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647315

PATENT REQUEST: STANDARD PATENT

We, IVOCLAR AG, being the person(s) identified below as the Applicant, request the grant of a standard patent to the person identified below as the Nominated Person, for an invention described in the accompanying complete specification.

Full application details follow.

Applicant:	IVOCLAR AG
Address:	Bendererstr. 2 FL-9494 Schaan LIECHTENSTEIN
Nominated Person:	IVOCLAR AG
Address:	Bendererstr. 2 FL-9494 Schaan LIECHTENSTEIN
Invention Title:	"Chlorohexidine adduct and method of preparing same"
Name(s) of Actual Inventor(s):	Dr Volker RHEINBERGER; Dr. Ulrich SALZ; Dr. Peter BURTSCHER
Address for service is:	F.B. RICE & CO., 28A Montague St, Balmain N.S.W. 2041
Attorney Code:	RI

BASIC CONVENTION APPLICATION(S) DETAILS

Application No	Country	Country Code	Date of Application
P4135397.8	Germany	DE	26 October 1991

We are not an eligible person described in Section 33 - 36 of the Act.

Drawing number recommended to accompany the abstract nil

Dated this 2 day of October 1992

IVOCLAR AG

By: _____
Registered Patent Attorney

S 032570 021092

SPP4/58533

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P/00/008
Section 29 (1)
Regulation 3.1(2)

NOTICE OF ENTITLEMENT

Dr V. Rheinberger *(To be filed before acceptance)*

I/~~We~~ Ivoclar AG, FL-9494 Schaan, Bendererstr. 2
of Principality of Liechtenstein

being *~~the applicant~~/*authorised by the applicant in respect of an application for a patent for an invention entitled Chlorohexidine adduct and method of preparing same
filed under Application No. _____, state the following:-

Part 1 - Must be completed for all applications.
The person(s) nominated for the grant of the patent:

~~[ ] *is/*are the actual inventor(s)~~

or

[X] has, for the following reasons, gained entitlement from the actual inventors(s):

through employment contract with the inventors

Part 2 - Must be completed if the application is a Convention application.
The person~~(s)~~ nominated for the grant of the patent *is/*~~are:~~

[X] the applicant~~(s)~~ of the basic application~~(s)~~ listed on the patent request form

or

~~[ ] entitled to rely on the basic application(s) listed on the patent request form by reason of the following:~~

Part 3 - must be completed if the application was made under the PCT and claims priority.
The person(s) nominated for the grant of the patent *is/*are:

[ ] the applicant(s) of the application(s) listed in the declaration under Article 8 of the PCT

or

[ ] entitled to rely on the application(s) listed in the declaration under Article 8 of the PCT by reason of the following:-

(continued over)

Part 4 - Must be completed if the application is a Convention application, or the application was made under the PCT and the applicant made a declaration under Article 8 of the PCT in respect of the basic application.

[X] The basic application~~(s)~~ *listed on the patent request form/~~*referred to in the declaration under Article 8 of the PCT~~ *is/~~*are~~ the application~~(s)~~ first made in a Convention country in respect of the invention.

Signed : _____
a) Dr. V. Rheinberger

Signed: _____ Date: August 13,1992
b) R. Mann

Status: a) Member of the Board
b) Head Clerk

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CHLOROHEXIDINE ADDUCT AND METHOD OF PREPARING SAME

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(71) Applicant(s)
IVOCLAR AG

(72) Inventor(s)
DR VOLKER RHEINBERGER; DR. ULRICH SALZ; DR. PETER BURTSCHER

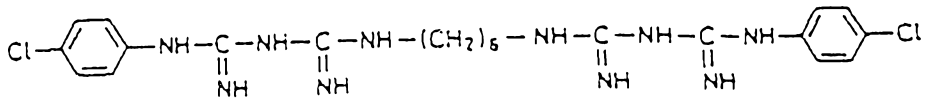
(74) Attorney or Agent
F B RICE & CO , 28A Montague Street, BALMAIN NSW 2041

(56) Prior Art Documents
EP 0110568

(57) The invention relates to a chlorohexidine adduct which can be used as an antiseptic and in particular as an antiseptic in dentistry and also as a therapeutic and prophylactic anti-plaque agent.

CLAIM

1. Chlorohexidine adduct having the following formula



· 6 HF

and its hydrates.

2. Process for preparing the chlorohexidine adduct according to claim 1, wherein

a) a solution of hydrogen fluoride is reacted with a solution of a chlorohexidine salt,

b) the molar ratio of hydrogen fluoride to chlorohexidine salt being at least 6:1, and

c) the resultant adduct is separated.

