplul 2. Compoziția B, având compoziția din tabelul 3 de mai jos, se prepară urmând procedeul din exemplul 1. Pasta de dinți B se încarcă apoi într-un tub de plastic laminat, sigilat şi apoi lăsat la 40°C timp de 2 luni. Conținutul tubului de plastic laminat se analizează după perioada de depozitare. Rezultatele analizei se găsesc în tabelul 4 de mai jos.

Tabelul 3

Compoziția B	
Ingredienți	G%
Glicerina	25,2486
Silice precipitată hidratată amorfă (Zeodent 115)	21,0000
Propilen glicol	17,8900
Bicarbonat de sodiu	1 2,0000
Apă deionizată	6,0000
Polietilen glicol 600	3,0000

Tripolifosfat de sodiu	3,0000
Silice amorfă hidratată	2,5000
Na_2CO_3	2,0000
Pirofosfat de tetrasodiu	2,0000
Lauril sulfat de sodiu	1,7000
Monofluorofosfat de sodiu	0,760
Aromă	1,00
Zaharină de sodiu	0,5000
Dioxid de titan	0,5000
Peroxid de calciu	0,5000
Gumă xantan	0,2000
Carboximetil celuloză de sodiu	0,2000
Colorant FD&C verde = 3	0,0014
TOTAL:	100,0000

Tabelul 4

Depozitarea compoziției B la 40□C

Inițial 2 luni

%	%	%	%	%	%
$Na_4P_2O_7$	Tripolifosfat de sodiu	Fluorură solubilă	$Na_4P_2O_7$	Tripoli fosfat de sodiu	Fluorură solubilă
1,8	3,1	0,096	2,0	2,7	0,097

Rezultatele înregistrate în tabelul 4 indică faptul că, Compoziția B este stabilă la depozitare cu o schimbare mică sau fără nici o schimbare în concentrațiile de $Na_4P_2O_7$, tripolifosfat de sodiu sau fluorură solubilă.

Revendicări

1. Pastă de dinți antitartru cu stabilitate mare la depozitare, **caracterizată prin aceea că**, cuprinde 0,5% până la 2% pirofosfat alcalin solubil în apă şi 0,5% până la 3% polifosfat alcalin solubil în apă.

2. Pastă de dinți conform revendicării 1, **caracterizată prin aceea că**, polifosfatul alcalin solubil în apă este tripolifosfatul de sodiu.

3. Pastă de dinți conform revendicării 1, **caracterizată prin aceea că**, pirofosfatul alcalin solubil în apă este pirofosfatul de sodiu.

4. Pastă de dinți conform revendicării 1, **caracterizată prin aceea că**, purtătorul acceptabil farmaceutic este în proporție de 40% până la 70% în compoziție şi are un conținut de apă între 5 şi 8% în greutate.

5. Pastă de dinți conform revendicării 1, **caracterizată prin aceea că**, conține 0,25%-5% compuşi peroxidici.

6. Pastă de dinți conform revendicării 5, **caracterizată prin aceea că**, compusul peroxidic este peroxidul de calciu.

7. Pastă de dinți conform revendicării 1, **caracterizată prin aceea că**, conține 10-2000 ppm ioni florură.

8. Pastă de dinți conform revendicării 7, **caracterizată prin aceea că**, compusul fluorurat este monofluorfosfat de sodiu.

9. Pastă de dinți conform revendicării 1, **caracterizată prin aceea că**, conține 8-15% compus bicarbonat.

10. Pastă de dinți conform revendicării 1, **caracterizată prin aceea că**, compusul bicarbonat este bicarbonatul de sodiu.

Invenția are drept obiect o compoziție de pastă de dinți antitartru constituită din 0,5 până la 3% polifosfat alcalin solubil în apă şi 0,5% până la 2% pirofosfat alcalin solubil în apă, asociați cu 40 - 70% purtător acceptabil farmaceutic, 0,25 - 5% compuşi peroxidici, 10 - 2.000 ppm ioni fluorură, 8-15 % bicarbonat, restul fiind agenți uzuali care întră în componența pastelor de dinți: agenți activi de suprafață, agenți de lustruire, agenți de îngroşare, coloranți, îndulcitori şi aromatizanți, procentele fiind exprimate în greutate.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [5]: A61K 7/16 — A1

(11) International Publication Number: WO 94/14407

(43) International Publication Date: 7 July 1994 (07.07.94)

(21) International Application Number: PCT/US93/11787

(22) International Filing Date: 6 December 1993 (06.12.93)

(30) Priority Data:
07/993,336 18 December 1992 (18.12.92) US
08/148,776 16 November 1993 (16.11.93) US

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(81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ORAL COMPOSITIONS CONTAINING ANTIPLAQUE, ANTICALCULUS AGENTS

(57) Abstract

This invention involves a composition for treating or preventing dental plaque, calculus and gingivitis, or malodor of the oral cavity, comprising: (a) (i) a source of a safe and effective amount of zinc ions; (ii) a source of citrate ions; and (iii) one or more anticalculus agents selected from the group consisting of pyrophosphate, phosphonate, diphosphonate and pharmaceutically-acceptable linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is an integer from 2 to 21; wherein the molar ratio of zinc:citrate is at most about 1:1; the molar ratio of zinc:pyro is at most about 1:1; and (b) and a pharmaceutically-acceptable topical oral carrier. This invention also involves methods for treating or preventing dental plaque, calculus and gingivitis, or malador of the oral cavity, comprising administering to the oral cavity of a human or other animal such a composition.

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ORAL COMPOSITIONS CONTAINING ANTIPLAQUE, ANTICALCULUS AGENTS

The subject invention relates to oral compositions, such as dentifrices and oral solutions, for the treatment or prevention of dental plaque, calculus and gingivitis, and mouth malodor.

Background of the Invention

The mouth is a habitat for microbial growth and colonization. Within the mouth, the gums, lips, oral mucosa (cheek), palate, tongue and teeth provide surfaces for the colonization and accumulation of bacteria. Teeth are unique in the oral cavity because they have hard, non-shedding surfaces where bacteria and their products (dental plaque) can significantly accumulate, especially in approximal areas and along the gingival crevice.

Dental plaque is a rough sticky film on the teeth that is made up of saliva, bacteria and food particles which adheres tenaciously to teeth at points of irregularity or discontinuity. Within a few hours of teeth cleaning, a film of salivary mucins, consisting primarily of proteins, forms on the teeth. Various oral bacteria colonize the mucins and multiply, forming a layer of plaque. Carbohydrate food debris adheres to the mucins and is digested by some types of plaque-causing bacteria. The digestion both produces by-products which add to the plaque, and produces acid which erodes tooth enamel. The bacterial by-products produced in the oral cavity also include foul smelling gases which can result in malodor of the oral cavity.

The oral bacteria in dental plaque includes many gram positive and gram negative microorganisms embedded in an extracellular matrix of insoluble polysaccharides, firmly attached to teeth and other oral surfaces. The colonization of bacteria to form dental plaque follows an ecological pattern where a few pioneer aerobic species, mostly gram-positive streptococci, colonize enamel surfaces. The plaque then progresses through stages of increasing microbial complexity. Mature plaques, often found in protected regions of the

teeth, such as cracks, approximal regions and in the gingival crevice, typically contain anaerobes. Saliva and crevicular fluid are a source of nutrients for the dental plaque. Local conditions affect the metabolic activity and composition of dental plaque.

If not prevented or removed, plaque may become embedded with mineral salts, containing calcium and phosphate, to form a hard crusty deposit, calculus or tartar, on the teeth. Calculus may be white or yellowish in color or may be stained or discolored by extraneous agents. Calculus tends to be more unsightly than plaque and much more difficult to remove from the teeth. The toxins in plaque and calculus can irritate the gingival tissues surrounding the coated teeth, causing inflammation and destruction of the gums which can lead to other complications.

Zinc is an anticalculus agent; however, compositions containing zinc generally taste astringent and unpleasantly bitter. Like the chemical and biological activities, the negative aesthetics of the zinc cation are dose dependent: higher concentrations of zinc exhibit poorer aesthetics; therefore, increasing the concentration of free zinc tends to increase efficacy at the expense of aesthetics. This coupled behavior between efficacy and aesthetics has limited the utility of zinc in oral compositions. Pyrophosphate is also an anticalculus agent and, likewise, has an unpleasant taste which worsens with increased pyrophosphate concentration. By carefully formulating zinc and pyrophosphate-containing compositions, applicants have surprisingly found that the level of zinc in an oral composition can be increased, thus increasing the corresponding anticalculus effect, without greatly increasing the negative aesthetics of the composition.

It has been surprisingly found that it is possible to uncouple the efficacy and aesthetics of zinc containing compositions. When zinc is formulated with citrate and pyro at certain ratios of zinc:citrate and zinc:pyro, it is possible to avoid the aesthetic negatives typically associated with the zinc ion.

It is an object of the subject invention to provide compositions for impeding calculus formation in the oral cavity.

It is also an object of the subject invention to provide compositions for impeding dental plaque formation in the oral cavity.

It is a further object of the subject invention to provide methods for impeding calculus formation in the oral cavity.

It is also an object of the subject invention to provide methods for impeding dental plaque formation in the oral cavity.

Summary of the Invention

This invention involves a composition for treating or preventing dental plaque, calculus and gingivitis, or malodor of the oral cavity, comprising:

(a) (i) a source of a safe and effective amount of zinc ions; (ii) a source of citrate ions; and (iii) one or more anticalculus agents selected from the group consisting of pyrophosphate, phosphonate, diphosphonate and pharmaceutically-acceptable linear condensed poly-phosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is an integer from 2 to 21;

wherein the molar ratio of zinc:citrate is at most about 1:1; the molar ratio of zinc:pyro is at most about 1:1; and

(b) and a pharmaceutically-acceptable topical oral carrier.

This invention also involves methods for treating or preventing dental plaque, calculus and gingivitis, or malodor of the oral cavity, comprising administering to the oral cavity of a human or other animal such a composition.

Detailed Disclosure of the Invention

The subject invention provides compositions effective against dental plaque formation, calculus formation, gingivitis, and mouth malodor.

"Pharmaceutically-acceptable topical oral carrier", as used herein, denotes a carrier for the active compounds of the subject invention (hereinafter "Actives") comprising solid or liquid filler diluents suitable for use in contact with the oral tissues of humans and lower animals without undue toxicity, incompatibility, instability, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio. Such topical oral carrier, when combined with Actives of the subject invention, results in a composition which is administered topically to the oral cavity. Preferably such compositions are held in the oral cavity for a period of time, and then largely

expectorated rather than being swallowed. Such compositions include mouthwashes, mouth rinses, mouth sprays, dental treatment solutions, toothpastes, dental gels, tooth powders, prophylaxis pastes, lozenges, chewing gums and the like and are more fully described hereinafter. Dentifrices and mouthwashes are the preferred compositions.

"Pyro", as used herein, refers to pyrophosphate; phosphonate; diphosphonate; and pharmaceutically-acceptable polyphosphates including, but not limited to, linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is an integer from 2 to 21.

"Free pyro", as used herein, refers to pyro that is not bound or chelated to the transition metal, zinc.

"Free zinc", as used herein, refers to hydrated zinc cationic species, such as $Zn(H_2O)_6^{2+}$.

As used herein, percentages listed are weight percentage of composition unless otherwise specified.

The amounts of pyro and citrate are expressed in terms of a ratio to the amount of zinc in the oral composition. On a molar basis, the amount of citrate relative to zinc is at least one when the molar amount of zinc is one (*i.e.* the molar ratio of zinc:citrate is at most about 1:1); and the amount of pyro relative to zinc is at least one when the molar amount of zinc is one (*i.e.* the molar ratio of zinc:pyro is at most about 1:1). Preferably the zinc:citrate ratio is from about 1:1 to about 1:20; more preferably from about 1:1 to about 1:4, more still preferably from about 1:1 to about 1:3. Preferred is a zinc:pyro ratio from about 1:1 to about 1:20 more preferably from about 1:1 to about 1:8, more preferably still from about 1:1.5 to about 1:6. Also preferred is a zinc:citrate:pyro ratio wherein the sum of the molar ratio amounts of citrate ions and pyro ions is from about 2 to about 9, more preferably from about 3 to about 9, when the ratio amount of zinc is 1.

