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## **Gel comprising chlorhexidine**

### **Technical Field**

- 5 The invention relates to the field of oral cavity hygiene and to compositions with active principles and ingredients for preserving oral cavity health. Thus, it relates to compositions usable in odontoiatric or odontostomatological field.

### **Background Art**

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According to World Health Organization (WHO), oral health is a state of being free from several disorders that affect the oral cavity, including chronic mouth and facial pain, oral and throat cancer, oral sores, birth defects such as cleft lip and palate, periodontal (gum) disease, tooth decay and tooth loss. Risk factors are the unhealthy diet, tobacco, harmful  
15 alcohol use, and poor oral hygiene. It is widely recognized that oral health contributes to total health and is an essential component of the quality of life.

Oral tissues require the maintenance of proper oral hygiene by tooth brushing, dental floss, dentifrices, gels, mouth rinses, etc. In particular, mouth rinses are used in addition to  
20 conventional tooth brushing, and for reducing accumulation of oral plaque. These mouth rinses are also used for patients.

These compositions for oral care are also used for treating malodor, mainly by controlling the growth of microorganisms in the oral cavity. For this reason, the compositions  
25 comprise compounds that allow reducing plaque formation and the activity of microorganisms, at the same time they are safe and respectful for gingival and dental tissues.

With this aim, they are widely known and marketed compositions for oral hygiene  
30 comprising chlorhexidine. Chlorhexidine is by now the most commonly used oral antiseptic, acting as bactericidal and bacteriostatic. It is a biguanide. Chlorhexidine (CHX) has some side effects, such as the staining of the teeth and lingual mucosa with an increased formation of supragingival calculus; additionally, taste disturbances have been reported as well as discoloration of some restorative materials.

35

Besides, hyaluronic acid (HA) is the main component of the extracellular matrix of many tissues, and it is present in human saliva acting as a lubricant. HA possesses a role in healing both acute and chronical oral lesions, especially periodontal alterations. HA forms a protective superficial film over oral mucosa. In vivo, the plaque growth inhibition activity

of HA in 4-day plaque regrowth model is comparable to CHX. HA is also known as a mucoadhesive agent.

5 Liquid compositions comprising both compounds are known. These are mouth rinses aiming preserving oral hygiene. Examples of these compositions are marketed and also disclosed in patent literature, such as in PCT application WO9852612, wherein water-based antiseptic compositions comprising among others hyaluronic acid and chlorhexidine are reported. Other examples of said compositions are the marketed products EllaDent Perio 020 mouthwash and the CURASEPT®ADS Perio mouthwash.

10

Using rinses implies the drawback that they have to be retained in mouth for a predetermined period to achieve the effect. Even more, they have to be used more than once per day, and frequently, to assure their effectiveness in case for example of wounds to the gums due to surgical intervention or due to a pathological process.

15

Long-lasting compositions for delivering actives are formulated as gels with appropriate consistency. The gels are applied onto gums and actives are released gradually.

20 Gels comprising only chlorhexidine include hydroxyethylcellulose for example as gelling agent (e.g.: *Curasept ADS 350 Gingival Gel*; *TrisDent Dental Gel*; and *Oralsan Gingival Gel*). On the other side, sodium hyaluronate in gel formulations can be manufactured, for example, with carbopol (also termed carbomer) (e.g.: *Neutrogena Hydro Boost Gel de Agua*; *Ultimate Hydration Gel*; *Bionect Gel*; and *Thealoz Duo Gel*). But the mixture of both gel types in order to have a gel with the two active ingredients, chlorhexidine and  
25 hyaluronic acid or one of their salts, gives as a result a jelly formulation with a chlorhexidine precipitate.

Nevertheless, disclosed in the prior art are gels comprising both chlorhexidine and hyaluronic acid. An example is the gel for feminine hygiene of the Swiss patent  
30 CH691030, wherein sodium hyaluronate and chlorhexidine, among other ingredients, are ingredients of a mixture comprising carragenan as gelling agent. Carragenan is mentioned as a proper gelling agent that together with hyaluronate provides a sliding, compact, filamentous, transparent, clean and incolour gel. Inventors of CH691030 propose the gel also for disinfecting oral cavity, although no specific examples are provided.

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Another gel composition comprising chlorhexidine and hyaluronic acid is disclosed in the Russian patent RU2286764. The gel is particularly mentioned for use in the treatment of inflammatory diseases of the oral cavity, and it comprises a combination of polyvinyl alcohol with sodium alginate as gelling agent.

Although there have been disclosed the above-mentioned gels, dentists and surgeons still administer separately chlorhexidine solutions and compositions with hyaluronic acid. This is mainly due to the fact that there are no commercially available gels with both actives, or  
5 even liquid compositions with both compounds to be used in oral cavity. One likely reason is, as indicated, due to the fact that chlorhexidine and hyaluronic acid tend to precipitate when they are together. This may be due to the fact that chlorhexidine is a cationic preservative. Cationic preservatives and HA are incompatible, resulting in their conjugation and precipitation, as disclosed in the PCT application WO2008144185. In this  
10 PCT application, hyaluronic acid and another cationic preservative, in particular the benzalkonium chloride were finally mixed together by first preparing separate solutions of HA and of benzalkonium chloride, and then combining them in order to avoid precipitation.

Thus, compositions with both ingredients are not stable for a long time. It is for this reason  
15 that there are no gel compositions in the market with chlorhexidine and hyaluronic acid, although it is a request made by dentists and surgeons.

On the other hand, some gels in which all desired ingredients could be stably embedded together in a gelling matrix have as disadvantage that their adhesive properties on tissue  
20 is not good or it is compromised, thus making them no useful.

In addition, many of the gelling agents are pH sensitive and do not perform its function at the final desired pH, generally about 7-8, for oral compositions. Also, some gelling agents can alter the final pH of compositions making them not useful for oral cavity treatment.  
25

Thus, it is evident that there is still in the field a need of alternative formulations avoiding the above referred drawbacks while being effective for oral hygiene.

### **Summary of Invention**

30 Inventors have determined that chlorhexidine, or a salt thereof, and hyaluronic acid, or a salt thereof, can be formulated together as a transparent gel composition with good adherence properties to oral cavity (in particular to tooth enamel and gums) and also to skin surfaces, if a carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof is used as gelling agent in the gelling matrix conforming the gel. In addition, the compositions have high  
35 moisturizing properties and are versatile in terms that a wide range of concentrations of chlorhexidine and of hyaluronic acid can be embedded in the gel.

Thus, a first aspect of the invention is a gel composition comprising:

- chlorhexidine (CHX) and/or a pharmaceutically or cosmetically acceptable salt thereof;  
- hyaluronic acid (HA) and/or a pharmaceutically or cosmetically acceptable salt thereof;  
and

- a gelling matrix comprising water, and a cellulose derivative, said cellulose derivative  
5 comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, together with  
pharmaceutically or cosmetically excipients and/or carriers.

The carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose in the gelling matrix acts as thickening or gelling agent  
and forms, optionally with other excipients or carriers, a hydrophilic matrix embedding the  
actives chlorhexidine and/or a pharmaceutically acceptable salt thereof, and the  
10 hyaluronic acid and/or a pharmaceutically acceptable salt thereof.

In this gel composition, hyaluronic acid and/or a pharmaceutically or cosmetically salt  
thereof, contributes also to conform the gel for being a polymeric compound that behaves  
as so when dissolved in water from the gelling matrix. Thus, it is also a thickening agent.  
15 In the particular case of the gel composition being used for oral cavity hygiene and/or  
treatment, this HA also acts as muco-adhesive.

This gel composition supposes a widely requested need for practitioners and citizens as a  
whole, since it allows the simultaneous administration of an antiseptic and of a compound  
20 for healing any tissue lesions (i.e. for oral cavity or for other injured mucosa).