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IVOCLAR AG

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Invention Title:

"Chlorohexidine adduct and method of preparing same"

The following statement is a full description of this invention including the best method of performing it known to us:-

The invention relates to a chlorohexidine adduct which can be used as an antiseptic and in particular as an antiseptic in dentistry and also as a therapeutic and prophylactic anti-plaque agent.

In the attempt to inhibit or completely stop the formation of plaque and thus also of caries, the effectiveness of substances with antibacterial properties such as e.g. chlorinated phenols, formaldehyde and quaternary ammonium compounds has been examined in the past. However, they have not been used in practice, because of their toxicity and their restricted action spectrum.

The currently most effective anti-plaque agent is chlorohexidine (1,6-bis-(N^5-p-chlorophenyl-N'-diguanido)-hexane), which is used in particular in the form of its water-soluble digluconate, but also as sparingly soluble diacetate and dihydrochloride (cf. A. Scheie in J. Dent. Res. 68, 1609 (1989) and P. Gjermo in J. Dent. Res. 68, 1602 (1989)). Known in addition to these chlorohexidine compounds is also chlorohexidine dihydrofluoride, which according to published German patent application 21 58 150 is used as an antiseptic agent in transparent tooth gels.

It has been shown that chlorohexidine as a chemotherapeutic product is effective against bacteria of the type Streptococcus mutans. Bacteria of this type play a key part in the formation of caries. It is therefore assumed that, with a reduction of their quantity on the surface of the teeth, caries formation can be countered effectively (cf. I. Ostela and J. Tenovuo in Scand. J. Dent Res. 98, 1 (1990)).

The bactericidal effect exerted by chlorohexidine vis-à-vis bacteria of the type Streptococcus mutans is, however, greatly weakened if it is used in small concentrations. Therefore, chlorohexidine is also subjected to clear restrictions in practical application if it is a matter of reducing tooth plaque which for its part can lead to the occurrence of parodontosis and caries. Moreover, the application of chlorohexidine in higher concentrations can lead to unwanted dis-

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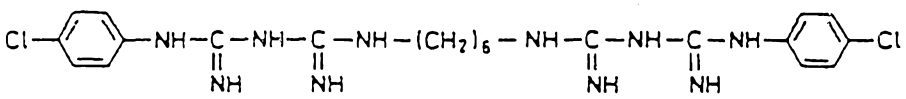
colorations of the tongue, teeth, prostheses and fillings (cf. L. Flötra, P. Gjermo, G. Rölla and J. Waerhaug in Scand. J. Dent. Res. 79, 119 (1971)).

It is therefore the object of the invention to make available a chlo-rohexidine adduct which is generally usable as an antiseptic and in particular can be used as an anti-plaque agent, said adduct effec-tively countering the renewal and growth of films on the teeth, even in very small concentrations, and moreover being able, by giving off fluoride, to protect the tooth enamel against demineralization, especially by acids.

This object is achieved by the novel chlorohexidine adduct according to claim 1 and the process for its preparation according to claims 2 to 6 as well as its use according to claims 7 and 8.

The chlorohexidine adduct according to the invention is a compound of the following formula:



· 6 HF

or its hydrates.

The adduct displays the IR spectrum according to Figure 1. It is not known how the six molecules of hydrogen fluoride in the adduct according to the invention are bound to the chlorohexidine molecule. It is conceivable in principle that the adduct according to the invention consists of uncharged molecules or is present in the form of ions and thus as salt.

The adduct according to the invention is prepared by reacting a solution of hydrogen fluoride with a solution of chlorohexidine salt, the molar ratio of hydrogen fluoride to chlorohexidine salt being at least 6:1, and separating the resultant adduct. If a molar ratio of hydrogen fluoride to chlorohexidine salt of less than 6:1 is used, the adduct according to the invention is also obtained, but in a smaller yield.

The chlorohexidine adduct according to the invention is preferably prepared by reacting a solution of hydrogen fluoride in water with a solution of chlorohexidine salt in water in a molar ratio of hydrogen fluoride to chlorohexidine salt of 6:1 to 30:1 at a temperature in the range from ambient temperature to reflux temperature, and separating the resulting precipitate.

To achieve high yields and prepare a precipitate of the chlorohexidine adduct according to the invention which is easily separable by filtration, a molar ratio of hydrogen fluoride to chlorohexidine salt of 10:1 to 20:1 is especially preferred. Solutions in a mixture of ethanol/water 90/10 vol.-% are used to advantage at reflux temperature instead of the aqueous solutions of the adducts. In this case, only a molar ratio of hydrogen fluoride to chlorohexidine salt of 8:1 is necessary. The adduct according to the invention is produced in a high yield of more than 95% in this case. Because of the smaller hydrogen fluoride requirement, this variant of the preparation process is especially preferred.