The amount of zinc suitable for the purposes of the subject invention is from about 0.005% to about 5% Zn; more preferably from about 0.03% to about 3% Zn; more preferably still from about 0.05% to about 2% Zn. In dentifrice compositions, the preferred amounts of zinc are from about 0.1% to about 2%, more preferably from about 0.25% to about 1%. In mouthwashes, mouth rinses, mouth sprays and

dental solutions, the preferred amount of zinc is from about 0.005% to about 1%, more preferably from about 0.05% to about 0.5%.

The amount of citrate anion suitable for the purposes of the subject invention is from about 0.015% to about 25% citrate. In dentifrice compositions, the preferred amounts of citrate anion are from about 0.2 % to about 17%, more preferably from about 0.7% to about 12%, more preferably still from about 1.5% to about 5%. In mouthwashes, mouth rinses, mouth sprays and dental solutions, the preferred amount of citrate anion is from about 0.01% to about 12%, more preferably from about 0.1% to about 6%, more preferably still from about 0.15% to about 1%.

The amount of pyro anion suitable for the purposes of the subject invention is from about 0.015% to about 25% pyro. In dentifrice compositions, the preferred amounts of pyro ion are from about 0.25% to about 16%, more preferably from about 0.6% to about 11%. In mouthwashes, mouth rinses, mouth sprays and dental solutions, the preferred amount of pyro anion is from about 0.01% to about 11%, more preferably from about 0.1% to about 5%.

Suitable sources of zinc ions include zinc oxides, zinc halides, zinc-strong acid complexes, $Zn(NO_3)_2$, $Zn(ClO_4)_2$, $ZnSO_4$, and zinc-organic acids sources such as zinc lactate, tartrate, citrate salts, zinc citrate trihydrate and sodium zinc citrate. Zinc sources that are unacceptable are zinc ethylenediaminetetraacetate (ZnEDTA) and zinc nitrilotriacetate (ZnNTA). Preferred sources of zinc ions include zinc oxide (ZnO) and zinc nitrate; more preferred is ZnO.

Suitable sources of citrate ions include zinc citrate; citric acid; alkali metal salts of citric acid, especially sodium citrate and potassium citrate; pharmaceutically acceptable hydrated and dehydrated salts of any of the above; and mixtures of any of the above.

Suitable sources of pyro ions are disclosed in U.S. Pat. No. 4,885,155, issued December 5, 1989 to Parran & Sakkab; U.S. Pat. No. 3,678,154, issued July 18, 1972 to Widder et al.; U.S. Pat. No. 3,737,522, issued June 5, 1973 to Francis et al.; and U.S. Pat. No. 4,627,977, issued December 9, 1986 to Gaffer et al.; each is incorporated herein by reference. Suitable pyro ion sources include tetrasodium pyrophosphate, sodium acid pyrophosphate

($Na_2H_2P_2O_7$), tetrapotassium pyrophosphate ($K_4P_2O_7$); phosphates including, but not limited to, linear condensed polyphosphates of the general formula: $M_{(n+2)}P_nO_{(3n+1)}$ wherein M is Na or K, and n is an integer from 2 to 21; phosphonates and diphosphonates, such as EHDP (ethane-1-hydroxy-1,1-diphosphonate) and AHP (azacycloheptane-2,2-diphosphonic acid); pharmaceutically-acceptable alkali metal salts of pyrophosphates, polyphosphates, phosphonates and diphosphonates; and mixtures of any of the above. Preferred pyro ions are pyrophosphate ions; preferred polyphosphate ions are those of the above formula wherein n is 6, 13, and 21. Preferred alkali metals are sodium and potassium for solubility reasons; mixtures of alkali metal salts are acceptable.

The pH of oral compositions of the subject invention is critical but can be varied to some extent. Preferably the oral compositions are at a pH of from about 6 to about 9, more preferably from about 6.25 to about 8.75, more preferably still from about 7.5 to about 8.5.

During manufacture of a composition of this invention, the conditions for addition of each component should be optimized such that the pH of the mixture does not drop below formulation pH at any time during mixing the indredients.

Compositions

By "safe and effective amount" as used herein is meant an amount of compound or composition sufficient to induce a significant positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of the compound or composition will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific compound or composition employed, the particular pharmaceutically-acceptable carrier utilized, and like factors.

By the term "comprising", as used herein, is meant that various additional components can be conjointly employed in the compositions of this invention.

Components of the topical, oral carrier are suitable for administration to the oral cavity of a human or lower animal and are compatible with one another and the other components, especially with the Actives, used in an oral composition of the subject invention. The term "compatible" as used herein, means that the components are capable of being co-mingled with one another, in a manner such that there is no interaction which would substantially reduce the efficacy of the oral composition under ordinary use conditions.

Preferred topical, oral carriers provide the desired characteristics for mouthwashes, mouth rinses, mouth sprays, dental treatment solutions, toothpastes, dental gels, toothpowders, prophylaxis pastes, lozenges, chewing gums, and the like. The topical, oral carriers of the subject invention comprise components typically used in such compositions which are well known to a skilled practitioner. Such components include, but are not limited to, anticaries agents, antiplaque agents, anticalculus agents, dental abrasives, surfactants, flavoring agents, sweetening agents, binders, humectants, thickening agents, buffering agents, preservatives, coloring agents and pigments, ethanol and water.

Water is an optional component of the topical, oral carriers of the compositions of the subject invention. Water employed in the preparation of the commercially suitable compositions should preferably be of low ion content and free of organic impurities. Water preferably comprises from about 2% to about 99%, more preferably from about 20% to about 95% of the compositions of the subject invention. When in the form of toothpaste, the compositions preferably comprise from about 2% to about 80%, more preferably from about 30% to about 60%, water, while mouthwashes comprise preferably from about 45% to about 99%, more preferably from about 75% to about 98%, water.

Dental abrasives useful in the topical, oral carriers of the compositions of the subject invention include many different materials. The material selected must be one which is compatible with the composition of interest and does not excessively abrade dentin. These include, for example, silicas, including gels and precipitates, calcium carbonate, dicalcium orthophosphate dihydrate, calcium

pyrophosphate, tricalcium phosphate, calcium polymeta-phosphate, insoluble sodium polymeta-phosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and other materials such as those disclosed by Cooley et al. in U.S. Pat. No. 3,070,510, issued December 25, 1962, incorporated herein by reference. Mixtures of abrasives may also be used.

Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. For this reason they are preferred for use herein.

The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 and 30 microns, preferably between about 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica xerogels described in U.S. Pat. No. 3,538,230, issued March 2, 1970 to Pader et al., and in U.S. Pat. No. 3,862,307, issued June 21, 1975 to DiGiulio, both incorporated herein by reference. Preferred are the silica xerogels marketed under the tradename Syloid® by the W.R. Grace & Company, Davidson Chemical Division. Preferred precipitated silica materials include those marketed by the J. M. Huber Corporation under the tradename, Zeodent®, particularly the silica carrying the designation Zeodent 119®. These silica abrasives are described in U.S. Pat. No. 4,340,583, Wason, issued July 20, 1982, incorporated herein by reference.

Mixtures of abrasives may be used. The amount of abrasive in the compositions described herein ranges from about 6% to about 70%, preferably from about 15% to about 50%, when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the composition is a tooth powder.

Flavoring agents can also be added to the oral compositions of the subject invention to make them more palatable. Suitable flavoring agents include menthol, oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, and oil of clove. Flavoring agents are

generally included in the subject compositions in amounts of from 0% to about 3%, preferably from about 0.04% to about 2% by weight.

Coloring agents may be added to compositions of the subject invention to improve appearance. If present, coloring agents typically are included at levels of from about 0.001% to about 0.5% by weight.

Sweetening agents are also preferred in the compositions of the subject invention to make them more palatable. Sweetening agents which can be used include aspartame, acesulfame, saccharin salts, dextrose, glucose, levulose thaumatin, D-tryptophan, dihydrochalcones, and cyclamate salts. Saccharin salts are preferred. Sweetening agents are generally used in the subject compositions in amounts of from 0% to about 6%, preferably from about 0.005% to about 5% by weight.

Oral compositions can also contain a surfactant. Suitable surfactants are those which are reasonably stable and form suds throughout a wide pH range, including nonsoap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents, and compatible mixtures thereof. Many of these suitable surfactants are disclosed in U.S. Pat. No. 4,051,234, issued to Gieske et al. on September 27, 1977, and in U.S. Pat. No. 3,959,458 issued to Agricola, Briner, Granger and Widder on May 25, 1976, both of which are incorporated herein by reference. Surfactants are typically present in compositions of the subject invention at a level of from 0% to about 20%, preferably from about 0.1, more preferably from about 1% to about 4% by weight. Surfactants may also be used as solubilizing agents to help retain sparingly soluble components, e.g., some flavoring agents, in solutions. Surfactants suitable for this purpose include polysorbates and poloxamers. Preferred are surfactants which are non-ionic at the formulation pH of the compositions.

In preparing oral compositions of the subject invention, it is desirable to add binders and/or thickening agents, particularly to toothpaste compositions to provide a desired consistency. Suitable binders for these compositions are natural gums such as gum karaya, gum arabic, and gum tragacanth; polysaccharide gums such as xanthan gum; and other natural products such as carrageenan;

chemically modified natural products such as those based on cellulose esters, that is, carboxylmethylcellulose (CMC), hydroxyethylcellulose (HEC), and hydroxypropylcellulose (HPC); and synthetic binders such as polyvinylpyrrolidone; and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Carboxyvinyl polymer binders are less desirable, but may be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Blends and mixtures of the suitable binders may significantly improve the characteristics of compositions made therewith. Preferred binders are chemically modified celluloses such as CMC or HEC; more preferred is HEC. Binders and thickening agents are generally present in the compositions of the subject invention in amounts of from about 0.1% to 10%, preferably from about 0.25% to about 7.5%, more preferably from about 0.5% to about 3.5%.

Another optional component of the oral carriers of the compositions of the subject invention is a humectant. The humectant serves to keep toothpaste compositions from hardening upon exposure to air, and to give mouthwash and toothpaste compositions a moist feel to the mouth. Certain humectants can also impart desirable sweetness of flavor to mouthwash and toothpaste compositions. The humectant, on a pure humectant basis, generally comprises from 0% to about 70%, preferably from about 2% to about 55%, by weight of the compositions herein. Suitable humectants for use in compositions of the subject invention include edible polyhydric alcohols such as glycerin, sorbitol, xylitol, polyethylene glycol, and propylene glycol, especially sorbitol and glycerin.

Opacifiers may also be used in toothpastes of the subject invention to render the toothpaste opaque. Suitable opacifiers include titanium dioxide and some abrasives including, for example, magnesium aluminum silicate. Opacifiers generally comprise from 0% to about 4%, preferably from about 0.5% to about 3% by weight of the compositions herein.

Other optional components of the compositions of the subject invention are preservatives. The preservatives prevent microbial growth in the compositions. Suitable preservatives include

methylparaben, propylparaben, benzoates and ethanol. If the preservative is ethanol, it generally comprises from 0% to about 35% by weight, preferably from about 5% to about 15%, of the compositions herein. Other preservatives generally comprise from 0% to about 5% by weight, preferably from about 0.1% to about 2%, of the compositions herein.

Antimicrobial, antiplaque agents can also optionally be present in the oral compositions of the subject invention, on the condition that they are compatible with the Actives. Such agents may include, but are not limited to, triclosan, 2,4,4'-trichloro-2'-hydroxydiphenyl ether, as described The Merck Index, 11th Ed. (1989), p. 1520 (entry No. 9573); chlorhexidine, (Merck Index, No. 2090); alexidine (Merck Index, No. 222); hexetidine (Merck Index, No. 4624); sanguinarine (Merck Index, No. 8320); benzalkonium chloride (Merck Index, No. 1066); salicylanilide (Merck Index, No. 8299); domiphen bromide (Merck Index, No. 3411); cetylpyridinium chloride, (CPC) (Merck Index, No. 2024); tetradecylpyridinium chloride, (TPC); N-tetradecyl-4-ethylpyridinium chloride (TDEPC); octenidine; delmopinol, octapinol, and other piperidino derivatives; nicin preparations; antibiotics such as augmentin, amoxicillin, tetracycline, doxycycline, minocycline, and metronidazole; and peroxides, such as cylium peroxide, hydrogen peroxide, and magnesium monoperthalate and its analogs as described in U.S. Patent No. 4,670,252; and analogs and salts of the above antimicrobial antiplaque agents. If present, the antimicrobial antiplaque agents may comprise from 0% to about 6%, preferably from about 0.1% to about 5% by weight of the compositions of the subject invention.

