

Description**"Improved mouthwash preparation"**Background of the art

Chlorhexidine is known since more than twenty
5 years as the gold standard for its antiplaque and
antibacterial activity.

It is in fact capable of inhibiting the
formation of new plaque and of disaggregating the
layers already deposited on the tooth surface acting
10 on its matrix thanks to its competitive mechanism
with the calcium ions.

Chlorhexidine based mouthwashes are very useful
in the treatment of periodontal pathologies and for
enhancing the post-surgical healing process.

15 The antiseptic effect of chlorhexidine is due to
its ability to establish chemical bonds with anionic
groups (phosphate, sulfate, carboxyl group) present
at the level of the bacterial cell wall and to induce
a marked increase in cell permeability and alteration
20 of the osmotic equilibrium.

Chlorhexidine has however the major drawback of causing brownish staining on the surface of the teeth as well as on prosthesis and tongue, which reduce significantly the patient compliance.

5 In order to overcome said problem, anti-discolorant systems (ADS) have been developed, which comprise adding in the chlorhexidine formulation sodium metabisulphite, for its property of preventing the Maillard reaction, and ascorbic acid, which
10 interfere with the formation of ferric disulfur organic compound.

Though the above, there is the need of improved mouthwash preparations, which could solve the problem of the teeth discoloration.

15 Summary of the invention

It has been surprising found that a combination of a metabisulfite salt of an alkali or an alkaline-earth metal thereof, ascorbic acid or an alkali or an alkaline-earth metal salt thereof, hyaluronic acid or
20 a salt thereof and polyvinylpyrrolidone-vinylacetate can be used as an improved anti-pigmentation system in a mouthwash preparation based on chlorhexidine.

Brief description of the figures

Fig. 1 shows the results of the test on the
25 composition of the invention.

Object of the invention

In a first object, the present invention discloses an anti-pigmentation system for a chlorhexidine based mouthwash.

5 The mouthwash comprising said system represents itself a further object of the invention.

According to another aspect, it is disclosed a process for the preparation of a mouthwash based on chlorhexidine and comprising the anti-pigmentation
10 system of the invention.

In a preferred aspect, it is disclosed a method for the prevention and treatment of plaque comprising the use of the mouthwash of the invention.

In a preferred aspect, it is disclosed a method
15 for the cosmetic prevention and treatment of plaque comprising the use of the mouthwash of the invention.

In a preferred aspect, it is disclosed a method for the prevention of stains on the surface of the teeth comprising the use of the mouthwash of the
20 invention.

In a preferred aspect, it is disclosed a method for the cosmetic prevention of stains on the surface of the teeth comprising the use of the mouthwash of the invention.

In ad additional aspect, it is disclosed the use of the mouthwash of the invention for the protection of gingiva and oral mucosa and for the prevention and treatment of gingivitis.

5 Detailed description of the invention

According to a first object of the invention, it is disclosed an anti-pigmentation system that can be used for preparing chlorhexidine based mouthwashes.

10 In particular, according to the present invention, the mouthwash comprises an amount of chlorhexidine of from about 0.01% to 0.3% (w/w) and preferably of from about 0.09% to 0.25% (w/w).

15 According to an even preferred embodiment, chlorhexidine is comprised in a quantity of about 0.2% (w/w).

Chlorhexidine may be present as such or in the form of a salt or a complex thereof.

A salt may be represented by chlorhexidine digluconate.

20 As per the anti-pigmentation system of the invention, it is represented by a composition comprising: a metabisulfite salt of an alkali or an alkaline-earth metal, ascorbic acid or an alkali or an alkaline-earth metal salt thereof, hyaluronic acid or
25 a salt thereof and polyvinylpyrrolidone-vinylacetate.

In particular, said metabisulfite salt can be present in a quantity of about 0.1% to about 0.5% and preferably of about 0.15% to about 0.28% (w/total volume of the mouthwash).

5 In a preferred embodiment, the metabisulfide salt is represented by sodium metabisulfite.

In a particular embodiment, the ascorbic acid or the salt above referred can be substituted, partially or completely, by citric acid and/or an alkali or an
10 alkaline-earth metal salt thereof.

For instance, sodium citrate tribasic can be used.

In a preferred embodiment, the ascorbic acid and a salt thereof, can be present in a quantity of about
15 1.0% to about 1.5% and preferably of about 1.0% to about 1.2% (total weight of the acid plus salt/total volume of the mouthwash).