Chlorohexidine digluconate is used preferably for the preparation of the adduct according to the invention. However, other chlorohexidine salts which are adequately soluble in the solvent used in each case, such as e.g. the dihydrochloride or the diacetate, can also be used.

24 hours are typically adequate as reaction duration in order to achieve a complete reaction. The reaction duration can vary, however, depending on the chosen reaction parameters. However, the

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reaction duration best suited in each case can easily be ascertained by routine experiments.

The chlorohexidine adduct which occurs predominantly as precipitate during the reaction is preferably separated and cleaned by filtration and subsequent washing with water and acetone. Further chlorohexidine adduct can be obtained by working up the mother liquors, so that overall yields of 91 to nearly 100% are achievable. The purified solid is then dried in a known manner and is present, depending on the degree of drying, in the form of hydrates with various water contents. The drying is preferably carried out at 50°C in the drying chamber.

Because of its pronounced antibacterial action, the chlorohexidine adduct according to the invention can be used generally as an antiseptic agent. It can be used both in pharmaceutical and cosmetic products as a therapeutic and prophylactic bactericide. However, it is preferably used in dental materials, such as e.g. tooth varnishes, fissure sealants, prophylactic pastes, mouthwashes, toothpicks, dental floss, dental chewing gum, dressings, tooth ointments, gum trainers, disinfectants for prostheses and modelling materials, drying agents, underfilling materials, cements, filling materials, adhesion promoters and endodontosis materials. The adduct according to the invention can be deposited on a fixed substrate, such as e.g. a toothpick or dental floss, or incorporated into dental materials, such as e.g. provisional filling materials and fissure sealants.

Particularly advantageous is the incorporation of the adduct according to the invention into dental materials which are to remain in the oral cavity for a limited period, such as e.g. provisional filling materials, dressings, modelling materials and temporary cements. If the adduct according to the invention is incorporated for example into a provisional filling material, one obtains after its removal a germ-free cavity into which the final filling can be placed immediately.

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As the chlorohexidine adduct displays only quite a low solubility in common solvents, it is preferably incorporated into the said dental materials as a solid. It is added to the dental materials in quantities of 0.1 to 20 wt.-%, preferably 1 to 10 wt.-%, and particularly preferably 3 to 7 wt.-%, relative to the total weight of the material. Examples of usable dental materials are those which contain 10 to 95 wt.-% of polymerizable organic binder, 5 to 90 wt.-% of inorganic and/or organic fillers and 0.01 to 5 wt.-% of catalysts, based on the total weight of the material.

Solutions containing 0.001 to 0.03 wt.-% of adduct according to the invention may also be used. Suitable as solvents are, for example, water, ethanol, acetone, ethyl acetate, triethylene glycol dimethacrylate and decandiol methacrylate. Synthetic or natural resins which are soluble in common solvents and become hard after the evaporation of the solvents can also be used. Examples of these are shellac, benzoin resin, polyvinyl pyrrolidone and rosin.

Another preferred application of the chlorohexidine adduct is that as a therapeutic or prophylactic anti-plaque agent. It prevents the renewal of films on teeth and inhibits the growth of already existing films on teeth. Diseases caused by the presence of films on teeth, such as e.g. parodontosis, primary and secondary caries and gingivitis, can thus be combatted effectively with the chlorohexidine adduct according to the invention.

With regard to its bactericidal effectiveness, the adduct according to the invention is completely comparable in a concentration of 0.03 wt.-% with the chlorohexidine currently rated as a very effective anti-plaque agent. Surprisingly, however, the effectiveness of chlorohexidine is clearly exceeded if both are used in concentrations smaller than or equal to 0.01 wt.-%. In this concentration range, the chlorohexidine adduct according to the invention is also clearly superior to stannous difluoride, a compound which is known for having very good bactericidal properties.

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The superiority of the adduct according to the invention especially in small concentrations is of particular importance for practical application, as deposited active ingredients are continuously diluted as a result of the permanent saliva flow in the oral cavity. An active ingredient like the chlorohexidine adduct according to the invention, which also displays a marked bactericidal effect in small concentrations, is therefore of particular advantage.

Another advantage compared to chlorohexidine is that, when the adduct according to the invention is used, there are no unwanted side-effects such as a bitter taste, discolorations of tooth materials and irritations of the mucosa.

Finally, the high fluorine content of the adduct according to the invention means that the latter protects the tooth enamel through fluoridation and can therefore also afford effective protection against the formation of caries in this respect.