Besides, the gel composition not only solves the problem of the precipitation of  
chlorhexidine in hyaluronic acid or of both when they are together in gels, but also that of  
maintaining pH at the desired values for oral use (namely pH from 7 to 8). Further and  
25 surprisingly, the gel composition maintains its consistency and transparency in case it is  
colorless (which means that at least no chlorhexidine precipitation is present) with a wide  
range of chlorhexidine and hyaluronic acid concentrations. Thus, no precipitation occurs.  
This later opens the option of preparing a wide variety of compositions with these active  
ingredients.

30 Moreover, as will be depicted in the examples below, the gel composition has the  
adequate adhesive properties allowing its use for a long period of time. Hence, if the gel is  
well-adhered onto the gums and/or teeth, or even in other surfaces, such as topically on  
skin surfaces, then low numbers of daily applications are required for achieving the  
35 desired effect.

In a second aspect, the invention encompasses a method for preparing a gel composition as defined in the first aspect and its embodiments, the method comprising:

- (a) forming an homogenized aqueous dispersion, said dispersion comprising  
5 chlorhexidine and/or a pharmaceutically or cosmetically acceptable salt thereof, dispersed in a solvent selected from the group consisting of polyalkylene glycol, glycerin, propylene glycol and mixtures thereof; and hyaluronic acid and/or a pharmaceutically or cosmetically acceptable salt thereof, dissolved in water; and  
(b) adding to the homogenized aqueous dispersion of step (a), a cellulose derivative, said  
10 cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, to obtain a gel composition.

Thus, the method comprises the gelation of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof in an homogenized aqueous dispersion comprising hyaluronic acid and/or a  
15 pharmaceutically or cosmetically acceptable salt thereof, dissolved in water and chlorhexidine and/or a pharmaceutically or cosmetically acceptable salt thereof, dispersed in a solvent selected from the group consisting of polyalkylene glycol, glycerin, propylene glycol and mixtures thereof.

For "gelation" of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose is to be understood that this ingredient is  
20 added in an aqueous solution and gel formation is promoted (or occurs).

Gel compositions as defined above, allow treating many of the oral cavity diseases, injuries or disorders, for which hyaluronic acid is effective and in which antiseptic conditions are required or desired. Besides, the gels of the invention are useful for  
25 preserving good oral cavity health, in particular of the gums, after brushing.

Thus, another aspect of the invention is a gel composition as defined above for use as a medicament.

30 The invention also relates, thus, to the use of the gel compositions as defined above as pharmaceutical or cosmetic topical compositions. Thus, the gel compositions can be applied to any skin or mucosa surface, where they rest enough time to allow all actives perform their effects. In addition, said gels, as above indicated, are colorless and transparent within the established stability test is the cosmetic and pharmacological field.  
35 If not colorless, no precipitation of chlorhexidine and/or of a salt thereof takes place.

Another aspect of the invention is the use of a gel composition as defined above as cosmetic care agent (or simpler as a cosmetic). This applies in particular when no diseases is present, but administration of the gel ameliorates appearance of the surface to

which it is applied. For example, ameliorating skin elasticity or oral cavity appearance, leading to an appearance of healthy gums and of mouth mucosa.

Thus, another aspect of the invention is a topical pharmaceutical or cosmetic composition which comprises an effective amount of the chlorhexidine and/or a salt thereof; hyaluronic acid and/or a salt thereof; and a gelling matrix comprising water and a cellulose derivative, said cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, together with one or more appropriate topical pharmaceutically or cosmetically acceptable excipients or carriers.

Yet another aspect of the invention is the use of the gel compositions comprising chlorhexidine, or a salt thereof, and hyaluronic acid, or a salt thereof, and a carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose in the gelling matrix, as an agent for oral cavity hygiene. This aspect is more related with the cosmetic effect of the combination of active ingredients, which allow a healthy appearance of gums and teeth. This aspect can also be formulated as a gel composition as defined above for use as oral cavity cosmetic care agent. Alternatively, as the use of a gel composition as defined above, comprising chlorhexidine, or a salt thereof; hyaluronic acid, or a salt thereof; and a carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose in the gelling matrix, as oral cavity cosmetic agent. The cosmetic use of the gel composition of the invention implies using cosmetically acceptable excipients or carriers that can be coincident with pharmaceutically acceptable excipients or carriers.

Also another aspect of the invention is the use of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof as chlorhexidine suspending agent in hyaluronic acid containing compositions in form of gels.

Therefore, to the best of inventors' knowledge, it is proposed for the first time a gel composition in which chlorhexidine is suspended (which means that no precipitation occurs) in hyaluronic acid containing gel compositions.

### **Brief Description of Drawings**

FIG. 1, related with Example 2, is a comparative graph of the mucoadhesion levels of a gel of the invention over time, registered by means of a gravimetric test on an inclined temperature-controlled plane treated with mucin. Error bars show the standard deviation for each data set. Adhesion score percentage (abbreviated AS (%)) in the Y-axis is indicated as percentage of adhesion. X-axis shows the time (T) in minutes (min). Each data set include data from water (first column in the set), data from water in a mucin containing inclined plane (second column in the set), sample (third column in the set) and

sample in a mucin containing inclined plane (forth column in the set).

### **Detailed description of the invention**

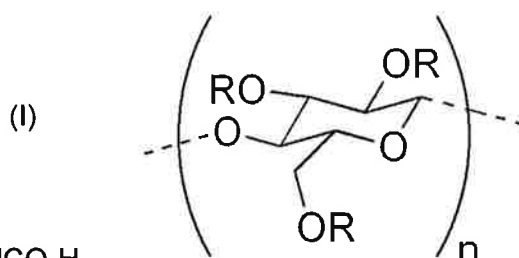
5 All terms as used herein in this application, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions for certain terms as used in the present application are as set forth below and are intended to apply uniformly through-out the specification and claims unless an otherwise expressly set out definition provides a broader definition.

10

A "gelling agent" (or gellant) is a thickening agent that forms a gel, dissolving in the liquid phase as a colloid mixture that forms a weakly cohesive internal structure. A thickening agent or thickener is a substance which can increase the viscosity of a liquid without substantially changing its other properties. Thickening agents used in cosmetics,  
 15 pharmaceutical or personal hygiene products include viscous liquids such as polyethylene glycol, synthetic polymers such as carbomer (a trade name for polyacrylic acid) and vegetable gums. A gel is a solid jelly-like material that can have properties ranging from soft and weak to hard and tough. Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when in the steady-state. By weight, gels are mostly liquid,  
 20 yet they behave like solids due to a three-dimensional cross-linked network within the liquid. It is the crosslinking within the fluid that gives a gel its structure (hardness) and contributes to the adhesive stick (tack). In this way gels are a dispersion of molecules of a liquid within a solid in which the solid is the continuous phase and the liquid is the discontinuous phase. The gel composition of the invention is also termed herewith as an  
 25 aqueous gel.

For "gelling matrix" is to be understood in the sense of present invention, as a composition comprising a solvent; in particular water, and a gelling agent. The gelling matrix maintains all solutes (active ingredients) fully solved or fully suspended in the solvent, all of them  
 30 embedded in the weakly cohesive internal structure formed by the gelling agent.

"Carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose" is a cellulose derivative with carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl groups (- (C<sub>1</sub>-C<sub>3</sub>)alkylCOOH) bound to some of the hydroxyl groups of the glucopyranose monomers that make up the cellulose backbone. It can be represented as in formula (I).  
 35 One particular example is carboxymethyl cellulose. Carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose is often used as its sodium salt, such as the sodium carboxymethyl cellulose.



R= H or  $-(C_1-C_3)\text{alkylCO}_2\text{H}$

Throughout the description and claims, the term  $(C_1-C_3)$ -alkyl, shall be construed as straight or branched.

Depending on the percentage by weight of the monomers of formula (I) and of the degree/amount of substitution, which is proportional to the average number of carboxymethyl groups in a monomer unit, the properties of the cellulose derivative can be modulated. For example, assuming concentration stays the same; adding more substitutions also increases viscosity.