Bleaching agents can also be present in the oral compositions of the subject invention. Suitable bleaching agents include organic and inorganic oxidizing agents such as hydrogen peroxide, alkali metal peroxides and superoxide and organic peroxides such as monoper-oxyphthalates and perbenzoic derivatives. If present, such bleaching agents may comprise from 0% to about 6%, preferably from about 1% to about 5% by weight of the compositions of the subject invention.

Nutrients can also be present in the oral composition of the subject invention, on condition that they are compatible with the Actives. Such agents may include folate, retinoids (Vitamin A), Vitamin C, Vitamin E. If present, the nutrients generally comprise from about 0.001% to about 10% by weight of the compositions of the subject invention.

Other optional ingredients include a safe and effective amount of a fluoride ion source, which typically is in the form of a water-soluble fluoride compound. This water-soluble fluoride compound is typically present in the compositions of the subject invention in an amount sufficient to give a fluoride concentration of from about 0.0025% to about 5.0% by weight, preferably from about 0.005% to about 2.0% by weight. Preferred fluoride sources are sodium fluoride, acidulated phosphate fluoride, and sodium monofluorophosphate. U.S. Pat. No. 3,678,154, issued July 18, 1972 to Widder et al., discloses such salts as well as others, and is incorporated herein by reference.

Preferred compositions of the subject invention are in the form of dentifrices, especially toothpastes. Components of toothpastes generally include a dental abrasive (from about 10% to about 50%), a surfactant (from about 0.5% to about 10%), a thickening agent (from about 0.1% to about 5%), a humectant (from about 10% to about 55%), a flavoring agent (from about 0.04% to about 2%), a sweetening agent (from about 0.1% to about 3%), a coloring agent (from about 0.01% to about 0.5%) and water (from about 2% to about 45%).

Other preferred compositions of the subject invention are mouth rinses, mouthwashes and mouth sprays. Components of such mouthwashes and mouth sprays include water (from about 45% to about 95%), ethanol (from 0% to about 25%), humectant (from 0% to about 50%), surfactant (from about 0.01% to about 7%), flavoring agent (from about 0.04% to about 2%), sweetening agent (from about 0.1% to about 3%), and coloring agent (from about 0.001% to about 0.5%). Such mouth rinses, mouthwashes and mouth sprays may also include an antiplaque agent (from about 0.1% to about 5%).

Other preferred compositions of the present invention are dental solutions. Components of such dental solutions generally include

water (from about 90% to about 99%), preservative (from about 0.01% to about 0.5%), thickening agent (from 0% to about 5%), flavoring agent (from about 0.04% to about 2%), sweetening agent (from about 0.1% to about 3%), and surfactant (from 0% to about 5%).

Methods of Use

Another aspect of the subject invention involves methods of treating or preventing mouth odor, dental plaque, calculus and gingivitis, by application of compositions comprising a safe and effective amount of Actives, to tissues of the oral cavity. Such compositions are described hereinabove.

These methods involve administering a safe and effective amount of Actives, typically by administering an oral composition of the subject invention, as described hereinabove, to the oral cavity. Generally an amount of composition comprising at least about 0.001g of the Actives is effective. The teeth and other oral cavity tissues are exposed to the Actives.

When the oral composition is a toothpaste, typically from about 0.3 grams to about 15 grams, preferably from about 0.5 grams to about 5 grams, more preferably from about 1 to about 2 grams, of toothpaste is applied to an applicating device e.g., a toothbrush. The applicating device is then contacted with the oral cavity surfaces in a manner such that the oral composition is contacted with tissue of the oral cavity, especially the teeth and gums. The applicating device may be further used to effect an even distribution of the oral composition to the tooth surface, for example by brushing. The application preferably lasts for a period of from about 15 seconds to about 10 minutes, more preferably from about 30 seconds to about 3 minutes, more preferably still from about 1 minute to about 2 minutes. Following application, the toothpaste residue is typically removed from the tooth surface by using a liquid acceptable to the oral cavity, typically water, to rinse and be expectorated from the oral cavity.

When the oral composition is a mouthwash, typically from about 1 ml. to about 20 ml., preferably from about 2 ml. to about 15 ml., most preferably from about 10 ml. to about 15 ml., of liquid mouthwash containing the antiplaque Active is introduced to the oral cavity. The liquid mouthwash is then agitated for from about 10 seconds to about

10 min., preferably from about 15 seconds to about 3 min., more preferably from about 30 seconds to about 2 minutes, within the oral cavity to obtain an improved distribution of the mouthwash over the tissue of the oral cavity. Following agitation, the mouthwash is typically expectorated from the oral cavity.

Application frequency is preferably from about 3 times weekly to about 4 times daily, more preferably from about once daily to about 3 times daily, more preferably still from about once to about twice daily. The period of such treatment typically ranges from about one day to a lifetime.

Oral Composition Examples

The following non-limiting examples further describe and demonstrate preferred embodiments within the scope of the subject invention. The examples are given solely for illustration and are not to be construed as limitations of the subject invention as many variations are possible without departing from the spirit and scope of the subject invention.

The compositions of the subject invention can be made using methods which are commonly used to produce oral care products.

EXAMPLES I-XI

The following are examples of dentifrice compositions of the subject invention and are made using conventional processes. The numbers listed are weight percentages of the compositions. During manufacture of each composition, a minimum pH of 7.5 is maintained.

Components	Ex. I	Ex. II	Ex. III	Ex. IV	Ex. V	Ex. VI
Sorbitol	21.17	21.17	14.2	18.3	21.17	31.65
PEG-6	3	3	3	3	3	
Citric Acid	0.69	0.34	0.51	0.51	1.03	1.46
Sodium Citrate	4.84	2.42	3.63	3.63	7.25	3.68
Zinc Nitrate						2.97
Zinc Sulfate				1.61		
Zinc Chloride	1.36				1.36	
Zinc Oxide		0.81	0.81			

Tetrapotassium Pyrophosphate (60% aqueous solution)	5.08	12.71	10.16	7.62	2.54	11.87
Sodium Acid Pyrophosphate	1.33	3.32	2.65	1.99	0.66	
Tetrasodium Pyrophosphate	1.28	3.19	2.55	1.91	0.64	
Sodium Fluoride	0.24	0.24	0.24	0.24	0.24	0.24
Sodium Saccharin	0.46	0.46	0.46	0.46	0.46	0.46
Titanium Dioxide	0.5	0.5	0.5	0.5	0.5	0.5
Silica	22	22	22	22	22	22
Glycerin	9	9	9	9	9	9
Carboxymethylcellulose	1	1	0.75		0.75	0.75
Xanthan Gum			0.75	0.75	0.75	0.75
Hydroxyethylcellulose				0.75		
Sodium Lauryl Sulfate (27.9% Aqueous solution)	4	4	4	4	4	4
Flavor	1.1	1.1	1.1	1.1	1.1	1.1
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
TOTAL	**100**	**100**	**100**	**100**	**100**	**100**

Slurry pH: 7.1 to 7.3

Component	Ex. VII	Ex. VIII	Ex. IX	Ex. X	Ex. XI
Sorbitol	31.65	31.65	14.2	31.65	31.65
PEG-6	3	3	3	3	3
Citric Acid(anhydrous or monohydate)	1.44	0.91	0.73	0.88	2.94
Sodium Citrate	3.23	0.144	4.62		
Zinc Oxide	0.81	0.407	0.81	0.374	0.13
Tetrapotassium Pyrophosphate (60% aqueous solution)	3.3		5.09	25.33	4.22
Sodium Acid Pyrophosphate			1.28		

Tetrasodium Pyrophosphate	2.66	6.65	1.33		
Sodium Fluoride	0.24	0.24	0.24	0.24	0.24
Sodium Saccharin	0.46	0.46	0.25	0.25	0.46
Titanium Dioxide	0.5	0.5	0.5	0.5	0.5
Silica	22	22	22	22	22
Glycerin	2.25	2.25	8	2.25	2.25
Carboxymethylcellulose	0.5	0.5	0.75		0.75
Xanthan Gum	0.4	0.4	0.75	0.75	0.75
Hydroxyethylcellulose				0.75	
Sodium Lauryl Sulfate (27.9% Aqueous solution)	4	4	4	4	4
Flavor	1.1	1.1	1	1	1
KOH/HCl and Water	q.s. to pH 7.5	q.s. to pH 8.0	q.s. to pH 8.0	q.s. to pH 8.0	q.s. to pH 8.5
Total	100	100	100	100	100

Slurry pH: 7.5 to 8.5

EXAMPLES XII-XVI

The following are examples of mouthwash and dental rinse compositions of the subject invention and are made using conventinal processes. The amounts listed are weight percentages of the compositions. During manufacture, the pH of the following compositions is maintained at a minimum of pH 7.5.

Component	**Ex. XII**	**Ex. XIII**	**Ex. XIV**	**Ex. XV**	**Ex. XVI**
Glycerin	10	10	10	10	10
Ethanol	10	10	10	10	10
Sodium Citrate	0.41	3.84			1.28
Citric Acid			11.40	3.80	
Zinc Chloride		1.36			
Zinc Oxide	0.081		1.63	0.81	0.41

Tetrapotassium Pyrophosphate (60% Sol'n)	1.10			5.51	1.1
Tetrasodium Pyrophosphate				2.66	0.27
Sodium Tripolyphosphate			7.36		0.37
Sodium Acid Pyrophosphate		6.66			0.22
Sodium Lauryl Sulfate	0.4	0.4	0.4	0.4	0.4
Sodium Saccharin	0.03	0.03	0.03	0.03	0.03
Flavor	0.22	0.22	0.22	0.22	0.22
NaOH/HCL & Water	q.s. 100% at pH 7.5	q.s. 100% at pH 8.5	q.s. 100% at pH 8.5	q.s. 100% at pH 7.5	q.s. 100% at pH 8.0

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications to the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of the subject invention.

Claims

1. A composition for treating or preventing dental plaque, calculus and gingivitis, or malodor of the oral cavity, comprising:

(a) (i) a source of a safe and effective amount of zinc ions; (ii) a source of citrate ions; and (iii) one or more anticalculus agents selected from pyrophosphate, phosphonate, diphosphonate and pharmaceutically-acceptable linear condensed poly-phosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is an integer from 2 to 21;

wherein the molar ratio of zinc:citrate is at most 1:1; the molar ratio of zinc:pyro is at most 1:1; and

(b) a pharmaceutically-acceptable topical oral carrier.

2. The composition according to Claim 1 wherein the molar ratio of zinc ions:citrate ions is from 1:1 to 1:20, preferably from 1:1 to 1:5, more preferably from 1:1 to 1:4, and the molar ratio of zinc ions to the anticalculus agents is from 1:1 to 1:20, preferably from 1:1 to 1:8, more preferably from 1:1 to 1:5.

3. The composition according to any of Claims 1-2 wherein the composition is at a pH of from 6 to 9, preferably from 7.5 to 8.5 and the sum of the molar ratio amounts of citrate ions and anticalculus agents is from 3 to 9.

4. The composition of any of Claims 1-3 which is in the form of a dentifrice, preferably wherein the pharmaceutically-acceptable topical oral carrier comprises a dental abrasive.

5. The composition according to any of Claims 1-4 which comprises from 0.1% to 2%, preferably from 0.25% to 1%, by weight zinc ions.

6. A composition according to any of Claims 1-3 which is in the form of a mouth rinse, preferably wherein the pharmaceutically-acceptable topical oral carrier comprises a material selected from a humectant, ethanol, and a nonionic surfactant.