The invention is explained in more detail in the following examples.

Example 1

To prepare the chlorohexidine adduct according to the invention, 42.5 ml of an aqueous 20% (0.01 mole) chlorohexidine digluconate solution were added under stirring dropwise within 2 hours to 45 ml of an aqueous 4.4% (0.11 mole) HF solution. The mixture was stirred further overnight, and the precipitate which formed was filtered and washed threetimes with 50 ml of water each time and then twice with 50 ml of acetone each time. The resultant precipitate was then dried at 50°C in the drying chamber. The chlorohexidine adduct according to the invention was obtained as a solid in a yield of 76% and had a melting point of 185 to 190°C.

The IR spectrum (KBr moulding) is reproduced in Fig. 1.

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Elementary analysis shows that the product is chlorohexidine hexahydrofluoride with one to two moles of crystal water.

Structure A:

$C_{22}\ H_{30}\ N_{10}\ Cl_2 \cdot 6HF \cdot H_2O$ MW = 642.9

Structure B:

$C_{22}\ H_{30}\ N_{10}\ Cl_2 \cdot 6HF \cdot 2H_2O$ MW = 660.9

Elementary analysis:

	found	theoretical	
		Structure A	Structure B
C	41.00%	41.06%	39.95%
H	5.15%	5.60%	5.45%
N	21.70%	21.78%	21.18%
Cl	10.85%	11.02%	10.73%
F	17.55%	17.73%	17.25%
H_2O*)	3.75%	2.80%	5.45%

*) H_2O content determined by the Karl Fischer method

The solubility of the adduct according to the invention in some common solvents and reactive diluents is given in the following Table I:

Table I

Water (pH value 2 to 9.7)	0.03 wt.-%
Ethanol	0.005 wt.-%
Acetone	0.03 wt.-%
Ethyl acetate	0.02 wt.-%
Triethylene glycol dimethacrylate (SR-205)	< 0.005 wt.-%
Decandiol dimethacrylate (D_3MA)	< 0.005 wt.-%

Example 2

By using 90 ml of an aqueous 4.4% (0.2 mole) HF solution and 42.5 ml of an aqueous 20% (0.01 mole) chlorohexidine digluconate solution - the reaction procedure otherwise being the same as in Example 1 - a precipitate was obtained which was more easily filterable than the one obtained according to Example 1.

The chlorohexidine adduct was obtained in a higher yield of 91 to 94%.

Example 3

42.5 ml (0.01 mole) of an aqueous 20% chlorohexidine digluconate solution were added dropwise to 200 ml (0.08 mole) of a solution of hydrogen fluoride in a 90/10 vol.-% mixture of ethanol/water at reflux temperature for 1 hour, accompanied by stirring, and the stirring was continued for a further hour. After the reaction mixture had cooled to ambient temperature the resultant precipitate was filtered off and washed threetimes, each time with 50 ml of a 90/10 vol.-% mixture of ethanol/water. In contrast to the preparation processes carried out at ambient temperature as in Example 1 and Example 2, the resultant precipitate was crystalline and thus easily filterable. Further product came out of the mother liquor within a further week. The total yield was 98%.

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Compared to the process variants according to Examples 1 and 2, the advantage with this process procedure in a mixture of ethanol/water at reflux temperature is that a better filterable precipitate occurs in a very high yield and the hydrogen fluoride requirement is much smaller.

Example 4

The antibacterial effectiveness of the chlorohexidine adduct according to the invention was demonstrated in the Agar diffusion test with Streptococcus mutans.

For this purpose, culture suspensions of Streptococcus mutans were added to a liquid Agar comprising yeast extract and dextrose. After the Agar plates had solidified, a hole of 10 mm diameter was cut out, into which 0.1 ml of the solution to be tested was poured in each case. After 24 hours of incubation at 37°C, the diameters of the inhibiting zones were measured for each sample, which were duplicated in each case. The results of these tests are reproduced in the following Table II.

Table II

Inhibiting zone diameters

Concentration	Solution A	Solution B	Solution C
0.03 wt.-%	17 mm	17 mm	20 mm
0.01 wt.-%	13 mm	15 mm	11 mm
0.003 wt.-%	11 mm	12 mm	10 mm*

* Not effective

Solution A: Aqueous solution of chlorohexidine digluconate

Solution B: Aqueous solution of the chlorohexidine adduct according to the invention

Solution C: Aqueous solution of stannous difluoride

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It transpires that in the concentration range of 0.03 wt.-% the antibacterial effectiveness of the chlorohexidine adduct according to the invention vis-à-vis Streptococcus mutans is comparable with that of chlorohexidine gluconate, while stannous difluoride displays an even stronger action in this concentration range. However, increasing dilution is accompanied by markedly declining effectiveness in the case of the known compounds, to such an extent indeed in the case of stannous difluoride at a concentration of 0.003 wt.-% that an antibacterial action can no longer be detected. Compared to this, the antibacterial effectiveness of the adduct according to the invention is still very high even at concentrations of 0.01 to 0.003 wt.-%. Its superiority especially in low concentrations thus makes it a very effective anti-plaque agent.