For "suspending agent" is to be understood according to this description, a compound that avoids precipitation of other compounds in a particular matrix (for example in a gelling matrix). In the present invention, carboxy $(C_1-C_3)$ -alkyl-cellulose, in particular carboxymethyl cellulose is used as suspending agent of CHX in an aqueous gel comprising hyaluronic acid or a salt thereof. Carboxy $(C_1-C_3)$ -alkyl-cellulose is also used as thickening or gelling agent.

The term "oral cavity" encompasses, according to this description, the two regions of mouth; the vestibule and the oral cavity proper. The vestibule is the area between the teeth, lips and cheeks. The oral cavity is bounded at the sides and in front by the alveolar process (containing the teeth) and at the back by the isthmus of the fauces. Its roof is formed by hard palate and soft palate and the floor is formed by the mylohyoid muscles and is occupied mainly by the tongue. A mucous membrane – the oral mucosa, lines the sides and under surface of the tongue to the gums, lining the inner aspect of the jawbone (mandible). It receives the secretions from the submaxillary and sublingual salivary glands.

The expression "pharmaceutically acceptable excipients or carriers" refers to pharmaceutically acceptable materials, compositions or vehicles. Each component must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the pharmaceutical composition. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation,

allergic response, immunogenicity or other problems or complications commensurate with a reasonable benefit/risk ratio.

5 The expression "therapeutically effective amount" as used herein, refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease which is addressed. The particular dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and the  
10 similar considerations.

The term "cosmetically acceptable" refers to that excipients or carriers suitable for use in contact with oral cavity mucosa and enamel without undue toxicity, incompatibility, instability, allergic response, among others. The term also refers to "dermatological  
15 acceptable" including excipients or carriers suitable for use in contact with human skin without undue toxicity, incompatibility, instability, allergic response, among others.

As indicated, a first aspect of the invention is, briefly, a gel composition comprising chlorhexidine and/or a pharmaceutically acceptable salt thereof, hyaluronic acid and/or a  
20 pharmaceutically acceptable salt thereof, and a gelling matrix comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, together with pharmaceutically excipients and/or carriers.

Chlorhexidine and/or a pharmaceutically acceptable salt thereof, hyaluronic acid and/or a  
25 pharmaceutically acceptable salt thereof are both in the gel composition in therapeutically effective or cosmetically effective amounts.

In a particular embodiment of the first aspect of the invention, the salts of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose are selected from alkali metal salts, alkaline-earth metal salts,  
30 quaternary ammonium salts, and mixtures thereof. In a more particular embodiment, the salts are alkali metal salts selected from sodium, potassium, and mixtures thereof. In a particular embodiment of the gels of the first aspect, the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose is carboxymethylcellulose or a salt thereof. In a particular embodiment, the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose salt is an alkali metal salt of carboxymethylcellulose. In a particular  
35 embodiment, the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose salt is sodium carboxymethylcellulose. In another particular embodiment the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose salt is an alkaline earth metal salt of carboxymethylcellulose.

Carboxymethylcellulose is known as a bioadhesive pharmaceutical carrier from US patent US5192802 or from US patent US6117415. In these documents, the carboxymethylcellulose is used in combination with xanthan gum or sodium alginate for promoting adhesion to mucous membranes and so releasing pharmaceutical actives of interest in a controlled way. In US6117415, it is also mentioned that carboxymethylcellulose grade and amount can be adjusted in toothpaste according to desired paste viscosity.

Gels of the invention are conceived and aimed to stay on the desired surface of application for a period of time allowing the actives in the gel to be released and then to perform their effect. Carboxymethylcellulose, or carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and salts thereof, provides to the gel of the invention this required adhesion and surprisingly, it results in an ingredient that allows the joint administration of two active ingredients that tend to precipitate when mixed together in gelling matrixes. In addition, with the presence of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose in the gelling matrix, wide ranges of key ingredients are allowed, in particular wide ranges of concentrations of hyaluronic acid or of a salt thereof and of chlorhexidine or of a salt thereof.

In an embodiment, the gel composition of the present invention is one wherein the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose has a carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl- moiety content from 15% to 30% by weight of the weight of the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose; preferably from 19% to 24% by weight of the weight of the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose. Measurement of the content of the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl- moieties can be performed by any method known in the art.

In another particular embodiment, optionally in combination with embodiments above or below, the gel composition of the present invention is one wherein the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose, in particular carboxymethylcellulose, has a degree of substitution from 1.15 to 1.45 measured according to American Standard ASTM D1439 . In a particular embodiment, the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose is Blanose 12M31P, a carboxymethylcellulose.

In another embodiment, the composition of the present invention is one wherein the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose has a viscosity from 1500 mPa.s to 6500 mPa.s; preferably from 3100 mPa.s to 6500 mPa.s. The term "viscosity" refers to the resistance of a fluid to shear, also called dynamic or shear viscosity and defined mathematically as a stress-to-shear rate quotient. Usually the viscosity is measured by using devices such as rotational viscometers or rheometers which measure the torque exerted on an axis in contact with the sample when it is rotated at a precisely controlled angular velocity. Converting torque and velocity to stress and share rate respectively is straight forward by multiplication by

calibration constants. In the present invention, viscosity measurements are performed using a (Brookfield Viscometer, #2 *spindle* (SP2), operating at 0.3 rpm).

5 In another particular embodiment, the percentage by weight of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose, in relation to the total weight of gel composition is from 1.0 % to 5.0%. More in particular it is from 1.0% to 4.0 %. Even more in particular, it is from 2.0 % to 3.0 %.

10 In another particular embodiment of the first aspect of the invention, the gel formulations comprise a pharmaceutically acceptable salt of chlorhexidine selected from the group consisting of chlorhexidine gluconate, chlorhexidine acetate, chlorhexidine chlorhydrate (or hydrochloride) and chlorhexidine base ,and mixtures thereof. In a more particular embodiment, optionally in combination with any embodiment above or below, the pharmaceutically acceptable salt of chlorhexidine is chlorhexidine gluconate. Chlorhexidine gluconate is also known as chlorhexidine digluconate (used herewith  
15 interchangeably).

In another particular embodiment, optionally in combination with any of the embodiments above or below, the chlorhexidine and/or its salts are in a percentage by weight from 0.05 to 1.5 %, in relation to the total weight of the gel formulation. More in particular, it is from  
20 0.10 to 1.0% by weight. Also more in particular from 0.2% to 0.5%, even more in particular from 0.1% to 0.3% by weight. Also more in particular, it is from 0.10 to 0.25 % by weight. Even more in particular is selected from 0.10 %, 0.15%, 0.20%, 0.21%, 0.22%, 0.23%, 0.24 % and 0.25%, all percentages by weight in relation to the total weight of the gel formulation.

25 As above indicated, hyaluronic acid is the main component of the extracellular matrix of many tissues, and it is present in human saliva acting as a lubricant. Hyaluronic acid is also a mucoadhesive agent that acts as healing agent in cases where tissues are injured due to surgical interventions or due to certain diseases. Therefore, hyaluronic acid is not  
30 only one of the active ingredients in the formulation when tissue is to be repaired, but also promotes adhesion. In the present invention adhesion to mucosa and/or enamel is also achieved due to the presence of the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose, as above exposed.

35 In a particular embodiment of the gels of the invention, optionally in combination with any embodiment above or below, hyaluronic acid and/or one of its salts has a molecular weight of at least 1.3 MDa. More in particular it is from 1.3 to 2.5 MDa.

In yet another particular embodiment of the first aspect, the pharmaceutically acceptable salt of hyaluronic acid is selected from the group consisting of alkali metal salts, alkaline

earth metal salts and combinations thereof. In a more particular embodiment, the salt is an alkali metal salt of hyaluronic acid. In yet a more particular embodiment, the gel composition comprises hyaluronic acid as the sodium salt (i.e.: sodium hyaluronate).