7. The composition according to any of Claims 1-3 and 6 comprising from 0.005% to 0.5% by weight zinc ions.

8. The composition according to any of Claims 1-7 wherein the anticalculus agent is selected from pyrophosphate, EHDP, AHP, and linear condensed polyphosphates of the general formula: $(P_nO_{(3n+1)})^{(n+2)-}$ wherein n is 6, 13, or 21, preferably the anticalc agent is pyrophosphate.

9. The composition according to any of Claims 1-8 which comprises a source of fluoride ions yielding from 0.0025% to 5% by weight fluoride ions.

10. A method for treating or preventing dental plaque, calculus or malador of the oral cavity comprising administering to the oral cavity of a human or lower mammal a safe and effective amount of a composition selected from Claims 1-9.

INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/US 93/11787

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GB,A,2 260 700 (COLGATE-PALMOLIVE COMPANY) 28 April 1993 see page 17, line 3 - line 6; example 1 see page 29, line 19 - line 28	1-10
X	EP,A,0 426 213 (UNILEVER PLC.) 8 May 1991 see examples e,f,j,l,m	1-10
X	RESEARCH DISCLOSURE no. 321 , January 1991 , EMSWORTH GB pages 80 - 81 'oral compositions' see paragraph 4; example 9	1-10
X	EP,A,0 295 116 (UNILEVER PLC.) 14 December 1988 see the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 1994	20.04.94

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/US 93/11787

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP,A,0 331 415 (UNILEVER PLC.) 6 September 1989 see the whole document	1-10
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X	US,A,4 869 898 (GAFFAR ET AL.) 26 September 1989 see the whole document	1-10
A	EP,A,0 251 542 (LION CORPORATION) 27 June 1986 see the whole document	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. J Application No
PCT/US 93/11787

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 469 722 A2**

(12) # EUROPEAN PATENT APPLICATION

(21) Application number : **91305967.1**

(51) Int. Cl.^{5} : **A61K 7/16**, B65D 35/10

(22) Date of filing : **01.07.91**

(30) Priority : **02.07.90 US 547642**

(43) Date of publication of application :
05.02.92 Bulletin 92/06

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB IT LI LU NL SE

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(54) **Anti-plaque dentifrice packaged in resilient squeezable dispensing container.**

(57) A dental composition, such as a paste or gel dentifrice containing triclosan, as an antibacterial agent which acts to decrease plaque on the teeth, is packaged in a hand holdable and squeezable dispensing container which is made of or includes a part or parts of a solid polymeric material, such as a polyfluoroethylene or polyvinyl chloride, which is compatible with triclosan, so that excessive loss of its anti-plaque activity on storage is avoided, which losses have been noted when various other plastics have been employed as dispensing container component materials. Alternatively, other more-reactive plastics may be employed for such dispensing container parts when a stabilizer, such as terpene, e.g., limonene, is present in the dentifrice. The dentifrice preferably also contains an anti-tartar proportion of polyphosphate, a tooth hardening proportion of a source of fluoride ions, a stabilizing proportion (in conjunction with the fluoride source) for the polyphosphate, of a polyvinyl methyl ether/maleic anhydride copolymer, and normal dentifrice components and adjuvants.

EP 0 469 722 A2

This invention relates to packaged anti-plaque dental compositions which comprise an antibacterial agent, triclosan, as an effective anti-plaque component, which compositions are packaged in a squeezable dispensing container which includes a polymeric plastic material in contact with the dental composition, which plastic is compatible with the triclosan in the composition.

Although various plastics may diminish the anti-plaque action of triclosan, certain plastics, such as polyfluoroethylene and polyvinyl chloride, have been found to be compatible with triclosan dentifrices and it has been discovered that they do not cause excessive losses of antibacterial and anti-plaque activities of such dentifrices contacting them during storage at room temperature, and even at elevated temperature. Also, applicant has discovered that when parts of the container that contact the dentifrice are of a plastic which is not in itself entirely compatible with triclosan, compatibility can be improved by incorporating in the dentifrice formula a stabilizing proportion of a material discovered by applicant to have stabilizing properties, such as a terpene, e.g., limonene, or an essential oil (natural or synthetic), which may be component of a flavoring material for the dentifrice, and thereby can perform of dual function in the packaged dentifrice. When the packaged dentifrice is in contact with a plastic that could otherwise inhibit the antibacterial and anti-plaque action of the triclosan such stabilizer will be present in sufficient proportion so that the dentifrice, as packaged and dispensed, is effective in anti-plaque action, which is a major object of this invention.

The packaged dentifrices of the invention preferably include in the dentifrice compositions an anti-tartar proportion of polyphosphate, fluoride or a source of fluorine ions for tooth hardening and anti-caries actions, and polyvinyl methyl ether/maleic anhydride copolymer, which, in conjunction with the fluoride, stabilizes the polyphosphate anti-tartar agent and improves the anti-plaque action of triclosan.

Plaque on teeth is considered to be a causative factor of negative periodontal conditions, and dental plaque is a precursor of calculi. Plaque may form on any part of the tooth surface, including the gingival margin. It makes the teeth appear dull and in addition to promoting development of calculi, it has been implicated in occurrences of gingivitis. Therefore, dentifrices that contain anti-plaque components, which prevent or inhibit the development of plaque on the teeth, are valuable dental care aids. Tartar,or dental calculus, is also known to be causative of gingivitis and dental decay, and makes the teeth appear dull and unattractive. Although it has been known that antimicrobial agents in dentifrices may reduce plaque, various other antibacterial compounds than triclosan and the like are often o disadvantageous characteristics which contrindicate their employment in such oral compositions. For example, cationic antibacterial compounds, such as quaternary ammonium halides, tend to discolor the teeth and may be inactivated by the presence of anionic materials in the oral preparations (and often it will be desirable to employ anionic surfactants or detergents in such oral compositions). Triclosan can be inactivated by nonionic surfactants and by various plastics, as has been discovered by applicants. Thus, an object of this invention has been to incorporate triclosan, and similar compounds, such as DDDE (2,2-dihydroxy-5,5-dibromo-diphenyl ether), in dental compositions for their anti-plaque activity and to store such compositions and dispense them from packages or containers in which they will not lose an excessive proportion of such activity on storage, before intended use, or during dispensing. In prior art triclosan dentifrices, as delivered from the dispenser, the triclosan delivery has not been in an effective amount to significantly reduce plaque when employed once or twice daily at 1.5 grams of dentifrice for one minute brushings, which is considered to approximate normal brushing practice. To be effective, such uses should result in at least a 25% reduction in plaque after three weeks use, compared to similar usage of a control toothpaste.

Triclosan is described in U.S. patent No. 4,002,880 as an antibacterial agent in combination with an anti-calculus agent (which provides zinc ions), and it is disclosed in German patent specification (OLS) No. 35,32 860 in combination with a copper compound. It is also mentioned in European patent applications No's. 0 161 898 and 0 161 899, and in European patent application No. 0 220 890 it is disclosed in dentifrices with polyethylene glycol and oil based flavor.

Various types of dentifrices are known, including paste, gel, powder, liquid, tablet, lozenge, sachet and packeted dentifrices. Such products have been packed in deformable or squeezable tubes, pressurized dispensers, packets, bottles, jars, pump dispensers and other containers. In recent years some such containers have been made of synthetic organic polymeric plastics or of laminates which include such plastics. Interactions between dentifrices and the materials of containers in which they were packed have been known, such as reactions between toothpastes and aluminum containers, and to prevent such reactions containers have been especially treated or different container materials have been employed. However, applicant does not believe that before their invention it had been known to the prior art that plastic dispenser materials of construction could adversely affect the anti-plaque activities of triclosan (and DDDE and similar anti-plaque agents) that had been included in contained dentifrices, in which they came into contact with such plastics, nor does he believe that it had been discovered that certain plastics could be employed for such container parts without causing losses of the anti-plaque activities of triclosan and related halogenated diphenyl ethers (triclosan only will be referred to later herein, for simplicity) or that losses of such anti-plaque activity of dentifrices packed in dispensers in

contact with "reactive" plastics (which react with, absorb or otherwise reduce the anti-plaque actions of the dentifrices) could be inhibited or prevented by incorporation in the dentifrices of terpenes, such as limonene, and other stabilizing components of flavoring materials.

Polyphosphates, which are anti-tartar compounds of the preferred packaged dentifrices, tooth hardening and stabilizing fluoride or other source of fluorine ions, and polymeric polycarboxylate, such as the polyvinyl methyl ether/maleic anhydride copolymers, which can increase the effectivenesses of the polyphosphate and fluoride, and act to inhibit development of calculi, are dental preparation components that are known to the art. U.S. patent application S.N. 07/398,772, filed August 25, 1989, U.S. patents 4,323,551, 4,515,772 and 4,627,977, and European patent application 89 200 710.5 are considered to be of relevance to such aspects of the present invention.

Squeezable and form maintaining resilient dispensing containers for viscous materials, which are the preferred dispensing containers for dentifrices in accordance with the present invention, are described in U.S. patent 4,842,165. The dispenser illustrated in that patent is of suitable tubular shape, vertically storable, resilient, lined with a flexible bag, and is equipped with check valve means to promote easy and complete dispensings.

In accordance with the present invention a resilient squeezable dispensing container of a viscous anti-plaque dentifrice comprises such a dentifrice, which comprises an effective anti-plaque proportion of triclosan, in a resilient squeezable dispensing container which has a walled dispensing chamber, in which container parts thereof that contact the dentifrice during storage and during dispensing thereof are of material(s) that is/are compatible with the triclosan in the dentifrice and do(es) not cause excessive loss(es) of anti-plaque properties of the dentifrice during storage thereof in and dispensing thereof from the squeezable dispensing container. The losses of anti-plaque activity are desirably held by the present invention to less than 25% on aging at room temperature and at elevated temperature, e.g., three weeks at 40°C., and such activity will preferably be maintained at such a level for at least a year at room temperature. Such stabilization of the triclosan (which is evidence by such limited losses of anti-plaque activity) is effected by employing in the dispenser parts that are compatible with the triclosan, such being of polyfluorocarbons, preferably of the polyfluoroethylene type, e.g., polytetrafluoroethylene, or polyvinyl compounds, preferably polyvinyl halides, e.g., polyvinyl chloride. However, an alternative technique is to include a stabilizing material in the dentifrice, which material may be a terpene, e.g., limonene, or a flavor incorporating such a terpene or other stabilizer. Such stabilizing action may be inhibition of chemical reactions of the triclosan with the plastic or with other materials in the presence of the plastic, may be inhibition of sorption of the triclosan by the plastic, or may be another mechanism, unknown at the present. For example, the terpenes may react with the plastics or components of the plastics and thereby prevent reactions thereof with the triclosan. The described dentifrices preferably also include the previously mentioned polyphosphates, fluorides, and copolymers in such proportions as to be effective for their desired functions.

The invention will be readily understood from the description thereof in this specification, taken in conjunction with the drawing, in which:

FIG. 1 is a disassembled elevational view of a preferred dispensing container of the invention, containing dentifrice ready to be dispensed;

FIG. 2 is a vertical sectional elevational view of the assembled package of FIG. 1; and

FIG. 3 is a horizontal sectional view of the package along plane 3-3 of FIG. 2.

In FIG. 1 there is illustrated a squeezable resilient dispenser of the type described in U.S. patent 4,842,165, which may be referred to as the squeeze dispenser. Dispensing container 11, containing dentifrice 15, includes a base 13, walled resilient elliptical or cylindrical tube 17, bag or liner 19, air check valve parts 21 and 23, suckback limiting parts 25 and 27, walled dispensing passageway 29, outlet, nozzle or orifice 31 and hinged cap 33.