Example 5

A light-curable fissure sealant contains the following constituents:

56.08 wt.-%	bisphenol A glycidyl methacrylate (Bis-GMA)
36.1 wt.-%	triethylene glycol dimethacrylate
0.45 wt.-%	cyanoethylmethylaniline
0.25 wt.-%	DL-camphor quinone
2.1 wt.-%	TiO_2
0.02 wt.-%	2,6-di-tert.-butyl-p-cresol
5.0 wt.-%	chlorohexidine adduct

The light-curable fissure sealant was obtained by mixing all the components. The sealant was applied with a brush onto the fissures in a molar tooth and hardened for 20 sec with the Heliolux® light-curable apparatus made by Vivadent/Liechtenstein. In this way the fissures were permanently sealed and, because of the fluoride liberated by the chlorohexidine adduct incorporated into the sealant, excellent protection against caries was achieved in the occlusal area.

As a result of the admixture of 1 to 5 wt.-% of the chlorohexidine adduct to the basic fissure-sealant formulation, no decrease in

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through-hardening depth was observed, as the following values for Vickers hardness show:

	HV 0.5
Fissure sealant without chlorohexidine adduct	188 MPa
Fissure sealant + 1% chlorohexidine adduct	248 MPa
Fissure sealant + 3% chlorohexidine adduct	212 MPa
Fissure sealant + 5% chlorohexidine adduct	180 MPa

To detect chlorohexidine and fluoride migration, 10 test specimens, each 50 mm in diameter and 0.5 mm high, were stored in dist. water at 37°C. The fluoride ion concentration was determined by means of a fluoroelectrode and the chlorohexidine concentration was ascertained by means of UV spectroscopy. The cumulative figure for liberated fluoride and chlorohexidine is summarized in Table III.

Table III

Migration time [days]	Fluoride liberated [µg/cm^2]	Chlorohexidine liberated [µg/cm^2]
1	0.95	3.86
2	1.48	5.56
3	1.91	6.84
4	2.22	7.58
7	2.91	9.26
10	3.45	10.30
17	4.22	11.60
24	4.92	12.30
30	5.58	13.20
44	6.56	14.40

The results are represented graphically in Figures 2 and 3.

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Example 6

A light-curable dental material with relatively high water absorption and thus high active ingredient release (e.g. suitable as provisional filling material or as a dressing) has the following composition:

43.6	wt.-%	polyester urethane dimethacrylate
0.25	wt.-%	cyanoethylmethylaniline
0.15	wt.-%	DL-camphor quinone
35.0	wt.-%	splinter polymerizate
21.0	wt.-%	amorphous SiO_2, silanized (BET surface 50 m^2/g)

The splinter polymerizate comprises:

59.4	wt.-%	urethane dimethacrylate
40	wt.-%	fine-particled SiO_2, silanized
0.6	wt.-%	benzpinacol.

The components are mixed together and polymerized at 120°C. The filled polymerizate is ground into a polymer powder.

The amorphous fine-particled silanized SiO_2 is Aerosil® OX 50 from Degussa AG.

A light-curable dental material was obtained by mixing all the components.

The water absorption of dental filling composites is normally in the range of 1 wt.-%; this material displays a water absorption in the range of 3 wt.-% (3 weeks H_2O storage at 37°C). The cumulative amount of fluoride and chlorohexidine liberated is summarized in Table IV.

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Table IV

Migration time [days]	Fluoride given off [µg/cm²]	Chlorohexidine given off [µg/cm²]
1	3.78	17.0
2	6.03	25.7
3	8.03	33.6
4	9.82	40.3
7	11.98	51.4
10	13.99	60.6
17	16.37	74.5
24	18.68	86.6
30	19.88	97.8
44	22.68	118.3

The results are represented graphically in Figures 2 and 3.

As the migration tests show, significant quantities of fluoride and chlorohexidine are released from this dental material, so that an adequate inhibition of the growth of microorganisms is also to be expected in this combination.

Since not all microorganisms react identically to released active ingredients, studies were conducted using the following microbes.