As indicated, due to the presence of the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose, both hyaluronic acid (or its salts) as well as chlorhexidine (or its salts) are stably embedded in the gel composition without the show of precipitation. This is accomplished, surprisingly, within a wide range of hyaluronic acid concentrations. Thus, in another particular embodiment, the percentage by weight of hyaluronic acid or of a salt thereof, in relation to the total weight of the gel composition is from 0.1 to 1.0 %. More in particular is from 0.1 to 0.30 %. More in particular, it is from 0.10 to 0.25 %. Even more in particular, it is selected from 0.10 %, 0.15%, 0.20%, 0.21%, 0.22%, 0.23%, 0.24 % and 0.25%.

In the gel composition according to the first aspect of the invention, the gelling matrix with carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose or a salt thereof, but also the hyaluronic acid or a salt thereof do contribute to the gel consistency of the composition, mainly due to its polymeric nature and behavior in water.

In another particular embodiment of the first aspect of the invention, the gelling matrix comprises, besides the water and the cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose or a salt thereof as gelling agent, in particular carboxymethylcellulose, additional gelling agents selected from the group consisting of propylene glycol, carbomers (such as Carbopol®), other cellulose derivatives (such as ethylcellulose, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose), magnesium aluminum silicate (such as Veegum®), polyvinyl alcohol, sodium alginate, tragacanth, xanthan gum, and mixtures thereof.

Thus, in another particular embodiment the gel composition according to the invention comprises:

- chlorhexidine (CHX) and/or a pharmaceutically or cosmetic acceptable salt thereof;
- hyaluronic acid (HA) and/or a pharmaceutically or cosmetic acceptable salt thereof; and
- a gelling matrix comprising water, and a cellulose derivative, said cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, together with pharmaceutically or cosmetically excipients and/or carriers; said gelling matrix comprising in addition a compound selected from the group consisting of polyalkylene glycol, glycerin, propylene glycol and mixtures thereof.

This compound selected from the group consisting of polyalkylene glycol, glycerin, propylene glycol and mixtures thereof is indeed a solvent, thus it acts as a solvent of the other ingredients. Therefore, in another particular embodiment of the first aspect of the invention, the gel further comprises a solvent selected from the group consisting of  
5 polyalkylene glycol, glycerin, propylene glycol and mixtures thereof.

Inventors observed that with the use of a solvent of polyol nature selected from the group consisting of propylene glycol, glycerin and mixtures thereof, chlorhexidine or one of its salts could be dispersed and mixed with an aqueous solution of hyaluronic acid or its salts,  
10 avoiding chlorhexidine precipitation. The presence further in the composition of the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose or a salt thereof allowed high stable gel compositions in which both, chlorhexidine and hyaluronic acid, are suspended and no precipitation occurs. In addition, the presence of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose or a salt thereof enhances  
15 adhesion to the surfaces on which the gel composition is applied. In particular, enhances adhesion to animal skin and to oral cavity tissues (tooth enamel and gums). Thus, the gel composition is a highly stable topical gel composition for skin and for oral cavity tissues.

Although with the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose or a salt thereof also as gelling agent in the gelling matrix no precipitation is observed, the gel composition comprises, in a  
20 particular embodiment, additional compounds aiding to avoid precipitation when the gel compositions comprise a great amount of ingredients. Thus, in a particular embodiment, the gel compositions of the first aspect comprise chelating compounds selected from the group consisting of EDTA, phosphonate compounds, gluconate compounds, citrate compounds and combinations thereof. In a particular embodiment, optionally in  
25 combination with any embodiment above or below, the chelating compound is comprised in a percentage by weight in relation to the total weight of the gel composition from 0.05 % to 1 %. More in particular, it is from 0.1 % to 0.40 %. More in particular, it is from 0.1% to 0.20%. More in particular, the chelating compound is ethylenediaminetetraacetic acid (EDTA) or a salt thereof, such as disodium EDTA. Even more in particular, EDTA or its  
30 sodium salt, are comprised in a percentage by weight from 0.1% to 0.20%. In another particular embodiment, the chelating compound is a gluconate compound or a salt thereof; in particular it is an alkali metal salt, more in particular it is sodium gluconate. In a more particular embodiment, the gluconate compound or the sodium gluconate are comprised in a percentage by weight from 0.2% to 0.40%. Yet in another particular  
35 embodiment, the chelating compound is a citrate compound or a salt thereof; in particular it is an alkali metal salt, more in particular it is sodium citrate. In a more particular embodiment, the citrate compound or the sodium citrate are comprised in a percentage by weight from 0.1% to 1.0 %.

These chelating compounds, also termed chelating agents, chelators, chelants or sequestering agents are polydentate molecules that establish coordinate bonds with metal ions. The chelation of metal ions improves its stability within the solvent where they are dissolved. In the present case in the solvent embedded in the gelling agent. More in particular in the water embedded in the gelling agent.

In another particular embodiment, the gel compositions of the present invention further comprise one or more compounds selected from the group consisting of an essential oil, a preservative, a flavor, an humectant, an emulsifier, a chelating agent, and additional gelling agent besides the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose, an antimicrobial agent, an aqueous vehicle (i.e. water), and mixtures thereof.

Among essential oils, the gel composition of the first aspect of the invention comprises in a particular embodiment oil selected from the group consisting of thyme oil, eugenol, eucalyptus oil, rosmarine oil, mint oil, cinnamon leaf oil, clover leaf oil, tea tree oil and organum oil.

Although chlorhexidine or one of its salts act by themselves as antimicrobial agent, in another particular embodiment of the first aspect, optionally in combination with any embodiment above or below, the gel composition comprises an additional antimicrobial agent. In a more particular embodiment, the additional antimicrobial agent is selected from the group consisting of salicylic acid or an ester or salt thereof, such as methylsalicylat, alexidine, triclosan, cetyl pyridinium chloride, delmopinol, amylmetacresol, benzalkonium chloride, octenidine (in the form of one of its salts), and mixtures thereof.

In another particular embodiment, optionally in combination with any of the embodiments above or below, the gel composition has a pH from 7.0 to 8.0. At this pH range, the gel is adequate for the particular use in oral cavity, as above indicated. In addition and advantageously, the gelling agent carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose does not alter this pH, which means that at the adequate pH no precipitation of chlorhexidine and/or one of its salts will take place.

The invention encompasses also a method for preparing a gel composition as defined above and comprising the steps of:

(a) forming an homogenized aqueous dispersion, said dispersion comprising chlorhexidine and/or a pharmaceutically or cosmetic acceptable salt thereof, dispersed in a solvent selected from the group consisting of polyalkylene glycol, glycerin, propylene glycol and mixtures thereof; and hyaluronic acid and/or a pharmaceutically acceptable

salt thereof, dissolved in water; and

(b) adding to the homogenized aqueous dispersion of step (a), a cellulose derivative, said cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, to obtain a gel composition.

5

In a particular embodiment of this method, the solvent in which chlorhexidine and/or a salt thereof is dispersed, is selected from the polyols propylene glycol, glycerin and mixtures thereof. In another particular embodiment, optionally in combination with any embodiment above or below, the solvent is selected from the polyethers polyethylene glycol,

10

polypropylene glycol and mixtures thereof, which are also termed in this description as polyalkylene glycols. In yet another particular embodiment the solvent in which chlorhexidine and/or a salt thereof is dispersed is a mixture of one or more polyols and one or more polyalkyleneglycols. More in particular the solvent is a mixture of polypropylene glycol and polyethylene glycol

15

In another particular embodiment, optionally in combination with any embodiment above or below, hyaluronic acid and/or a pharmaceutically or cosmetically acceptable salt thereof is dissolved in deionized water.

20

Thus, in a particular embodiment, and in order to improve the dissolution of chlorhexidine, or a salt thereof, and of hyaluronic acid, or a salt thereof, a pre-mixture can be prepared with a solvent of polyol nature, more in particular with propylene glycol, glycerin or a mixture of both, said polyol acting as dispersant of chlorhexidine or of a salt thereof.

25

Optionally, said aqueous pre-mixture is in another particular embodiment derivatized with polyalkylene glycols, said polyalkylene glycols soluble in water and with a molecular weight from 50 to 200 Da. The solvent is in another particular embodiment optionally derivatized with oils. Examples of oils to be added in the pre-mixture include Castor oil.