The tubular container body 17, bottom 13, air check valve parts 21 and 23 and other parts of the dispensing container that do not come into contact with the contained dentifrice, during storage or discharge thereof, may be of any suitable material, such as synthetic organic polymer of the type normally referred to as "plastic". However, it is desirable that all parts that are in contact with the dentifrice, especially those parts which are in contact therewith during lengthy storage, should be of a material which does not adversely affect the triclosan component of the dentifrice (and other components thereof, for that matter). Thus, it is especially important that the bag or liner 19 be of a material which does not substantially adversely affect the triclosan and it is desirable that the passageway 29, orifice 31, suckback limiting parts 25 and 27 and cap 33 should be of non-reactive plastic, but if the materials of construction of any such parts are such as tend to react with triclosan or otherwise adversely affect its anti-plaque activity in the dentifrice composition, the dentifrice formula should contain a stabilizing material, such as a terpene, e.g., limonene.

Among the highly preferred polymers which are substantially non-reactive with triclosan in the present dentifrices are polyfluorocarbons, such as polytetrafluoroethylene, and polyvinyl halides, such as polyvinyl chloride.

Also non-reactive, although their physical properties may militate against their use for some parts of the dispensing container, are polycarbonates and polysulfones. Sometimes it will be desirable for the parts to be made entirely of one of such materials or of laminates or of other combinations thereof but often certain required physical properties and/or economics may favor employment of a different polymer, even such a polymer as may be objectionably reactive with triclosan. Among such polymers there may be mentioned poly-lower alkylenes, such as polyethylene (both low density and high density) and polypropylene, polyethers, polyesters, such as polyethylene terephthalate, nylons, polyacrylates, polyallomers and polymethyl pentenes. Such materials are employable in contact with the dentifrice if a suitable stabilizer is present in the dentifrice composition. For such materials to be useful as materials of construction for the flexible bags of the present dispensers they will normally have to be flexible enough and capable of being made thin enough so as to be turnable inside-out as dentifrice is dispensed, so as to force substantially all the dentifrice out of the dispensing container. Normally such materials will be in thin sheet or film form but sometimes they may be applied as melts or solvent solutions in thin coatings onto other films or sheet materials. The total thickness of such a bag or laminate of such material(s) will normally be in the range of 0.001 to 0.005 inch, or 0.02 to 0.1 mm. In a desirable embodiment of the invention the laminate may be of 0.02 mm. thick polyethylene, 0.01 mm. thick polyethylene terephthalate, 0.002 mm. thick aluminum and 0.02 mm. polyethylene, reading from inside to outside. The squeezable resilient outer body portion of the dispensing container may be of any suitable resilient material, such as polyethylene or polyvinyl chloride, with the main requirement for it being that it should be resilient enough to return to initial position immediately after release of squeezing forces thereon.

In operation, upon squeezing of tube 17 (after removal of cap 33) air check valve part 21 closes the opening in part 23, thereby preventing escape of air from any clearance 35 between the inner portion of tube 17 and the outer surface of bag 19. Then, squeezing forces and the internal air pressure built up force viscous dentifrice 15 through openings 37 and 39 of suckback limiting part 27 and past flaps 41 and 43 of part 25, through passageway 29 and out through orifice 31. Upon release of squeezing pressure the valve part 21 moves away from part 23, allowing entry of air into the container, and flaps 41 and 43 close off openings 37 and 39 and thereby prevent excessive sucking back into the bag or liner, of dentifrice, and of an equal volume of air into the discharge passageway. Because of the limiting of the sucking back of material upon the release of squeezing forces, undesirable air "belching" on the next dispensing is avoided.

Essentially complete discharge of the viscous dentifrice from the bag or liner is obtainable because the bag or liner is turned "inside-out" during dispensing due to the fact that it is held at its circumference, along a band 45, to the interior of tube 17 by suitable means, such as cementing or fusing. However, some material will be left in the discharge passageway and this too can be discharged by finger pressure on the exterior of such passageway material providing that such material is flattenable by such finger pressure.

In the description of the invented package of FIG.'s. 1-3 the terms "upwardly" and "downwardly" are used in a relative sense only and it will be apparent to the reader of this specification that dispensings of the package's contents may be effected while the container is held in various orientations, including inverted positions.

The various internal parts of the pump dispensers that contact the dentifrice are preferably of plastic(s) that do not inactivate triclosan but if it is not feasible to utilize plastics that have the necessary physical properties for the various contacting parts and still are compatible with triclosan other plastics may be employed, preferably such as adversely affect triclosan less than do other plastics, and more preferably, only slightly. Such dentifrices preferably include a stabilizing substance, such as limonene or other stabilizing terpene or flavor component. However, it is considered best, if feasible, to avoid employing any co-polyester/polyether elastomers, such as have sometimes in the past been used for internal membranes or liners, which plastic appears to be especially detrimental to triclosan stability in dentifrices.

Because triclosan is to some extent photosensitive, it will sometimes be desirable for the pump dispensers of this invention to include containers, closures and caps which are coated or laminated with a chemical or physical light screening material, many of which materials are known, to prevent transmissition to the dentifrice and to the triclosan therein of any inactivating radiation, e.g., ultraviolet light. Also, such containers may desirably be opaque to prevent such actinic radiation from inactivating the triclosan in the dentifrice.

The cause(s) of inactivation by plastics of triclosan's anti-plaque action in packaged dentifricec has/have not yet been estabilished. Research to date has not pinpointed the mechanism responsible for losses of such desirable activity and so far test results do not conclusively point either to chemical reactions or to physical absorptions. Tests of some oral preparations containing triclosan show that when they are aged in dispensing containers at room temperature, 38°C. and 49°C., for up to twelve weeks, there can be "excessive" losses (over 25% of the effect of the initial concentration of triclosan being lost) when such a preparation has been in contact with such container walls and parts of low density polyethylenes, high density polyethylenes, polyethylene terephthalates, polypropylenes, nylons, polyallomers and polymethylpentenes. Similarly, high losses result when such storage is in containers with inner walls or parts of co-polyester/polyether elastomers, such as those

which had previously been employed in membranes for dispensing containers. In other experiments it was found that polyfluorocarbons and polyfluoroethylenes, such as polytetrafluoroethylenes, polyvinyl chlorides, polycarbonates and polysulfones, did not absorb or react with excessive proportions of triclosan. However, polycarbonates and polysulfones are brittle and hence can be unsuitable for employment for some dispensing container parts. Polyvinyl chlorides can sometimes impart a foreign taste to dentifrices, and therefore might be avoided as a packaging material, except in cases where such taste is compatible with the taste of the flavoring employed. Thus, of all the polymeric plastic materials available, polyfluorocarbons or polyfluoroethylenes are especially satisfactory materials for use in the present containers or packages, and do not seriouly diminish the anti-plaque activity of triclosan. However, as was indicated previously, by incorporation in the oral compositions of suitable stabilizing compounds for triclosan, such as terpenes, of which limonene is representative, essential oils (which often contain terpenes) and other flavor components with similar "stabilizing" properties, one is able to reduce the activity losses of the triclosan when dentifrices containing it are in contact with containers or container parts made of the various mentioned polymeric plastics which are "stabilizable", so that excessive losses in anti-plaque activity do not occur. Therefore, one needs not be dependent on polyfluoroethylene as a dispenser material, providing that the dentifrice also contains a stabilizing proportion of terpene or other suitable "stabilizer". When such stabilizer is present in the oral compositions or when polyfluoroethylene (or polyvinyl chloride, polycarbonate polysulfone or any combination thereof is/are the only polymeric plastic(s) in contact with the oral composition, storage losses of anti-plaque activity are less than 25%, and preferably will be less than 10%, even after ambient to relatively high temperature storage, for example, at 20° to 40°C., for periods of time of several weeks up to a year or more. It is considered that the most stable dentifrices are those which include a stabilizing proportion of terpene or other suitable stabilizer and also include contacting container parts of polyfluoroethylene (and/or any of the other "unreactive" plastics) only. Although the terpenes and essential oils are the primary stabilizers utilizable in accordance with the present invention, other flavor components may also contribute to the stabilization of the anti-plaque material by interfering with any destabilizing chemical reaction or by inhibiting absorption of the triclosan by the plastic (or by other mechanism). It has been proposed that some components of dentifrices that tend to solubilize triclosan can act to maintain it in the dentifrice and inhibit or prevent its migration into the plastic but, on the other hand, it has also been theorized that such a solubilizing action could promote migration of the solubilized triclosan into the plastic. Because the issue has not been resolved applicants should not be considered to be bound by either theory. Also, while it is desirable for the terpenes and other stabilizers to be flavor components, that is not necessary, and the stabilizer may be useful solely for its stabilization function.

Although it is preferred that the packages of this invention should include internal surfaces, liners and other parts which come into contact with the packaged dentifrices that are of or are lined with synthetic organic polymeric plastic material, it is within the invention to utilize other solid (and/or film-forming) polymeric materials, whether or not they are synthetic, organic or even plastic. Thus, polyethylene glycols and methoxypolyethylene glycols, such as those of the Carbowax® type, e.g., Carbowax 4,000 and Carbowax 6,000 may sometimes be employed as coatings or lining materials for parts of the present dispensers. Well known silicon polymers, such as siloxanes, and natural organic film-forming materials, such as gums, e.g., carrageenan, tragacanth, karaya, may also be useful for such purposes, as may be other solid polymeric materials, such as cellulose, starches and derivatives thereof.

The dentifrices of this invention are comprised of three classes of components, vehicle, polishing material and surfactant (or detergent). Triclosan is normally present in the vehicle of the packaged dentifrices, which vehicle usually comprises about 10 to 80%, preferably 50 to 80% (the figures are on a final composition basis) of the dentifrice. Of the vehicle, about 20 to 90%, preferably 30 to 80%, will be water, about 20 to 80%, preferably 30 to 60%, will be humectant, such as glycerol, sorbitol, propylene glycol, polyethylene glycol or any suitable mixture thereof, and 0.5 to 10%, preferably 1 to 5%, will be gelling agent, such as sodium carboxymethyl cellulose, Irish moss, iota carrageenan, calcium carrageenan, or hydroxyethyl cellulose or the like, including any suitable mixtures thereof. Although triclosan is essentially insoluble in water it is soluble or at least readily dispersible in the described dentifrice vehicle. The polishing material of the dentifrice will normally be from about 10 to 50%, preferably 15 to 25% thereof,and such polishing material may be colloidal silica, precipitated silica, hydrated silica, sodium aluminosilicate, insoluble sodium metaphosphate, hydrated alumina, calcined alumina, dicalcium phosphate dihydrate, anhydrous dicalcium phosphate or calcium carbonate, or other known polishing agent, or any suitable mixture thereof. The surfactants include anionic, nonionic, cationic and zwitterionic surfactants but often the employment of nonionic surfactant is avoided in the packaged dentifrices of this invention because of its adverse affect on triclosan, and the employments of cationic and zwitterionic surfactants are also often avoided because they tend to stain or darken the teeth. Thus, synthetic organic anionic surfactants, which are also detergents, are the preferred cleaning agents in the present dentifrices, and of these, sodium lauryl sulfate and other sodium higher alkyl sulfates of 10 to 18 carbon atoms in the alkyl groups thereof, and ethoxyl-

ated such sulfates, of 1 to 15 ethoxy groups per mole, are preferred, although various other well known sulfated, ethoxysulfated and sulfonated detergents, preferably of similar carbon chain lengths, may be substituted for them, at least in part. The surfactant or detergent content, usually anionic detergent content, is normally in the range of 0.2 to 10%, preferably 0.5 to 5%, and more preferably 1 to 3%.

In the packaged dentifrices of this invention there will very preferably also be present an effective anti-tartar (and anti-calculus) proportion of polyphosphate. Representative examples of suitable polyphosphates, for the purpose of this description, include metaphosphates, such as sodium hexametaphosphate, polyphosphates, such as sodium tripolyphosphate, and pyrophosphates, such as tetrasodium pyrophosphate (which is more preferred), disodium diacid pyrophosphate and trisodium monoacid pyrophosphate, the corresponding potassium salts, and the like. Such polyphosphates also include the linear molecularly dehydrated polyphosphate salts which are generally employed in the forms of their wholly or partially neutralized water soluble alkali metal (e.g., potassium and preferably sodium) or ammonium salts, and any mixtures thereof. Linear polyphosphates corresponding to the formula $(NaPO_3)_n$, wherein n is in the range of about 2 to about 125, are includable as anti-tartar agents. In the present invention the polyphosphates are present in the dentifrices in concentrations of 0.1 to 3%, preferably 0.5 to 3% and more preferably 1.5 to 2.5%, e.g., about 2%. Particularly desirable are tetraalkali metal pyrophosphates, including mixtures thereof, such as tetrasodium pyrophosphate, tetrapotassium pyrophosphate and mixtures thereof.