In the other preferred embodiment, citric acid can be present in a quantity of about 0.01% to about
20 0.02% (w/total volume of the mouthwash), while if present, a citrate salt can be present in a quantity of about 0.8% to about 2.0% and preferably of about 1% to about 1.5% (w/total volume of the mouthwash).

As per the hyaluronic acid, it can be present in the form of sodium or potassium salt or a mixture of the two salts.

Preferably, the hyaluronic acid or the
5 hyaluronate salt is present in an amount of about 0.01% to about 1.5% and preferably of about 0.05% to about 1.2% (w/total volume of the mouthwash).

The mouthwash of the invention may further comprise additives like: sweeteners and/or flavorings,
10 a source of fluorine, humectant, preservatives, surfactants, pH regulators, coloring agents.

Preferably, flavorings are present in an amount of about 0.05-0.15% (w/total volume of the mouthwash) and can be selected in the group comprising
15 peppermint, menthol, anethole, *viridis* mint, cinnamon, clove, eucalyptus, etc.

Sweeteners can be present in a quantity of about 6-10% (w/total volume of the mouthwash).

In a preferred aspect, sweeteners can be selected
20 in the group comprising non-cariogenic sugars like xylitol, saccharin or an alkali or alkaline-earth metal salts thereof, acesulfame or an alkali or alkaline-earth metal salts thereof, sucralose, *Stevia rebaudiana* extract.

The source of fluorine can be represented by fluoride or alkali or alkaline-earth metal salts thereof.

Humectants can be present in a quantity of about
5 0.1-0.2% (w/total volume of the mouthwash).

Preferably, the humectant may be selected in the group comprising sorbitol, glycerin or propylene glycol.

Preservatives may be selected in the group
10 comprising the benzoates, phenossietanolo, chlorphenesin.

The surfactants are present in an amount of about 1.0-3% (w/total volume of the mouthwash).

In a preferred embodiment, the surfactants may be
15 selected in the group comprising hydrogenated castor oil PEG40, Poloxamer 407 or other surfactants suitable for the purposes of the present invention.

pH regulators can be selected in the group comprising citric acid and its salts, like sodium
20 salt.

Coloring agents may be present in an amount of about 0.0005-0.001% (w/total volume of the mouthwash) selected among those agents suitable for use in the field, like for instance CI 1940, CIU 42090, CI 17200.

As per the polyvinylpyrrolidone-vinylacetate, according to the present invention, it can be comprised in an amount of about 0.02% to about 0.5% (w/total weight of the mouthwash).

5 Preferably, the polyvinylpyrrolidone-vinylacetate may be comprised in an amount of about 0.02% to about 0.5%, preferably of about 0.15% to about 0.2% and more preferably it is comprised in an amount of about 0.09% to about 0.12% (w/total weight of the mouthwash).

10 As above indicated, the mouthwash comprising the anti-pigmentation system disclosed represents a further object of the invention.

According to another aspect, it is disclosed a process for the preparation of a mouthwash based on
15 chlorhexidine and comprising the anti-pigmentation system of the invention.

In an additional object, it is disclosed a method for the prevention and treatment of plaque comprising the use of the mouthwash of the invention.

20 In a preferred aspect, it is disclosed a method for the cosmetic prevention and treatment of plaque comprising the use of the mouthwash of the invention.

In an additional object, it is disclosed a method for the prevention of stains on the surface of the

teeth comprising the use of the mouthwash of the invention.

In a preferred aspect, it is disclosed a method for the cosmetic treatment of stains on the surface of
5 the teeth comprising the use of the mouthwash of the invention.

In another object, it is disclosed the use of the mouthwash according to the invention for the therapeutic prevention and treatment of plaque.

10 In a still further object, it is disclosed the use of the mouthwash of the invention for the cosmetic prevention and treatment of plaque.

In a still further object, it is disclosed the use of the mouthwash of the invention for the
15 prevention of stains on the surface of the teeth.

In another object, it is disclosed the use of the mouthwash according to the invention for the cosmetic prevention of stains on the surface of the teeth.

In a still further object, it is disclosed the
20 use of the mouthwash of the invention for the prevention, protection and treatment of gingivitis.

In particular, for the purposes of the present invention, the use of the disclosed mouthwash once or twice a day for at least one minute and for a period
25 of from 7 to 15 days may be helpful in the prevention

and treatment of plaque and/or of gengivitis, in the prevention of the bacteria growth, as an anti-bacterial.