30

This pre-mixture is further completed with the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, which evolves to a gel consistency once it contacts the aqueous pre-mixture.

As above indicated, this carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, in particular carboxymethylcellulose, allows chlorhexidine and hyaluronic acid and/or their salts be stably suspended in the aqueous gel.

35

The gel composition of the first aspect is for use as a medicament. In a more particular embodiment it is for use in the treatment of oral cavity diseases or disorders selected from the group consisting of plaque and calculus, decay, gingivitis, periodontitis, mucositis, oral ulcers and tooth sensitivity. This aspect may also be formulated as the use of the gel

composition as defined above for the manufacture of a medicament for the treatment or prevention of an oral cavity diseases or disorder selected from the group consisting of plaque and calculus, decay, gingivitis, periodontitis, mucositis, oral ulcers and tooth sensitivity. The present invention also relates to a method for the treatment or prevention of oral cavity diseases or disorders selected from the group consisting of plaque and calculus, decay, gingivitis, periodontitis, mucositis, oral ulcers and tooth sensitivity, comprising administering a pharmaceutically effective amount of compound the gel as defined above, together with pharmaceutically acceptable excipients or carriers, in a subject in need thereof, including a human.

Thus, the invention relates in particular to the use of the gel composition in the treatment of oral cavity diseases affecting gums and/or teeth and/or the oral mucosa.

Dental plaque is a biofilm or mass of bacteria that grows on surfaces within the mouth. It is a sticky colorless deposit at first, but when it forms tartar (also known as calculus), it is often brown or pale yellow. It is commonly found between the teeth, on the front of teeth, behind teeth, on chewing surfaces, along the gumline, or below the gumline cervical margins. Dental plaque is also known as microbial plaque, oral biofilm, dental biofilm, dental plaque biofilm or bacterial plaque biofilm. Progression and build-up of dental plaque can give rise to tooth decay – the localised destruction of the tissues of the tooth by acid produced from the bacterial degradation of fermentable sugar – and periodontal problems such as gingivitis and periodontitis; hence it is important to disrupt the mass of bacteria and remove it. Plaque control and removal can be achieved with correct daily or twice-daily tooth brushing and use of interdental aids such as dental floss and interdental brushes. Oral hygiene is important as dental biofilms may become acidic causing demineralization of the teeth (also known as dental caries) or harden into dental calculus.

Decay is or tooth decay, also known as dental caries or cavities, is a breakdown of teeth due to acids made by bacteria. The cavities may be a number of different colors from yellow to black. Symptoms may include pain and difficulty with eating. Complications may include inflammation of the tissue around the tooth, tooth loss, and infection or abscess formation. The main cause of caries is acid from bacteria dissolving the hard tissues of the teeth (enamel, dentin and cementum). The acid is produced from food debris or sugar on the tooth surface. Simple sugars in food are these bacteria's primary energy source and thus a diet high in simple sugar is a risk factor. Risk factors include conditions that result in less saliva such as: diabetes mellitus, Sjogren's syndrome and some medications. Medications that decrease saliva production include antihistamines and antidepressants. Caries is also associated with poverty, poor cleaning of the mouth, and receding gums resulting in exposure of the roots of the teeth.

Gingivitis ("inflammation of the gum tissue") is a non-destructive disease that occurs around the teeth. The most common form of gingivitis, and the most common form of periodontal disease overall, is in response to bacterial biofilms (also called plaque) that is attached to tooth surfaces, termed plaque-induced gingivitis. While some cases of gingivitis never progress to periodontitis, data indicates that periodontitis is always preceded by gingivitis. Gingivitis is reversible with good oral hygiene; however, without treatment, gingivitis can progress to periodontitis, in which the inflammation of the gums results in tissue destruction and bone resorption around the teeth. Periodontitis can ultimately lead to tooth loss.

- 10 Periodontitis also known as gum disease and pyorrhea, refers to a set of inflammatory diseases affecting the tissues surrounding the teeth. Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth. Periodontitis is caused by microorganisms that adhere to and grow on the tooth's surfaces, along with an over-aggressive immune response
- 15 against these microorganisms. A diagnosis of periodontitis is established by inspecting the soft gum tissues around the teeth with a probe (i.e., a clinical examination) and by evaluating the patient's X-ray films (i.e., a radiographic examination), to determine the amount of bone loss around the teeth.

- Mucositis is the painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer. Mucositis can occur anywhere along the gastrointestinal (GI) tract, but oral mucositis refers to the particular inflammation and ulceration that occurs in the mouth. Oral mucositis is a common and often debilitating complication of cancer treatment. Oral and gastrointestinal (GI) mucositis affects almost all patients undergoing high-dose
- 20 chemotherapy and hematopoietic stem cell transplantation (HSCT), 80% of patients with malignancies of the head and neck receiving radiotherapy, and a wide range of patients receiving chemotherapy.

- Oral ulcers or mouth ulcers are ulcers that occurs on the mucous membrane of the oral cavity. Mouth ulcers are very common, occurring in association with many diseases and by many different mechanisms, but usually there is no serious underlying cause. The two most common causes of oral ulceration are local trauma (e.g. rubbing from a sharp edge on a broken filling) and aphthous stomatitis ("canker sores"), a condition characterized by recurrent formation of oral ulcers for largely unknown reasons. Mouth ulcers often cause pain and discomfort, and may alter the person's choice of food while healing occurs (e.g. avoiding acidic or spicy foods and beverages).
- 30
- 35

Tooth sensitivity or dentin hypersensitivity (abbreviated to DH, or DHS, and also termed sensitive dentin, dentin sensitivity, cervical sensitivity, and cervical hypersensitivity) is dental pain which is sharp in character and of short duration, arising from exposed dentin surfaces in response to stimuli, typically thermal, evaporative, tactile, osmotic, chemical or electrical; and which cannot be ascribed to any other dental disease. A degree of dentin sensitivity is normal, but pain is not usually experienced in everyday activities like drinking a cooled drink. Therefore, although the terms dentin sensitivity and sensitive dentin are used interchangeably to refer to dental hypersensitivity, the latter term is the most accurate. The main cause of DH is gingival recession (receding gums) with exposure of root surfaces, loss of the cementum layer and smear layer, and tooth wear. Receding gums can be a sign of long-term trauma from excessive or forceful toothbrushing, or brushing with an abrasive toothpaste (dental abrasion), or a sign of chronic periodontitis (gum disease).

On the other hand, the gels defined above, comprising chlorhexidine, hyaluronic acid and a gelling matrix with carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose are, according to another aspect, for use as oral cavity cosmetic care. This means, that they are in particular for use in ameliorating appearance of gums and teeth.

Thus, the gel compositions of the invention are used as cosmetic care agents. More in particular they are used as cosmetic topical compositions.

The gel composition as defined above is used, according to another aspect of the invention, as an oral cavity cosmetic care agent. Therefore, the invention relates also to gel compositions for use in cosmetics. These cosmetic gel compositions comprise an effective amount of chlorhexidine and/or a salt thereof; hyaluronic acid and/or a salt thereof; and a gelling matrix comprising water and a cellulose derivative, said cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, together with appropriate cosmetically excipients and/or carriers.

These cosmetic effect is achieved in any of the tissues of oral cavity, in particular in gums, teeth and oral mucosa, but the cosmetic gel compositions of the invention can also be applied onto the skin, since due to the gel consistency it remains appropriate time to the surface and there allows absorption of any of the actives that the gel contains.

Thus, the topical cosmetic gel compositions as defined above are used also as a skin care agent, wherein the skin care comprises ameliorating at least one of the following symptoms: roughness, flakiness, dehydration, tightness, chapping, scar reduction, and lack of elasticity.