Gram-positive bacteria:	Streptococcus mutans Staphylococcus aureus
Gram-negative bacteria:	Pseudomonas auruginosa Escherichia coli
Fungus:	Candida albicans

Test specimens (d = 10 mm, h = 2 mm) were inserted into the moist microorganism cultures at 37°C over a period of 24 hours and the inhibiting zone was then determined.

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	Inhibiting zone diameter [mm]
Streptococcus mutans	15
Staphylococcus aureus	16
Pseudomonas auruginosa	17
Escherichia coli	15
Candida albicans	12

A clear inhibition of growth can be established for these different microorganisms.

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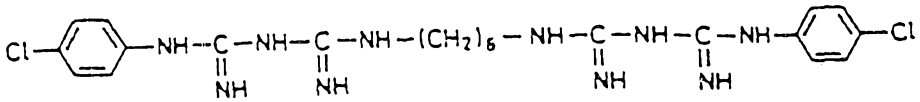
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. Chlorohexidine adduct having the following formula



· 6 HF

and its hydrates.

2. Process for preparing the chlorohexidine adduct according to claim 1, wherein

a) a solution of hydrogen fluoride is reacted with a solution of a chlorohexidine salt,

b) the molar ratio of hydrogen fluoride to chlorohexidine salt being at least 6:1, and

c) the resultant adduct is separated.

3. Process according to claim 2, wherein

a) aqueous solutions are used,

b) the molar ratio of hydrogen fluoride to chlorohexidine salt is 6:1 to 30:1 and

c) the reaction is carried out at a temperature in the range from 20°C to reflux temperature.

4. Process according to claim 2, wherein

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a) solutions in a mixture of ethanol and water are used,

b) the molar ratio of hydrogen fluoride to chlorohexidine salt is at least 8:1 and

c) the conversion is carried out at reflux temperature.

5. Process according to claim 4, wherein a 90/10 vol.-% mixture of ethanol and water is used in step a).

6. Process according to one of claims 2 to 4, wherein chlorohexidine digluconate is used as chlorohexidine salt.

7. An antiseptic composition comprising the chlorohexidine adduct or its hydrates according to claim 1.

8. An anti-plaque composition for the prevention of caries comprising the chlorohexidine adduct or its hydrates according to claim 1.

DATED THIS 2nd DAY OF OCTOBER 1992

IVOCLAR AG

Patent Attorneys for the Applicant:-

F.B. RICE & CO.

ABSTRACT

A chlorohexidine adduct comprising one molecule of chlorohexidine with six molecules of hydrogen fluoride and a process for its preparation are described, said adduct displaying a high anti-bacterial effectiveness vis-à-vis Streptococcus mutans even in very small concentrations and being valuable as anti-plaque agent and for caries prevention.