To improve the anti-calculus and anti-tartar effectiveness of the oral composition an inhibitor against enzymatic hydrolysis of the polyphosphate is desirably present. Such an agent is a fluorine ion source sufficient to supply 25 p.p.m. to 5,000 p.p.m., preferably 500 to 3,000 p.p.m. of fluorine ions (or fluoride ions) in the dentifrice.

Sources of fluorine ions or fluorine ion-providing components for inhibiting the actions of acid phosphatase and pyrophosphatase enzymes on polyphosphate (and thereby for increasing anti-tartar and anti-calculus effectiveness of the polyphosphate) in the present dentifrices are well known in the art, and usually also function as tooth hardeners and anti-caries agents. These compounds may be slightly soluble in water or may be fully water soluble. They are characterized by their ability to release fluorine (or fluoride) ions in water and by their relative inertness toward other components of the oral preparations. Among these material are inorganic fluoride salts, such as soluble alkali metal and alkaline earth metal salts, e.g., sodium fluoride, potassium fluoride, ammonium fluoride, zinc fluoride, barium fluoride, tin fluoride, sodium fluorosilicate, ammonium fluorisilicate, sodium fluorozirconate, ammonium fluorozirconate, sodium monofluorophosphate, aluminum mono- and difluorophosphates, and fluorinated sodium calcium pyrophosphate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate (MFP®) and mixtures thereof are preferred.

The amount of fluorine-providing compound in the present dentifrices is dependent to some extent upon the type of compound, its solubility, and the type of dentifrice, but it should be a non-toxic amount, generally in the range of about 0.005 to about 3.0% and preferably in the range of 0.05 to 1%, in the dentifrice.

Typically, in the cases of alkali metal fluorides, this component is present in an amount up to about 2% by weight, e.g., 0.05 to 2%, based on the weight of the preparation, and preferably in the range of about 0.1 to 1%, e,g., about 0.33% or 0.3%. In the case of sodium monofluorophosphate, the compound may be present in an amount of about 0.1 to 3%, typically 0.5 to 1%, e.g., about 0.76% or 0.8%.

In another preferred aspect of this invention the dentifrice comprises an agent that is effective to enhance the antibacterial and anti-plaque effect of the triclosan. Such antibacterial enhancing agent (AEA) is preferably of an average molecular weight in the range of about 1,000 to about 1,000,000 and desirably contains a functional group which enhances the antibacterial effect and an organic group which enhances retention of such antibacterial effect on treated surfaces.

The AEA is preferably a synthetic anionic polymeric polycarboxylate which is also an inhibitor of alkaline phosphatase enzyme. In U.S. patent 4,627,977 (Gaffar et al.) there is described the use of polycarboxylates for inhibiting salivary hydrolysis of pyrophosphate anticalculus agents in combination with a compound providing a source of fluoride ion. It is to be understood that the synthetic anionic polymeric polycarboxylates so disclosed, when containing or modified to contain the retention-enhancing group mentioned above, are operative as AEA's in the packaged compositions of this invention and are components of preferred embodiments thereof.

The mentioned synthetic anionic polymeric polycarboxylates may be employed in the forms of their free acids but preferably are partially and more preferably fully neutralized water soluble or water swellable (hydratable, gel/forming) alkali metal (e.g., potassium and preferably sodium) or ammonium salts. Preferred are 1:4 to 4:1 copolymers of maleic anhydride or equivalent acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether/maleic anhydride copolymers with a molecular weight (M.W.) of about 30,000 to about 1,000,000. These copolymers are available from GAF Corporation as, for example, Gantrez® AN 139 (M.W. = 500,000), Gantrez AN 119 (M.W. = 250,000), and preferably Gantrez S-97 Pharmaceutical

Grade (M.W. = 70,000).

Other polymeric polycarboxylates which are operative as AEA's and contain or are modified to contain retention-enhancing groups include those disclosed in U.S. patent No. 3,956,480, such as the 1:1 copolymers of maleic anhydride with ethyl acrylate, hydroxyethyl methacrylate, N-vinyl-2-pyrollidone, or ethylene, the latter being available for example as Monsanto EMA No. 1103, M.W. 10,000 and EMA Grade 61, and 1:1 copolymers of crylic acid with methyl or hydroxyethyl methacrylate, methyl or ethyl acrylate, isobutyl vinyl ether or N-vinyl-2-pyrollidone.

Additional operative polymeric polycarboxylates are those disclosed in U.S. patents No's. 4,138,477 and 4,183,914, which contain or may be modified to contain retention-enhancing groups. These include copolymers of maleic anhydride with styrene, isobutylene or ethyl vinyl ether, polyacrylic, polyitaconic and polymaleic acids, and sulfoacrylic oligomers of a M.W. as low as 1,000, available as Uniroyal ND-2.

Other suitable anionic polymers that may be employed as AEA's are described in greater detail in U.S. patent 3,956,480 and in S.N. 07/398,605, both of which are incorporated herein by reference. The percentage of such AEA(s) in the described compositions will normally be in the range of 0.2 to 5%, preferably being 0.5 to 4% and more preferably 1 to 3%, e.g., 2%.

In dentifrice compositions the effective amount of triclosan will normally be in the range of 0.1 to 1.0%, more preferably 0.2 to 0.5 or 0.6%, e.g., about 0.3%, and often not exceeding 0.8% because of possible mouth numbing effects at high concentrations, and not being less than indicated to avoid ineffectiveness against plaque when the dentifrice is brushed on the teeth in normal manner. Preferably the dispensed compositions will contain proportions of triclosan within the given ranges but when the initial concentration thereof is within the given range a loss of up to 25% will be acceptable and such dispensed compositions are effective in removing plaque.

For stabilized oral compositions that are to be packaged in dispensing containers containing plastic walls or other parts, contacting the dentifrice, when such plastics are those which are reactive with triclosan, 0.01 to 2% of terpene(s) or stabilizer(s), preferably 0.05 to 1% and more preferably 0.1 to 0.5% will be present in the dentifrice. Such stabilizers may be present in a suitable flavoring agent for the dentifrice, if desired (and it often is), and will normally be at least 5% of the flavor, preferably at least 10%, more preferably at least 25% and most preferably at least 50% thereof.

The various plastics that were previously described as the components of dispensing container parts have been described only briefly because it is considered that their chemical natures and degrees of polymerization are well known, so detailing thereof is unnecessary in this specification. If further details are wanted reference may be made to Modern Plastics Encyclopedia, which has been published on an annual basis by McGraw-Hill Inc., New York, New York.

The stabilizing terpenes, which term, for the purpose of this specification, includes terpene hydrocarbons and oxygenated derivatives thereof, include such compounds as dl-limonene, menthol, ionone, diterpenes, polyterpenes and derivatives thereof, many of which are found in various essential oils and other flavors. In addition to being useful as stabilizers for triclosan they often contribute desirable flavors to the present oral compositions. Of the terpenes and their derivatives it is considered that limonene best balances these properties, although other terpenes, such as menthol and pinene, and including those which are not flavors, are also useful, as are other emulsifiable lipophilicessential oils and flavoring agents which contain stabilizing components.

For other details of formulations, components, adjuvants, manufacturings and uses, see the patents and applications previously mentioned in this specification, which are hereby incorporated by reference, as are text and periodical references.

Manufacture of the described dentifrices is by any of various standard techniques for producing such compositions. Referring to specific examples for simplicity, the triclosan is dispersed and/or dissolved in the vehicle portion of the dentifrice and the terpene is present in the flavoring agent. To make the dentifrice, the vehicle is prepared, containing glycerol, sorbitol, and/or propylene glycol, gelling agents, triclosan and suitable adjuvants (including Gantrez S-97), and the vehicle and aqueous anionic detergent (preferably sodium lauryl sulfate or a mixture thereof with sodium methyl cocoyl taurate) solution are mixed, followed by blending in of the polishing agent component, which may include the polyphosphate and fluoride. Finally, flavoring agent, including terpene, desirably dissolved in ethanol, is affixed and the pH is adjusted, as desired, usually to the range of 6 to 10, preferably 7 to 9, e.g., about 8.

In packaging of the dentifrice in the dispensing container it will be desirable to avoid contacting of the dentifrice with any parts made of co-polyester/polyether elastomer and it will also be desirable to avoid contacting of any compositions not containing stabilizing agent (such as terpene or flavor containing it) with plastic parts made of those plastics previously listed in this specification as reactive with triclosan and other such antibacterial and anti-plaque compounds. It will be especially important to avoid the mentioned plastic parts for holding tanks or any other containers, piping, pumps or equipment, in which the triclosan or the dentifrice containing

it may be held for any appreciable length of time or held for shorter lengths of time at elevated temperatures.

Even when the packaged compositions of this invention are prepared and contacts of the dentifrices containing triclosan with the reactant plastics are avoided it will still be desirable to minimize exposures of such packaged dentifrices to heat and to light, both of which have been found to accelerate losses of anti-plaque activity. Thus, the invented compositions are preferably stored and packaged in opaque dispensers or ones that filter out actinic light, at a temperature in the range of 10° to 38°C. Otherwise, the packaged dentifrices may be stored and used in normal manner and the desirable anti-plaque and anti-tartar effects thereof will be obtained. Such effects have been verified by laboratory testing and by evaluations of the teeth of volunteers serving on human panels, who employed various packaged dentifrices and controls as directed. Significant improvements in anti-plaque activities of the compositions of this invention packaged in the described dispensers are obtainable compared to control dentifrices similarly packaged but wherein the dispenser includes plastic parts that are "reactive" with the triclosan and wherein the dentifrice does not contain any stabilizing agent. Such improvements are also found when dispensers made of "reactive" plastics (but not copolyester/polyether elastomers) are employed with dentifrices containing terpenes and are compared to controls in which the dentifrice contains no stabilizing terpenes and/or flavoring agents.

The following examples illustrate but do not limit the invention. Unless otherwise indicated, all percentages and proportions in these examples, the specification and the appended claims are by weight, and all temperatures are in °C.

EXAMPLE 1

Component	Percent
Propylene glycol	10.00
Iota carrageenan	0.75
Sodium fluoride	0.33
Sorbitol (70% aqueous solution)	30.00
Sodium saccharin	0.30
Titanium dioxide	0.50
Sodium hydroxide (50% aqueous solution)	0.80
+ Luviform™ (35% aqueous solution)	4.76
++ Zeodent™ 113	20.00
+++ Sident™ 22S	2.00
Sodium lauryl sulfate (94% active)	1.60
* Flavor	0.95
** Triclosan	0.30
	100.00

+ 35% Aqueous solution of polyvinyl methyl ether/maleic anhydride copolymer (BASF Corp.)

++ Silica polishing agent (J.M. Huber Corp.)

+++ Silica thickening agent (Degussa Co.)