The term "safe and effective amounts" is defined as any amount sufficient to significantly improving the cosmetic appearance of the skin without substantial irritation, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgement. The safe and effective amount of chlorhexidine and/or a salt thereof and of hyaluronic acid and/or a salt thereof will vary with the age and physical condition of the consumer, the condition of the oral mucosa or skin, the duration of the treatment, the nature of any concurrent treatment, the specific combination of active ingredients employed, the particular cosmetically acceptable carrier utilized, and like factors in the knowledge and expertise of any attending physician.

The invention relates also to gel compositions comprising chlorhexidine and/or a pharmaceutically acceptable salt thereof, hyaluronic acid and/or a pharmaceutically acceptable salt thereof, and carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, together with pharmaceutically excipients and/or carriers, wherein the excipients and or carriers comprise a cellulose derivative selected from the group consisting of hydroxypropylcellulose (hydroxylC<sub>3</sub>-C<sub>6</sub>cellulose), hydroxypropyl methylcellulose and mixture thereof, which excipient(s), optionally substitute the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof.

Throughout the description and claims the word "comprise" and variations of the word, are not intended to exclude other technical features, additives, components, or steps. Furthermore, the word "comprise" encompasses the case of "consisting of". Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples are provided by way of illustration, and they are not intended to be limiting of the present invention. Furthermore, the present invention covers all possible combinations of particular and preferred embodiments described herein.

30

### **Examples**

#### Example 1.- Aqueous gel formulations for topical use

Next Table 1 shows a particular gel composition of the invention with chlorhexidine gluconate and sodium hyaluronate.

Table 1. FORMULA for colorless gel composition for 100 g and 5000 g

|                                                | 100 g   | 5.000 g     |
|------------------------------------------------|---------|-------------|
| Chlorhexidine digluconate at 20%               | 1,065 g | 53,250 g    |
| Hyaluronic acid (sodium salt)                  | 0,24 g  | 12,000 g    |
| Rosmarine essential oil                        | 0,05 g  | 2,500 g     |
| Sodium methylparabene (Sodium Nipagin M)       | 0,40 g  | 20,000 g    |
| Sodium Ethylparaben (Sodium Nipagin A)         | 0,04 g  | 2,000 g     |
| Phr. grade propyleneglycol.                    | 50,00 g | 2.500,000 g |
| Blanose 12M31P (Sodium carboxymethylcellulose) | 3,00 g  | 150,000 g   |
| PEG-40 Castor Oil                              | 0,20 g  | 10,000 g    |
| Disodium EDTA                                  | 0,10 g  | 5,000 g     |
| Optamint E7171/266165 aroma                    | 0,27 g  | 13,500 g    |
| Crystalized menthol                            | 0,05 g  | 2,500 g     |
| Eugenol                                        | 0,010 g | 0,500 g     |
| Methyl salycilate                              | 0,07 g  | 3,500 g     |
| Citric acid q.s. pH 7,0-8,0                    | 0,13 g  | 7,56 g      |
| Purified water q.s. 100 g                      |         |             |

This composition did not show any precipitate of chlorhexidine and/or hyaluronic acid.

- 5 Next Table 2 shows the appearance and consistency of several gel compositions comprising chlorhexidine and hyaluronic acid. The presence of the carboxymethyl cellulose gave proper gel consistency (colorless or white) but with no precipitation observed.

- 10 Table 2\_ Other gel compositions of the invention.

|                                  | 1608G<br>Transparent gel with adequate aspect and consistency | 1609G<br>Transparent gel with adequate aspect and consistency | 1701G<br>Transparent gel with adequate aspect and consistency. Initially whitening due to air bubbles that disappear | 1702G<br>Transparent gel with adequate aspect and consistency. Initially whitening due to air bubbles that disappear |
|----------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| Chlorhexidine digluconate at 20% | 1,065g                                                        | 1,065g                                                        | 1,50g                                                                                                                | 1,50g                                                                                                                |

|                                                | <b>1608G</b><br>Transparent gel with adequate aspect and consistency | <b>1609G</b><br>Transparent gel with adequate aspect and consistency | <b>1701G</b><br>Transparent gel with adequate aspect and consistency. Initially whitening due to air bubbles that disappear | <b>1702G</b><br>Transparent gel with adequate aspect and consistency. Initially whitening due to air bubbles that disappear |
|------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Hyaluronic acid (sodium salt)                  | 0,24g                                                                | 0,24g                                                                | 0,50g                                                                                                                       | 0,50g                                                                                                                       |
| Rosmarine essential oil                        | 0,05g                                                                | 0,05g                                                                | 0,05g                                                                                                                       | 0,05g                                                                                                                       |
| Sodium methylparabene (Sodium Nipagin M)       | 0,40g                                                                | 0,40g                                                                | 0,40g                                                                                                                       | 0,40g                                                                                                                       |
| PEG-40 Castor Oil                              | 0,20g                                                                | 0,20g                                                                | 0,20g                                                                                                                       | 1,00g                                                                                                                       |
| Ar. Optamint E7171/266165                      | 0,27g                                                                | 0,27g                                                                | 0,27g                                                                                                                       | 0,27g                                                                                                                       |
| Crystalized menthol                            | 0,05g                                                                | 0,05g                                                                | 0,05g                                                                                                                       | 0,05g                                                                                                                       |
| Eugenol                                        | 0,01g                                                                | 0,01g                                                                | 0,01g                                                                                                                       | 0,01g                                                                                                                       |
| Methyl salicylate                              | 0,07g                                                                | 0,07g                                                                | 0,07g                                                                                                                       | 0,07g                                                                                                                       |
| Citric acid q.s. pH 7,0-8,0                    | 0,14g                                                                | 0,13g                                                                | N.D.                                                                                                                        | 0,12g                                                                                                                       |
| Water (for 100 g)                              |                                                                      |                                                                      |                                                                                                                             |                                                                                                                             |
| Disodium EDTA                                  | 0,10g                                                                | 0,10g                                                                | 0,10g                                                                                                                       | 0,10g                                                                                                                       |
| Phr. grade propyleneglycol.                    | 50,00g                                                               | 50,00g                                                               | 50,00g                                                                                                                      | 50,00g                                                                                                                      |
| Sodium Ethylparaben (Sodium Nipagin A)         | 0,04g                                                                | 0,04g                                                                | 0,04g                                                                                                                       | 0,04g                                                                                                                       |
| Blanose 12M31P (Sodium carboxymethylcellulose) | 3,00g                                                                | 3,00g                                                                | 3,00g                                                                                                                       | 3,00g                                                                                                                       |
| Sodium citrate                                 |                                                                      |                                                                      |                                                                                                                             |                                                                                                                             |
| Glycerin                                       |                                                                      |                                                                      |                                                                                                                             |                                                                                                                             |