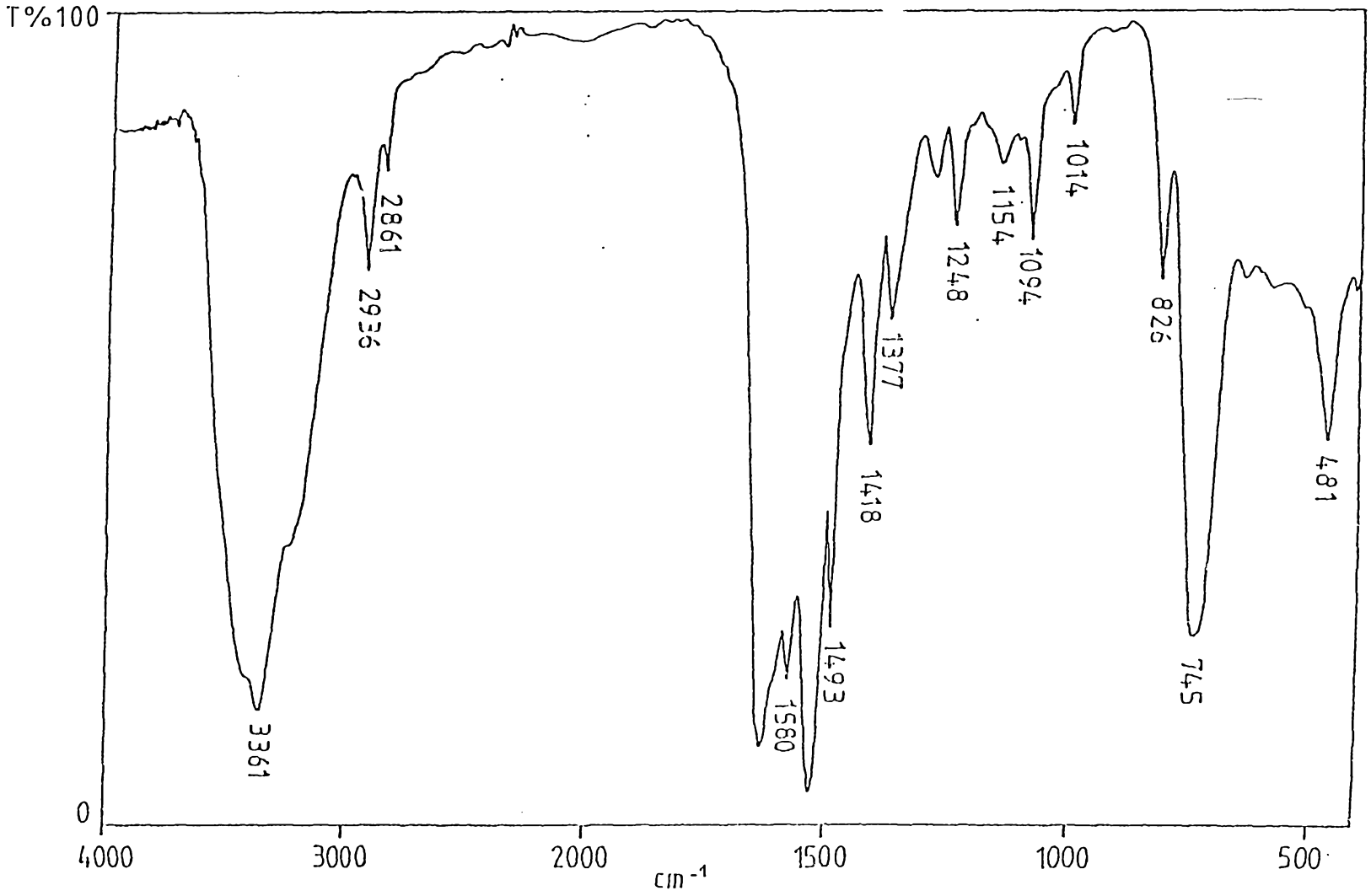

FIGURE 1

CUMULATIVE CHLOROHEXIDINE RELEASE

CHLOROHEXIDINE ADDUCT

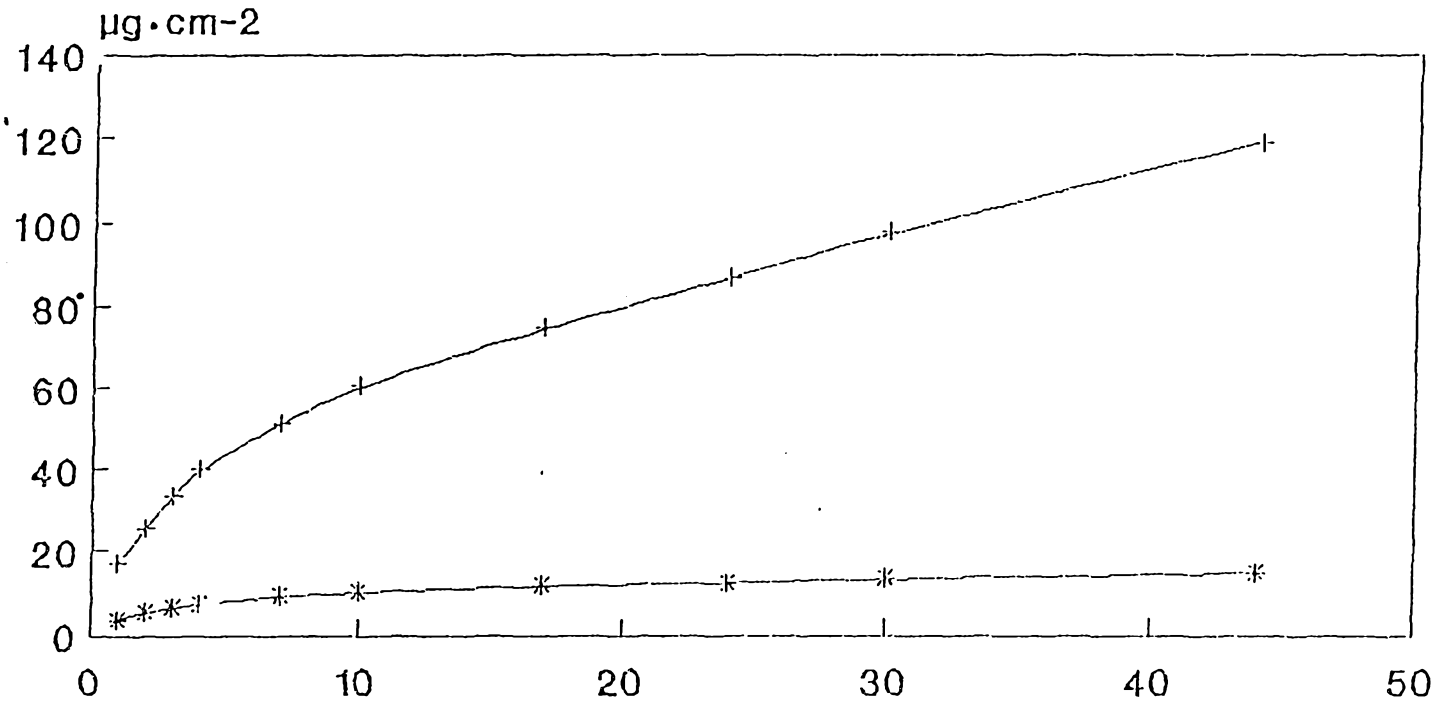