* Contains at least 25% of terpenes, e.g., limonene

** Irgasan® DP 300, mf'd. by CIBA-GEIGY

A dentifrice of the above formulation is made in normal manner and is employed as a medium for testing the stability of triclosan when such dentifrice is exposed to different plastics which are employed as materials of dispensing containers or parts thereof in which or in contact with which such dentifrice is stored and dispensed. The plastics for the tests are Pibiflex™ 46, mf'd. by Inmont, and Arnitel™ 460 EM, mf'd. by AKZO, which are plastics that have previously been employed as the membrane or bellows of a pump dispenser, the so-called Guala dispenser, and which are also employable as parts of squeeze-type dispensers, such as that shown in the drawing. Six samples of plastics are tested, three of each of the mentioned plastics, with each of the three being treated with a different mold release agent (to determine whether the nature of the release agent is relevant to the problem of triclosan stability in contact with plastics during storage). The release agents are Silicone Master™ (5% silicone oil and 95% polypropylene), Silicone Master plus Silicone Oil (with extra silicone oil) and Armid O Master™ (5% oleyl amide and 95% polypropylene), respectively. After two weeks storage of the test samples in contact with the dentifrice at different temperatures (room temperature, 38°C. and 49°C.), the dentifrice samples are removed from the plastic container materials and the plastics are washed with water and immersed in methanol to dissolve any triclosan which might have been taken up by the during storage. The

methanol washings are collected and are analyzed, using high performance liquid chromatrography. It is found that essentially the same types of absorptions of triclosan take place with the different membrane materials and although there are variations between them and such are somewhat dependent on the release agents employed, the results are essentially the same in all cases. The co-polyester/polyether elastomers are found to absorb significant percentages of triclosan from the dentifrice (more than 25% of that which is present initially) which results are confirmable when the co-polyester/polyether elastomers are used as materials in dispensers containing the described dentifrice and other dentifrices within the invention. Accordingly, it is considered undesirable to employ co-polyester/polyether elastomers in contact with the present dentifrices and that is even so when the dentifrices contain terpenes or contain flavoring materials which include terpenes (which are present in the flavoring of the dentifrice formulation), to the extent of at least 0.1% of the dentifrice.

When the tests are repeated, using squeeze dispensers having bags or liners which are of Arnitel™, as the co/polyester/ polyether elastomer, losses of anti-plaque activity of triclosan are unacceptable but when the co-polyester/polyether elastomer is replaced by other less incompatible plastics, e.g., Teflon® polyfluoroethylene, the triclosan activity is improved to within acceptable limits. Also, other plastic parts of such dispensers, such as polyethylene, polypropylene, nylon, polyethylene terephthalate and polymethyl methacrylate,do not absorb excessive amounts of triclosan and do not seriously decrease the anti-plaque activity of the dentifrice, apparently due to the presence of terpenes in-the flavoring agent of the contained dentifrice.

A panel test is run, involving at least ten human subjects, who employ the dentifrice of this example, dispensed from polyethylene terephthalate- and polyethylene-lined dispensing containers, in twice-a-day brushings for one month, during which time plaque evaluations of the subjects' teeth are made by trained observers. The test results establish that the dentifrice composition has a definite anti-plaque activity and also prove that the triclosan has not been unacceptably inactivated, and still is present in an effective antibacterial and anti-plaque proportion in the dentifrice. Similar good results are obtainable when squeeze dispensers like that illustrated in FIG's. 1-3 are employed and comprise parts of high and low density polyethylenes, polypropylenes, polyallomers, nylons, acrylics, polyethylene terephthalates, polymethyl methacrylates, polyfluorocarbons, polyvinyl halides, polycarbonates, and/or polysulfones. Such stability of the trictosan is also obtainable when the terpene content is decreased or when terpenes are omitted, providing that the plastic parts are of polytetrafluoroethylene, polyvinyl chloride, polycarbonate and/or polysulfone.

The dentifrice formula will desirably also include 1.5 to 2.5%, e.g., 2%,of a polyphosphate (sodium hexametaphosphate, tetrasodium pyrophosphate, or sodium tripolyphosphate, or a mixture thereof), preferably the pyrophosphate, to give the dentifrice desired anti-tartar action. It is also highly preferable for such compositions to contain a fluorine ion releasing compound, such as 0.3% of sodium fluoride or 0.8% of sodium monofluorophosphate, and 2% of polyvinyl methyl ether/maleic anhydride copolymer, for their functions that were previously mentioned herein. The compositions resulting by such modifications of the basic formula are also effective as anti-plaque dentifrices despite storage in and dispensing from plastic squeeze dispensers that include materials previously indicated to be reactive with triclosan. Adding of the mentioned materials to the formula is compensated for by decreasing the water content accordingly.

EXAMPLE 2

Component	Percent
Glycerol	7.00
Propylene glycol	3.00
Iota carrageenan	0.75
Sorbitol (70%)	30.00
Sodium saccharin	0.30
Sodium fluoride	0.33
Titanium dioxide	0.50
Gantrez S-97 (13% solution)	15.00
Deionized water	16.07
Sodium hydroxide (50% aqueous solution)	0.80
*** Zeodent 113	20.00
° Syloden® 15	3.00
Flavoring agent (containing at least 25% of terpenes)	0.95
Sodium lauryl sulfate	2.00
Triclosan	0.30
	100.00

*** Polishing agent (J.M. Huber Corp.)

° Silica thickening agent (W.R. Grace Corp.)

A toothpaste of the above formula is made and is stored in squeeze dispensers of the type illustrated in the drawing, which include a laminate of 0.001 inch of polyethylene next to the dentifrice, 0.0001 inch of aluminum, 0.0005 inch of polyethylene terephthalate and 0.001 inch of polyethylene, as the material of construction of the bag or liner, and other of the satisfactory (with terpene stabilizer) plastics, e.g., polyethylene, polypropylene and polytetrafluoroethylene, for the other parts (passageway, orifice, check valve and suckback valve parts) that contact the dentifrice. The dentifrice is also filled into the dispensing containers and contacts the polyethylene of the laminated bag, after which the other upper parts are installed and the package is closed. The dentifrices are aged at 5°C., 25°C., and 39°C., for two, four and six weeks. After such aging periods, the dentifrices are dispensed at the rate of about 1.5 grams per day and at weekly intervals the triclosan contents of the dispensed dentifrice are determinable by analyses. Triclosan stability will be satisfactory and the dispensed composition will be effective as an anti-plaque dentifrice.

Incorporation of tetrasodium pyrophosphate, sodium tripolyphosphate or sodium hexametaphosphate, as in Example 1, (preferably 2% of the pyrophosphate) makes the dentifrice anti-tartar, as well as anti-plaque, and additions of fluorine ion supplying compounds and Gantrez, as in Example 1, also contribute their desired effects.

Gel dentifrice formulations in such dispensers behave similarly to toothpastes with respect to triclosan stability after storage and on dispensing.

In similar tests, using polyethylene terephthalate (PET) lined dispensing containers, bags or liners or laminates having PET films as the interior surface thereof, as parts of the dispensing containers, and having other container parts of polyethylene and/or polypropylene little loss (less than 5%) triclosan will result, indicating that the presence of the terpene(s) (0.1% or more of the composition), including limonene, in the flavoring agent or as the flavoring agent, can prevent loss of the triclosan or inactivation thereof. When polyfluoroethylene lined or surfaced bags and other parts are employed there will be little loss of triclosan, even when the flavoring agent is omitted from the dentifrice composition, and such is also the case when polyvinyl chloride is employed as a primary bag material in contact with the dentifrice and/or when polysulfone or polycarbonate is/are used for other package parts in contact with the dentifrice.

In the above formulas the polishing systems are siliceous rather than being based on alumina. When the polishing agents are changed to aluminas, the triclosan stability problems previously mentioned as having been noted with some plastics are decreased, but they still exist. Also, the presence of terpenes in the dentifrices promotes triclosan stability in the presences of the "reactive plastics", as such terpenes do in similar dentifrice packages wherein the compositions are based on siliceous polishing agents.

EXAMPLE 3

The dentifrices of the foregoing examples may be varied in composition ±10% and ±25% for various components thereof, providing that such percentages are not outside ranges given elsewhere in this specification, and operative and effective anti-plaque products are obtainable, which are dispensable in effective anti-plaque state from the mentioned dispensing containers that are made of compatible plastics. Such products will also behave in similar manners, with the triclosan anti-plaque agent being sufficiently stable in the presence of polyfluoroethylene, polyvinyl chloride, polycarbonate and polysulfone packaging or package component materials, even when no flavoring agent and no terpenes are present in the dentifrices, and being stable in the presence of polyethylenes, polypropylenes, polyethylene terephthalates, polyesters, polyethers, polymethyl methacrylates, polyacrylates, polyallomers, nylons and polymethyl pentenes, as package or component materials, when a stabilizing terpene, such as limonene, or a stabilizing flavor component is present in the dentifrice. The packaged dentifrices of this example that contain polyphosphate, source of fluorine ions and AEA are also of effective anti-tartar, anti-calculus, anti-carries, tooth hardening and stabilizing (of the polyphosphate against enzymatic action) properties. When the AEA materials and fluoride are omitted the polyphosphate's anti-tartar and anti-caluli properties can be adversely affected by enzymatic action of the saliva but some will be present. As with the other packaged dentifrices previously discussed, because of excessive absorption or other adverse action with respect to triclosan by co-polyester/polyether and other such elastomers, uses of such materials will preferably be avoided.

In addition to changing the dentifrice formula, other changes may be made in the dispensing container. Thus, it is not necessary for the container to incorporate a suckback limiting valve for the dentifrice to be effective in fighting plaque. Sometimes the absence of such a valve may be compensated for by utilizing an air venting mechanism (at the container "bottom") which is larger and more readily able to vent air back into the container, thereby decreasing any suction applied to the dentifrice that had been partially discharged, as squeezing forces are removed. Also, one can employ a more viscous dentifrice or smaller opening(s) in part 25. Alternatively the user could release squeezing forces more gradually.

Dentifrices of the formulas of Examples 1 and 2 are made and are dispensed after one months storage at 30°C., from containers lined with polyethylene, in one case, and polyethylene terephthalate, in another, onto bristled toothbrushes. The amounts of toothpaste on the tootbrushes are in the range of 0.8 to 2.0 grams with 1 to 1.5 g. being preferred. When 1.5 g. is dispensed the active triclosan in the dentifrice on the brush will be about four milligrams (with only 10% of the triclosan being inactivated). When storage is for a longer time or at a higher temperature or with a more destabilizing plastic in contact with the dentifrice during storage and dispensing the content of triclosan in the composition can be increased so that the dispensed composition will contain about 3.5 or 4 mg. of triclosan in the 1.5 g. of dentifrice on the brush.

The described dispensed dentifrices are employed to brush the teeth, with typically about 0.8 to 2 g. being dispensed onto toothbrushes for each brushing. Brushings are twice a day, morning and night, one minute at a time, for four weeks, after which definite improvement in anti-plaque action will be apparent, compared to similarly stored and dispensed control dentifrice that contains no triclosan, and when polyphosphate is also present, especially with a source of fluorine ion and an AEA, anti-tartar effects are also noticeable. Improvement in anti-plaque action is also obtainable compared to an unflavored control (containing no terpene) that contains triclosan which is dispensed from polyethylene and polyethylene terephthalate lined containers.

For more details about the dispensers, materials of construction thereof and dentifrice composition components of the invention, if desired, please seethe previously mentioned or referred to patents, applications,

texts, bulletins and/or articles, which are hereby incorporated herein by reference.

The invention has been described with respect to various examples, illustrations and embodiments thereof but is not to be limited to these because it is evident that one of skill in the art, with the present specification before him/her, will be able to utilize substitutes and equivalents without departing from the invention.

According to broad aspects of the present invention a resilient squeezable dispensing container of a viscous anti-plaque dentifrice comprises such a dentifrice, which comprises an effective anti-plaque proportion of triclosan, in a resilient squeezable dispensing container which has a walled dispensing chamber, in which container parts thereof that contact the dentifrice during storage and during dispensing thereof are of material(s) that is/are compatible with the triclosan in the dentifrice and do(es) not cause excessive loss(es) of anti-plaque properties of the dentifrice during storage thereof in and dispensing thereof from the squeezable dispensing container. The parts of the dispensing container that contact the dentifrice are preferably of solid synthetic organic polymeric plastic material and the dentifrice is preferably in paste or gel form. The parts of the dispensing container that contact the dentifrice during storage in and dispensing from it are preferably of material(s) selected from the group consisting of polyfluorocarbons, polyvinyl halides, polyethylene terephthalates, poly-lower alkylenes, polymethyl pentenes, polyallomers, nylons, polyacrylates, polymethyl methacrylates, polyesters, polyethers, polycarbonates and polysulfones, and mixtures and pluralities thereof.

The dentifrice preferably comprises 0.1 to 1% of triclosan. The dentifrice preferably also comprises an effective anti-tartar proportion of polyphosphate, e.g. 0.1 to 3% of polyphosphate. The dentifrice desirably also comprises an effective proportion of an antibacterial enhancing agent (AEA) which is a synthetic anionic polymeric polycarboxylate. The AEA is preferably methyl vinyl ether/ maleic anhydride copolymer of average molecular weight in the range of 1,000 to 1,000,000.