Continuation table 2

|                                                | <b>1703G</b><br>Transparent gel with adequate aspect and consistency | <b>1704G</b><br>Transparent gel with adequate aspect and consistency. Initially whitening due to air bubbles that disappear | <b>1705G</b><br>Transparent gel with adequate aspect and consistency. Initially whitening due to air bubbles that disappear | <b>1706G</b><br>Transparent gel with adequate aspect and consistency. Initially whitening due to air bubbles that disappear |
|------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Chlorhexidine digluconate at 20%               | 1,065g                                                               | 1,50g                                                                                                                       | 2,50g                                                                                                                       | 5,00g                                                                                                                       |
| Hyaluronic acid (sodium salt)                  | 0,24g                                                                | 0,50g                                                                                                                       | 1,00g                                                                                                                       | 1,00g                                                                                                                       |
| Rosmarine essential oil                        | 0,05g                                                                | 0,05g                                                                                                                       | 0,05g                                                                                                                       | 0,05g                                                                                                                       |
| Sodium methylparabene (Sodium Nipagin M)       | 0,40g                                                                | 0,40g                                                                                                                       | 0,40g                                                                                                                       | 0,40g                                                                                                                       |
| PEG-40 Castor Oil                              | 0,20g                                                                | 0,20g                                                                                                                       | 0,20g                                                                                                                       | 0,20g                                                                                                                       |
| Ar. Optamint E7171/266165                      | 0,27g                                                                | 0,27g                                                                                                                       | 0,27g                                                                                                                       | 0,27g                                                                                                                       |
| Crystalized menthol                            | 0,05g                                                                | 0,05g                                                                                                                       | 0,05g                                                                                                                       | 0,05g                                                                                                                       |
| Eugenol                                        | 0,01g                                                                | 0,01g                                                                                                                       | 0,01g                                                                                                                       | 0,01g                                                                                                                       |
| Methyl salicylate                              | 0,07g                                                                | 0,07g                                                                                                                       | 0,07g                                                                                                                       | 0,07g                                                                                                                       |
| Citric acid q.s. pH 7,0-8,0                    | 0,18g                                                                | 0,16g                                                                                                                       | 0,17g                                                                                                                       | 0,14g                                                                                                                       |
| Water (for 100 g)                              |                                                                      |                                                                                                                             |                                                                                                                             |                                                                                                                             |
| Disodium EDTA                                  | 0,10g                                                                | 0,10g                                                                                                                       | 0,10g                                                                                                                       | 0,10g                                                                                                                       |
| Phr. grade propyleneglycol.                    | 50,00g                                                               | 50,00g                                                                                                                      | 50,00g                                                                                                                      | 50,00g                                                                                                                      |
| Sodium Ethylparaben (Sodium Nipagin A)         | 0,04g                                                                | 0,04g                                                                                                                       | 0,04g                                                                                                                       | 0,04g                                                                                                                       |
| Blanose 12M31P (Sodium carboxymethylcellulose) | 3,00g                                                                | 3,00g                                                                                                                       | 3,00g                                                                                                                       | 3,00g                                                                                                                       |
| Sodium citrate                                 |                                                                      |                                                                                                                             |                                                                                                                             |                                                                                                                             |
| Glycerin                                       |                                                                      |                                                                                                                             |                                                                                                                             |                                                                                                                             |

Continuation Table 2

|                                                   | <b>1707G</b><br>Transparent<br>gel with<br>adequate<br>aspect and<br>consistency.<br>Initially<br>whitening due<br>to air bubbles<br>that disappear | <b>1714G</b><br>Transparent<br>gel with<br>adequate<br>aspect and<br>consistency | <b>1715G</b><br>White gel with<br>adequate liquid<br>aspect and<br>consistency |
|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Chlorhexidine digluconate at 20%                  | 5,00g                                                                                                                                               | 1,0650g                                                                          | 1,0650g                                                                        |
| Hyaluronic acid (sodium salt)                     | 1,00g                                                                                                                                               | 0,24g                                                                            | 0,24g                                                                          |
| Rosmarine essential oil                           | 0,05g                                                                                                                                               | 0,05g                                                                            | 0,05g                                                                          |
| Sodium methylparabene<br>(Sodium Nipagin M)       | 0,40g                                                                                                                                               | 0,40g                                                                            | 0,40g                                                                          |
| PEG-40 Castor Oil                                 | 1,00g                                                                                                                                               | 0,20g                                                                            | 0,20g                                                                          |
| Ar. Optamint E7171/266165                         | 0,05g                                                                                                                                               | 0,27g                                                                            | 0,27g                                                                          |
| Crystalized menthol                               | 0,07g                                                                                                                                               | 0,05g                                                                            | 0,05g                                                                          |
| Eugenol                                           | 0,01g                                                                                                                                               | 0,01g                                                                            | 0,01g                                                                          |
| Methyl salicylate                                 | 0,07g                                                                                                                                               | 0,07g                                                                            | 0,07g                                                                          |
| Citric acid q.s. pH 7,0-8,0                       | 0,12g                                                                                                                                               | 0,14g                                                                            | 0,10g                                                                          |
| Water (for 100 g)                                 |                                                                                                                                                     |                                                                                  |                                                                                |
| Disodium EDTA                                     | 0,10g                                                                                                                                               | *                                                                                | 0,10g                                                                          |
| Phr. grade propyleneglycol.                       | 50,00g                                                                                                                                              | 50,00g                                                                           | *                                                                              |
| Sodium Ethylparaben<br>(Sodium Nipagin A)         | 0,04g                                                                                                                                               | 0,04g                                                                            | 0,04g                                                                          |
| Blanose 12M31P (Sodium<br>carboxymethylcellulose) | 3,00g                                                                                                                                               | 3,00g                                                                            | 3,00g                                                                          |
| Sodium citrate                                    |                                                                                                                                                     | 1,00g                                                                            |                                                                                |
| Glycerin                                          |                                                                                                                                                     |                                                                                  | 50,00g                                                                         |

Example 2.- Assay for evaluation of the mucoadhesive properties of a topical product

The colorless gel of Example 1 (Table 1) was tested in order to evaluate the mucoadhesion properties through gravimetric test on an inclined temperature-controlled plane treated with mucin.

The goal of the test is evaluating the mucoadhesive properties of a topical product through the analysis of kinetic detachment of the sample from a steel inclined plane, with and without a mucin biofilm. The actual mucoadhesion of the sample is determined from the delay in sample slipping and in the detachment from the plane caused by the mucin.

The steel plane was positioned horizontally and the temperature control was set 60 minutes in advance. 4 ml of the analyzed sample or deionized water were positioned at the pre-defined run distance and left to settle for 2 minutes- To start the run, the plane was set at 45° inclination. The amount of sample detached from the plane dropped in a petri dish and was weighed automatically every 60 seconds. For the gravimetric measures, an Ohaus Explorer Pro analytical scale fitted with a thermal printer was used. The timed recording of the measurement was directly controlled by the software of the scale.

The sample was tested undiluted. Each run was performed in three replicas and the performed runs included: Deionized water without mucin; deionized water with mucin; analyzed sample without mucin; and analyzed sample with mucin.

The plane was accurately cleaned and prepared before each run. For the runs with the mucin film, the plane was pre-coated with a 8 % suspension in water of porcine gastric mucin type II (Sigma-Aldrich) spread to make an evenly film.

The test conditions for the sample were as follows:

Temperature: 36 °C

Inclination of the steel plane: 45°

Length of the run surface: 10 cm

Duration of the run: 60 seconds.

To determine a mucoadhesion value, the average of the registered weight at each time unit was considered, together with its standard deviation. Each value was also compared with the total weight of the applied sample in order to build an adhesion vs. time plot.

Percentage of adhesion was calculated according to the following formula:

$$\text{Adhesion \%} = (P_0 - P_t) / P_0 * 100$$

Where:  $P_0$  is the weight of the sample applied on the plane at  $T = 0$ ;

- 5  $P_t$  is the weight of the sample detached from the steel plane at each endtime  $t$ .

In order to display mucoadhesive properties, a sample has to show a percentage of adhesion vs. the mucin-less control significantly higher ( $p < 0.05$ ) than the one displayed by water, which interacts with the protein through hygroscopic absorption only.

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Results are reported as follows in Table 3 as the adhesion percentage over time  $\pm$  standard deviation.