Figure 2

Example 6 Example 5

Figure 2

Cumulative Fluoride Release

Chlorohexidine Adduct

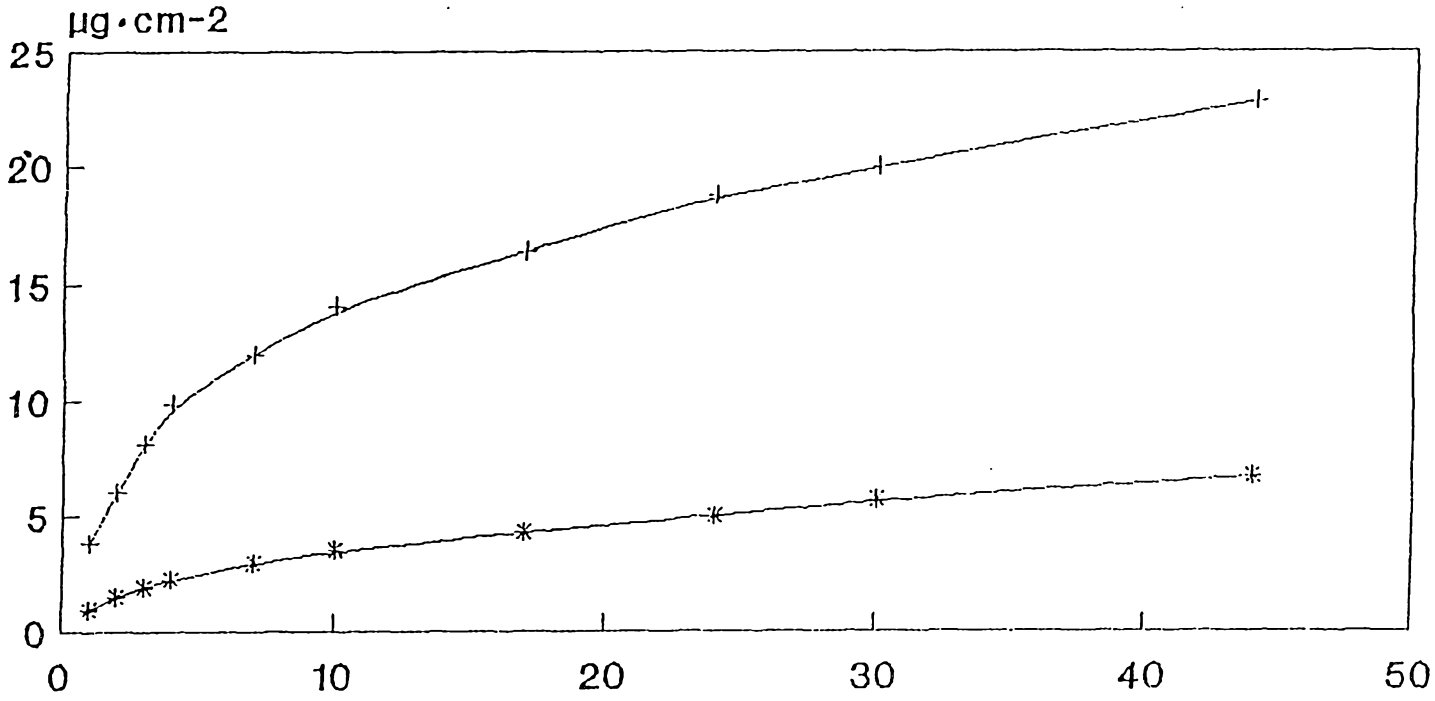

Figure 3