According to a further embodiment, the mouthwash
5 of the invention can be used in the treatment of parodontitis when used once or twice a day for at least one minute and a period of from 7 to 15 days at the concentration of 0.2% followed by the use once or twice a day for at least one minute for about 21 days
10 at the concentration of 0.12%.

According to an additional object of the invention, it is disclosed the use of polyvinylpyrrolidone-vinylacetate combined with chlorhexidine in a mouthwash for the treatment of or
15 the prevention of the formation of plaque.

EXAMPLE 1

According to the above description, the following mouthwash preparation can be:

20

COMPONENT	QUANTITY
water	q.b. to 100%
sugar	6-10%
humectants	0.1-0.2%
surfactants	1.0-3%

Ascorbic acid	0.1-1.5% (w/v)
Chlorhexidine digluconate	0.05-0.3% (w/w)
PVP-VA copolymer	0.05-0.3%
sodium hyaluronate	0.05-1.2%
arome	0.05-0.15%
sodium metabisulfite	0.1-0.5% (w/v)
sodium citrate	1.0-1.5%
citric acid	0.01-0.015
coloring agent	0.0005-0.0009%

EXAMPLE 2

The purpose of the clinical trial was to evaluate the effectiveness against pigmentations by a dental mouthwash containing 0.2% chlorhexidine, PVP-VA, hyaluronic acid and ADS® (Anti Discoloration System) compared to a mouthwash only containing 0.2% chlorhexidine and the ADS® system.

Materials and Methods

17 volunteers have been enrolled in the study, selected at the Clinica Universitaria at the IRCCS Istituto Ortopedico Galeazzi (Milan).

Patients had to meet the following requirements:

1. Patients in good health, absence of systemic diseases;
2. Adhesion through informed consent;
3. Older than 18 years;
- 5 4. Non-smokers or light smokers (less than 5 cigarettes a day);
5. Good oral hygiene with low levels of plaque index (FMPS FMBS and $\leq 25\%$).

Before the study, patients have been subjected to
10 professional oral hygiene session, in order to remove possibly plaque and pigmentations already present on the dental surface. There have been prepared anonymous packs marked only with two letters:

A:	mouthwash (HA + ADS)
B:	mouthwash (ADS)

Patients volunteers have been then divided into
15 two groups randomly and they have been given a box corresponding to the randomization list.

Patients have been asked to suspend the
operations of mechanical oral hygiene in the V
sextant, i.e. only in the lower 33 to 43 (6 teeth in
20 all).

In the remaining areas, the subjects continued to brush but with no toothpaste.

Everyone handed an identical toothbrush: model Curaprox 5460.

Patients have thus made a first cycle of rinses keeping the product in the mouth for one minute, twice
5 a day, for 7 days, after which they recurred to the center investigator for clinical evaluations.

Soon after, a second session of oral hygiene was performed, to remove the stains and plaque formed, and the patient have been asked to recur after another 7
10 days.

So, with the same mode of the previous rinse cycle, the patient have made a second rinse cycle with the mouthwash that had not received during the first cycle.

15 During the visits at time zero (baseline) and after 7 days there have been detected the plaque index (PI, according to Loe and Silness, 1964), gingival index (GI, according to Loe, 1967) and the index of pigmentation (SI, according to Lobene, 1968).

20 Information has been gathered about any adverse events or problems that emerged during the study through a questionnaire.

In this, patients have noted also the intake of chromogenic substances such as coffee, tea,

cigarettes, red wine, spinach and green vegetables in general.

At each session, intraoral photographs have been taken for the assessment of the pigmentation and the same has been made for the evaluation of the extent of pigmentation. The assessment of the Stain Index has been independently performed by 3 different experts operators.

Results

Of the 17 subjects enrolled, 4 failed to meet the protocol because they performed mechanical procedures for the oral hygiene on the affected area, and have been therefore excluded. The remaining 13 subjects in the study completed the rinse cycles with good compliance.

The results are shown in Figure 1.

With respect to the accumulation of plaque, both mouthwashes proved to be effective in combating the dental plaque, which resulted mostly present at 7 days, although there was no evidence of any substantial deposits for the both 2 mouthwashes.

Even the Gingival Index was similar in the 2 mouthwashes, but in this case the presence of inflammation has been detected only in one patient in the group A and two patients in group B.