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Table 3: adhesion percentage over time

| Time (min)         | 1      | 2      | 3      | 4      | 5      | 10     | 15     | 20     | 25     | 30     | 35     | 40     | 45     | 50     | 55     | 60     |
|--------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| water (%)          | 13,17% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% | 12,33% |
| Deviation (±%)     | 4,37%  | 2,65%  | 2,60%  | 3,05%  | 2,65%  | 3,05%  | 3,13%  | 3,61%  | 3,28%  | 3,13%  | 2,60%  | 2,18%  | 3,51%  | 3,01%  | 4,01%  | 9,20%  |
| water + mucin (%)  | 18,83% | 18,17% | 18,67% | 19,00% | 19,17% | 19,50% | 20,17% | 20,83% | 20,83% | 21,33% | 21,00% | 21,00% | 20,50% | 20,17% | 21,00% | 19,67% |
| Deviation (±%)     | 3,51%  | 2,79%  | 2,65%  | 2,30%  | 2,30%  | 1,50%  | 1,00%  | 0,50%  | 1,00%  | 2,30%  | 2,50%  | 3,01%  | 3,01%  | 4,28%  | 4,78%  | 5,65%  |
| Sample (%)         | 99,91% | 94,17% | 55,78% | 48,41% | 43,44% | 26,31% | 26,22% | 22,37% | 22,37% | 22,37% | 22,37% | 22,37% | 22,37% | 22,37% | 22,37% | 22,37% |
| Deviation (±%)     | 0,29%  | 19,20% | 17,44% | 9,65%  | 14,40% | 9,44%  | 8,85%  | 6,76%  | 6,03%  | 6,53%  | 6,51%  | 6,50%  | 7,02%  | 6,25%  | 6,01%  | 5,77%  |
| Sample + mucin (%) | 99,83% | 99,91% | 98,37% | 77,89% | 65,21% | 46,70% | 45,42% | 45,76% | 45,67% | 46,02% | 46,02% | 46,27% | 45,93% | 46,27% | 46,10% | 46,02% |
| Deviation (±%)     | 0,58%  | 0,29%  | 5,06%  | 38,43% | 10,54% | 0,76%  | 5,06%  | 5,22%  | 5,22%  | 5,39%  | 5,58%  | 5,77%  | 5,89%  | 6,11%  | 6,38%  | 6,56%  |

As deducible from this Table 3, sample of example 1 showed a mucoadhesion of 46.1 % when stabilized vs. a percentage of deionized water equal to 12.33 %. The corresponding percentage of the sample's adhesion without mucin was 22.37 %. Since the differential adhesion vs. the negative control was statistically significant ( $p < 0.0001$ ), it could be concluded that the tested sample (Example 1) did show mucoadhesion properties.

Data are also derivable from FIG. 1, wherein there is a comparative graph of the mucoadhesion levels of a gel of the invention over time, registered by means of a gravimetric test on an inclined temperature-controlled plane treated with mucin. Error bars show the standard deviation for each data set. Adhesion score (%) in the Y-axis is indicated as percentage of adhesion. X-axis shows the time in minutes (min). Each data set include data from water (first column in the set), data from water in a mucin containing inclined plane (second column in the set), sample (third column in the set) and sample in a mucin containing inclined plane (forth column in the set).

All these data allow concluding by the one side that, using the particular carboxy( $C_1$ - $C_3$ )alkyl-cellulose and/or a salt thereof, the mixture comprising sodium hyaluronate and chlorhexidine gluconate had a gel consistency in which no precipitation of chlorhexidine was observed. Thus, it was a colorless gel composition. On the other side, the gel had mucoadhesive properties, thus being able to be topically applied in any surface, such as skin or even mucin-containing surfaces such as the gums of the oral cavity. These adhesive properties allow any active contained in the gel, for example the sodium hyaluronate and the chlorhexidine, among other actives, to rest on the surface enough time to provide their effects.

## Citation List

### Patent Literature

- WO9852612
- CH691030
- RU2286764
- WO2008144185
- US5192802
- US6117415

**Claims**

1. A gel composition comprising:
  - 5 - chlorhexidine and/or a pharmaceutically or cosmetically acceptable salt thereof;
  - hyaluronic acid and/or a pharmaceutically or cosmetically acceptable salt thereof; and
  - a gelling matrix comprising water and a cellulose derivative, said cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, together with pharmaceutically or cosmetically excipients and/or carriers.
- 10 2. The gel composition according to claim 1, wherein the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose is carboxymethylcellulose or a salt thereof.
3. The gel according to any of claims 1-2, wherein the pharmaceutically or cosmetically acceptable salt of chlorhexidine is selected from the group consisting of chlorhexidine  
15 gluconate, chlorhexidine acetate, chlorhexidine chlorhydrate and mixtures thereof.
4. The gel composition according to any of claims 1-3, wherein the pharmaceutically or cosmetically acceptable salt of chlorhexidine is chlorhexidine gluconate.
- 20 5. The gel composition according to any of claims 1-4, wherein the pharmaceutically or cosmetically acceptable salt of hyaluronic acid is selected from the group consisting of alkali metal salts, alkaline earth metal salts, and mixtures thereof.
6. The gel composition according to claim 5, wherein pharmaceutically or cosmetically  
25 acceptable salt of hyaluronic acid is the alkali metal salt sodium hyaluronate.
7. The gel composition according to any of claims 1-6, which further comprises a solvent selected from the group consisting of polyalkylene glycol, glycerin, propylene glycol and mixtures thereof.
- 30 8. The gel composition according to any of claims 1-7, which further comprises a one or more compounds selected from the group consisting of an essential oil, a preservative, a flavor, an humectant, an emulsifier, a chelating agent, and additional gelling agent besides the carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose , an antimicrobial agent, an aqueous vehicle and  
35 mixtures thereof.

9. The gel composition according to any of claims 1-8, wherein the percentage by weight of chlorhexidine or of a pharmaceutically or cosmetically acceptable salt thereof, in relation to the total weight of the gel composition is from 0.05 % to 1.5 %.

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10. The gel composition according to any of claims 1-9, wherein the percentage by weight of hyaluronic acid or of a pharmaceutically or cosmetic acceptable salt thereof, in relation to the total weight of the composition is from 0.1 % to 1.0 %.

10 11. The gel composition according to any of claims 1-10, wherein the percentage by weight of carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, in relation to the total weight of the composition is from 1.0 % to 5.0%.

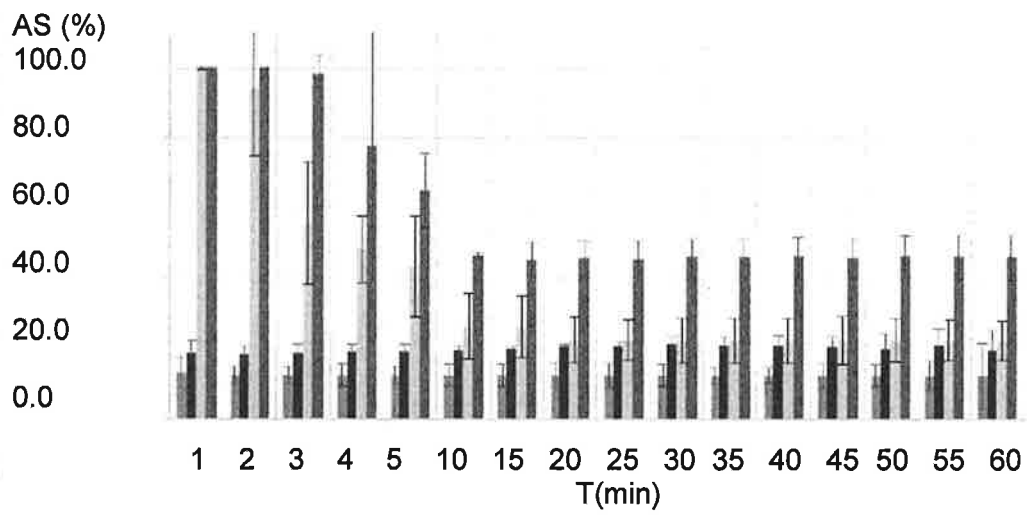
15 12. The gel composition according to any of claims 1-11, wherein the pH is from 7.0 to 8.0.

13. A method for preparing a gel composition as defined in any of claims 1-12 comprising:

(a) forming an homogenized aqueous dispersion, said dispersion comprising  
 20 chlorhexidine and/or a pharmaceutically or cosmetically acceptable salt thereof, dispersed in a solvent selected from the group consisting of polyalkylene glycol, glycerin, propylene glycol and mixtures thereof; and hyaluronic acid and/or a pharmaceutically acceptable salt thereof, dissolved in water; and  
 (b) adding to the homogenized aqueous dispersion of step (a), a cellulose derivative, said  
 25 cellulose derivative comprising carboxy(C<sub>1</sub>-C<sub>3</sub>)alkyl-cellulose and/or a salt thereof, to obtain a gel composition.

14. A gel composition as defined in any of claims 1-12 for use as a medicament.

30 15. Use of a gel composition as defined in any of claims 1-12 as cosmetic care agent.

**FIG. 1**