The dentifrice desirably also comprises an effective proportion of a source of fluorine ion sufficient to stabilize the polyphosphate against enzymatic hydrolysis. The source of fluorine ion may be 0.005 to 3% of an inorganic fluoride or monofluorophosphate.

In a preferred form of the invention in a container of dentifrice according to the invention the dentifrice is in aqueous paste or gel or mixture thereof, which comprises a vehicle, a polishing agent, a surfactant and triclosan, and the container is hand holdable and squeezable and comprises a walled resilient tube, a flexible bag or liner, a bottom for such tube, an air check valve to prevent passage of air out from between the bag and the tube, near the bottom thereof, during squeezing of the package, and to permit entrance of air during resilient return of the tube to normal shape after release of squeezing forces, a dispensing passageway and an outlet, with the passageway communicating the dentifrice in the bag or liner with the outlet, and dentifrice suckback limiting means between the dispensing outlet and the flexible bag, which limit entry of air into the dispensing container through the outlet and thereby prevent belching of air from the dispensing container during use thereof.

The dentifrice preferably comprises 0.2 to 0.8% of triclosan, 0.5 to 3% of polyphosphate, 0.005 to 3% of a source of fluorine ions and 0.2 to 5% of synthetic anionic polymeric polycarboxylate. In the squeezable dispensing container the portion of the bag or liner that contacts the dentifrice is preferably of polytetrafluoroethylene or polyvinyl chloride.

The bag or liner of the container may be a laminate which may include a barrier layer of metal.

The dentifrice preferably comprises a stabilizing proportion of a terpene or a flavouring agent which stabilizes the triclosan in the presence of polymeric plastic dispensing container part(s).

The dentifrice may comprise 0.01 to 2% of stabilizing terpene(s) and/or flavour(s). The plastic dispensing container parts may be of a plastic selected from the group consisting of polyfluorocarbons, polyvinyl halides, poly-lower alkylenes, polymethyl pentenes, polyallomers, nylons, polyacrylates, polyesters, polyethers, polycarbonates and polysulfones, and mixtures and pluralities thereof.

In a more preferred form of the invention the dentifrice is an aqueous paste or gel or mixture thereof, which comprises a vehicle, a polishing agent, a surfactant and triclosan and the container is hand holdable and squeezable and comprises a walled resilient tube, a flexible bag or liner, a bottom for such tube, an air check valve to prevent passage of air out from between the bag and the tube, near the bottom thereof, during squeezing of the tube, and to permit entrance of air during resilient return of the tube to normal shape after release of squeezing forces, a dispensing passageway and an outlet, with the passageway communicating the dentifrice in the bag or liner with the outlet, and dentifrice suckback limiting means between the dispensing outlet and the flexible bag, which limit entry of air into the dispensing container through the outlet and thereby prevent belching of air from the dispensing container during use thereof.

The dentifrice may comprise 0.1 to 1% of triclosan. The dentifrice may comprise 0.1 to 3% of polyphosphate. The dentifrice may comprise 0.05 to 1% of a source of fluorine ions. The dentifrice may comprise 0.2 to 5% of synthetic anionic polymeric polycarboxylate. Preferably the dentifrice comprises 0.1 to 1% of triclosan, 0.1 to 3% of tetrasodium pyrophosphate, sodium tripolyphosphate or sodium hexametaphosphate or any mixt-

ure thereof, 0.05 to 1% of sodium fluoride or sodium monofluorophosphate or a mixture thereof, 0.2 to 5% of polyvinyl methyl ether/ maleic anhydride copolymer, and 0.05 to 1% of stabilizing terpene(s).

The portion of the bag or liner that contacts the dentifrice is preferably of polyethylene, or of a laminate of polyethylene and polyethylene terephthalate.

The bag or liner laminate preferably has an aluminium coating between polyethylene and polyethylene terephthalate laminae.

The invention also extends to a resilient squeezable dispensing container of a viscous anti-plaque dentifrice comprising such a dentifrice, which comprises 0.1 to 1% of triclosan, in a resilient squeezable dispensing container which has a walled dispensing chamber, in which container parts thereof that contact the dentifrice during storage and during dispensing thereof is/are of material(s) that is/are compatible with the triclosan in the dentifrice and do(es) not cause excessive loss(es) of anti-plaque properties of the dentifrice dispensing container, which material is a synthetic organic polymeric plastic selected from the group consisting of polyfluorocarbons, polyvinyl halides, polyethylene terephthalates, poly-lower alkylenes, polymethyl pentenes, polyallomers, nylons, polyacrylates, polymethyl methacrylates, polyesters, polyethers, polycarbonates and polysulfone and mixtures and pluralities thereof.

The dentifrice preferably contains 0.1 to 0.8% of triclosan and the parts of dispensing container that contact the dentifrice are of a synthetic organic polymeric plastic selected from the group consisting of polytetrafluoroethylenes, polyvinyl chlorides, polycarbonates and polysulfones.

The invention also extends to a resilient squeezable dispensing container of a viscous anti-plaque, anti-tartar dentifrice comprising such a dentifrice which comprises 0.1 to 1% of triclosan, 0.1 to 3% of polyphosphate and 0.01 to 2% of a stabilizing terpene or stabilizing flavouring agent which stabilizes the triclosan in the presence of synthetic organic polymeric plastic container parts, in a resilient squeezable dispensing container which has a walled dispensing chamber in which container parts thereof that contact the dentifrice during storage and during dispensing thereof are of material(s) that is/are compatible with the triclosan in the dentifrice and do(es) not cause excessive loss(es) of anti-plaque properties of the dentifrice during storage thereof in and dispensing thereof from the squeezable dispensing container, which material is a synthetic organic polymeric plastic selected from the group consisting of polyfluorocarbons, polyvinyl halides, polyethylene terephthalates, poly-lower alkylenes, polymethyl pentenes, polyallomers, nylons, polyacrylates, polymethyl methacrylates, polyesters, polyethers, polycarbonates and polysulfones, and mixtures and pluralities thereof.

The parts of the dispensing container that contact the dentifrice preferably include a bag or liner of a laminate of polyethylene and polyethylene terephthalate.

Claims

1. A resilient squeezable dispensing container of a viscous anti-plaque dentifrice comprising such a dentifrice, which comprises an effective anti-plaque proportion of triclosan, in a resilient squeezable dispensing container which has a walled dispensing chamber, in which container parts thereof that contact the dentifrice during storage and during dispensing thereof are of material(s) that is/are compatible with the triclosan in the dentifrice and do(es) not cause excessive loss(es) of anti-plaque properties of the dentifrice during storage thereof in and dispensing thereof from the squeezable dispensing container.

2. A dispensing container of dentifrice as claimed in Claim 1 characterised in that the parts of the dispensing container that contact the dentifrice are of solid synthetic organic polymeric plastic material and the dentifrice is in paste or gel form.

3. A container of dentifrice as claimed in Claim 1 or Claim 2 in which the parts of the dispensing container that contact the dentifrice during storage in and dispensing from it are of material(s) selected from the group consisting of polyfluorocarbons, polyvinyl halides, polyethylene terephthalates, poly-lower alkylenes, polymethyl pentenes, polyallomers, nylons, polyacrylates, polymethyl methacrylates, polyesters, polyethers, polycarbonates and polysulfones, and mixtures and pluralities thereof.

4. A container of dentifrice as claimed in Claim 1, 2 or 3 characterised in that the dentifrice is an aqueous paste or gel or mixture thereof, which comprises a vehicle, a polishing agent, a surfactant and triclosan, and the container is hand holdable and squeezable and comprises a walled resilient tube, a flexible bag or liner, a bottom for such tube, an air check valve to prevent passage of air out from between the bag and the tube, near the bottom thereof, during squeezing of the package, and to permit entrance of air during resilient return of the tube to normal shape after release of squeezing forces, a dispensing passageway

and an outlet, with the passageway communicating the dentifrice in the bag or liner with the outlet, and dentifrice suckback limiting means between the dispensing outlet and the flexible bag, which limit entry of air into the dispensing container through the outlet and thereby prevent belching of air from the dispensing container during use thereof.

5. A container of dentifrice as claimed in Claim 4 characterised in that in the squeezable dispensing container the portion of the bag or liner that contacts the dentifrice is of polytetrafluoroethylene or polyvinyl chloride.

6. A container of dentifrice as claimed in Claim 4 or Claim 5 characterised in that the bag or liner is a laminate which may include a barrier layer of metal.

7. A container of dentifrice as claimed in Claim 4 or Claim 6 when appendant to Claim 4 characterised in that the portion of the bag or liner that contacts the dentifrice is of polyethylene.

8. A container of dentifrice as claimed in Claim 7 characterised in that the bag or liner is of a laminate of polyethylene and polyethylene terephthalate.

9. A container of dentifrice as claimed in Claim 6 or Claim 8 characterised in that the bag or liner laminate has an aluminium coating between laminae, e.g. polyethylene and polyethylene terephthalate laminae.

10. A dispensing container of dentifrice as claimed in any one of Claims 1 to 9 characterised in that the parts of dispensing container that contact the dentifrice are of a synthetic organic polymeric plastic selected from the group consisting of polytetrafluoroethylenes, polyvinyl chlorides, polycarbonates and polysulfones.

11. A container of dentifrice as claimed in any one of the preceding claims characterised in that the dentifrice comprises 0.1 to 1% of triclosan, e.g. 0.1 to 0.8% of triclosan.

12. A container of dentifrice as claimed in any one of the preceding claims characterised in that the dentifrice comprises an effective anti-tartar proportion of polyphosphate.

13. A container of dentifrice as claimed in Claim 12 characterised in that the dentifrice comprises 0.1 to 3% of polyphosphate.

14. A container of dentifrice as claimed in any one of the preceding claims characterised in that the dentifrice comprises an effective proportion of an antibacterial enhancing agent (AEA) which is a synthetic anionic polymeric polycarboxylate.

15. A container of dentifrice as claimed in Claim 14 characterised in that the AEA is methyl vinyl ether/maleic anhydride copolymer of average molecular weight in the range of 1,000 to 1,000,000.

16. A container of dentifrice as claimed in any one of the preceding claims characterised in that the dentifrice comprises an effective proportion of a source of fluorine ion sufficient to stabilize the polyphosphate against enzymatic hydrolysis.

17. A container of dentifrice as claimed in Claim 16 characterised in that the source of fluorine ion is 0.005 to 3% of an inorganic fluoride or monofluorophosphate.

18. A container of dentifrice as claimed in any one of the preceding claims characterised in that the dentifrice comprises 0.2 to 0.8% of triclosan, 0.5 to 3% of polyphosphate, 0.005 to 3% of a source of fluorine ions and 0.2 to 5% of synthetic anionic polymeric polycarboxylate.

19. A container of dentifrice as claimed in any one of the preceding claims characterised in that the dentifrice comprises a stabilizing proportion of a terpene or a flavouring agent which stabilizes the triclosan in the presence of polymeric plastic dispensing container part(s).

20. A container of dentifrice as claimed in Claim 19 characterised in that the dentifrice comprises 0.01 to 2% of stabilizing terpene(s) and/or flavour(s).

21. A resilient squeezable dispensing container of a viscous anti-plaque, anti-tartar dentifrice comprising such a dentifrice which comprises 0.1 to 1% of triclosan, 0.1 to 3% of polyphosphate and 0.01 to 2% of a stabilizing terpene or stabilizing flavouring agent which stabilizes the triclosan in the presence of synthetic organic polymeric plastic container parts.

22. A container of dentifrice as claimed in any one of the preceding claims characterised in that the dentifrice comprises 0.1 to 1% of triclosan, 0.1 to 3% of tetrasodium pyrophosphate, sodium tripolyphosphate or sodium hexametaphosphate or any mixture thereof, 0.05 to 1% of sodium fluoride or sodium monofluorophosphate or a mixture thereof, 0.2 to 5% of polyvinyl methyl ether/maleic anhydride copolymer, and 0.05 to 1% of stabilizing terpene(s).