Regarding the Stain Index, a trend towards less pigmentation has been detected for the mouthwash with ADS + Hyaluronic Acid + PVP-VA. The level of pigmentation tends to be low also for the mouthwash
 5 with only ADS, the effectiveness of which has been known for a long time.

	PI 7 days	GI 7 days	SI 7 days
Mouthwash A	1.3	0.3	0.2
Mouthwash B	1.4	0.2	0.4

The values of PI, GI e SI have been determined considering a modification of at least 30% of the
 10 dental elements in order to give a value corresponding to an index in the corresponding scale (values 1, 2 or 3). For instance, in a healthy subject with 28 dental elements (teeth) at least 10 teeth must have slight stain in order to be given value 1 of Stain Index, to
 15 the contrary, 0 is given.

According to the above, there will be evident to the person skilled in the art the advantages provided by the anti-pigmentation system of the invention.

20 First of all, the mouthwash comprising said system has proved to limit to a much wider extent the formation of stain on the tooth surface, with respect

to a mouthwash comprising an anti-pigmentation system that does not include hyaluronic acid.

When polyvinylpyrrolidone-vinylacetate is also included in the anti-pigmentation system of the invention, it has been observed a synergic action with chlorhexidine against bacteria and against the formation of the bacterial biofilm.

In addition to that, polyvinylpyrrolidone-vinylacetate has also been seen as acting in synergy with hyaluronic acid in the formation of a mechanical barrier, which can protect both the teeth surface and the soft tissues (gingiva and oral mucosa).

Polyvinylpyrrolidone-vinylacetate (PVP-VA) is a safe ingredient: no adverse reactions after intake are known at present, PVP VA is widely used on industrial scale in cosmetics, food preparations and medications. The value of the acceptable daily dose is high (i.e., 50 mg/kg), and is far above the values established for food and pharmacological products. In addition, the component is highly soluble in water.

Surprisingly, the above advantageous effects have been noticed to be not be to the detriment of the anti-bacterial effect.

Those skilled in the art will be able to make modifications or adaptations to the present invention,

without anyhow departing from the scope of the claims
set forth below.

* * *

5

CLAIMS

1. A mouthwash comprising chlorhexidine in a quantity of 0.01% to 0.3% (w/w), preferably of 0.09% to 0.25% (w/w), and an anti-pigmentation system,
5 said anti-pigmentation system comprising a metabisulfite salt of an alkali or an alkaline-earth metal, ascorbic acid or an alkali or an alkaline-earth metal salt, hyaluronic acid or a salt thereof and polyvinylpyrrolidone-vinyl
10 acetate, wherein polyvinylpyrrolidone-vinyl acetate is comprised in an amount of 0.02% to 0.5% (w/total weight of the mouthwash), preferably in an amount of 0.15% to 0.2%, more preferably of 0.09% to 0.12% (w/total volume of the
15 mouthwash).

2. The mouthwash according to claim 1, wherein chlorhexidine is comprised in a quantity of 0.2% (w/w).

3. The mouthwash according to claim 1 or claim
20 2, wherein chlorhexidine is in the form of a salt or a complex thereof.

4. The mouthwash according to the any one of the preceding claims, wherein chlorhexidine is in the form of chlorhexidine digluconate.

5. The mouthwash according to any one of the preceding claims, wherein the metabisulfite salt is comprised in an amount of 0.1% to 0.5% and preferably of 0.15% to 0.28% (w/total volume of the mouthwash).

5 6. The mouthwash according to any one of the preceding claims, wherein the metabisulfite salt is sodium metabisulfite.

7. The mouthwash according to any one of the preceding claims, wherein the ascorbic acid and a
10 salt thereof can be present in a quantity of 1.0% to 1.5% and preferably in an amount of 1.0% to 1.2% (total weight acid and salt/total volume of the mouthwash).

8. The mouthwash according to claim 7, wherein
15 the ascorbic acid or a salt thereof, can be substituted, partially or completely, by a citric acid or an alkali or an alkaline-earth metal salt thereof.

9. The mouthwash according to claim 8, wherein
20 the alkali or the alkaline-earth metal salt of citric acid is sodium citrate tribasic.

10. The mouthwash according to claim 8 or claim 9, wherein the citric acid can be present in a quantity of 0.01% to 0.02% (weight/total volume of the

mouthwash), while if present a citrate salt can be present in a quantity of 0.8% to 2.0% and preferably of 1% to 1.5% (w/total volume of the mouthwash).

11. The mouthwash according to any one of the
5 preceding claims, wherein the hyaluronic acid salt thereof can be present in the form of sodium or potassium salt or a mixture of the two salts.

12. The mouthwash according to any one of the preceding claims, wherein hyaluronic acid or a salt
10 thereof is comprised in an amount of 0.01% to 1.5% and preferably of 0.05% to 1.2% (w/total volume of the mouthwash).

13. The mouthwash according to any one of the preceding claims, further comprising one of more of
15 the following additives: sweeteners and/or flavorings, a source of fluorine, humectant, preservatives, surfactants, pH regulators, coloring agents.

14. The mouthwash according to claim 13, wherein
20 the sweetener is selected in the group comprising non-cariogenic sugars like xylitol, saccharin or an alkali or alkaline-earth metal salts thereof, acesulfame or an alkali or alkaline-earth metal salts thereof, sucralose, Stevia rebaudiana extract.

15. The mouthwash according to claim 13 or claim 14, wherein the flavoring is selected in the group comprising peppermint, menthol, anethole, *viridis* mint, cinnamon, clove, eucalyptus.

5 16. The mouthwash according to any one of claims 13 to 15, wherein the flavorings are present in an amount of 0.05% to 0.15% (w/total volume of the mouthwash).

10 17. The mouthwash according to any one of claims 13 to 16, wherein the source of fluorine is represented by fluoride or alkali or alkaline-earth metal salts thereof.

15 18. The mouthwash according to any one of claims 13 to 17, wherein the humectant is selected in the group comprising sorbitol, glycerin or propylene glycol.

20 19. The mouthwash according to any one of claims 13 to 18, wherein the humectants are present in an amount of 0.1% to 0.2% (w/total volume of the mouthwash).

20 20. The mouthwash according to any one of claims 13 to 19 wherein the preservatives are selected in the group comprising the benzoates, phenossietanolo, chlorphenesin.

21. The mouthwash according to any one of claims 13 to 20, wherein the surfactant is present in an amount of 0.1% to 0.2% (w/total volume of the mouthwash).

5 **22.** The mouthwash according to any one of claims 13 to 21, wherein the surfactant is selected in the group comprising hydrogenated castor oil PEG40, Poloxamer 407 or other suitable surfactants.

23. The mouthwash according to any one of claims 10 13 to 22, wherein the pH regulators is selected in the group comprising citric acid and its salts, like sodium salt.

24. The mouthwash according to any one of claims 13 to 23, wherein the coloring agent is selected in 15 the group comprising CI 1940, CIU 42090, CI 17200 and other suitable coloring agents.

25. The mouthwash according to any one of claims 1 to 24, for use in the therapeutic prevention and treatment of plaque.

20 **26.** The mouthwash according to any one of claims 1 to 24, for use in the therapeutic prevention and treatment of gingivitis.

27. The mouthwash according to any one of claims 1 to 24, for use in the prevention of stains on the surface of the teeth.

28. The mouthwash according to any one of claims 1 to 24, for use in the protection of gingiva.

29. Use of chlorhexidine in a quantity of 0.01% to 0.3% (w/w) and preferably of 0.09% to 0.25% (w/w); and an anti-pigmentation system for a chlorhexidine based mouthwash, comprising a metabisulfite salt of an alkali or an alkaline-earth metal, ascorbic acid or an alkali or an alkaline-earth metal salt, hyaluronic acid or a salt thereof and polyvinylpyrrolidone-vinylacetate, wherein polyvinylpyrrolidone-vinyl acetate is in an amount of 0.02% to 0.5% (w/total weight of the mouthwash); in the manufacture of a medicament in the form of a mouthwash according to any one of claims 1 to 24 for the prevention and treatment of plaque and/or gingivitis.

30. Use of chlorhexidine in a quantity of 0.01% to 0.3% (w/w) and preferably of 0.09% to 0.25% (w/w); and an anti-pigmentation system for a chlorhexidine based mouthwash, comprising a metabisulfite salt of an alkali or an alkaline-earth metal, ascorbic acid

or an alkali or an alkaline-earth metal salt,
hyaluronic acid or a salt thereof and
polyvinylpyrrolidone-vinylacetate, wherein
polyvinylpyrrolidone-vinyl acetate is in an amount
5 of 0.02% to 0.5% (w/total weight of the
mouthwash); in the manufacture of a medicament in the
form of a mouthwash according to any one of claims 1
to 24 for the protection of gingiva and oral mucosa.