

LUBRICATING COMPLEX FOR THE MOUTH

The object of the present invention is pharmaceutical compositions comprising at least one humectant, a gelling agent
5 and a film-forming agent for its use in the symptomatic treatment of hyposialia or asialia.

Saliva is a highly complex product having many functions: cleaning, buffer, lubrication, perception of taste, protection against demineralization, defense. Normal saliva contains
10 antibodies, enzymes and buffer solutions. It plays an important role in talking, tasting, chewing, swallowing, digesting, feeding, as well as in the protection of the mouth, of the lips and of the esophagus. Thus, saliva plays a key role in maintaining oral health because of several factors. Firstly, the
15 salivary flow exerts a cleaning action on bucco-dental surfaces. Next, saliva promotes re-mineralization of beginning carious lesions via its buffer effect and the presence of mineral ions. Further, the presence of an enzyme such as amylase is essential for digestion, a long and complex process beginning in the mouth.
20 To conclude, the presence of antibacterial substances allows inhibition of the metabolism of bucco-dental pathogenic microorganisms. These reasons make saliva play an essential role in the process of regulation which aims at counter-balancing the pathogenic action of bacteria of the buccal flora, and the latter
25 can only play its protective role when it is produced in a sufficient amount by the salivary glands. But saliva also plays a role of a lubricant since it allows better slipping of the mucosae and of the teeth between them and also gives a sensation of humectation of the mouth, essential for talking, swallowing,
30 chewing and finally for wellness. Salivation is an innate reflex, but which may be acquired, as shown by the Pavlov experiment. Secretion of saliva is highly variable from one individual to another which may range from 500 ml to 1,200 ml per day, 70% of parotid origin, 20% of sub-maxillary origin, 10% of sublingual

origin and from other accessory glands which are disseminated under the whole surface of the buccal, labial, jugal, palatal and velar mucosae. The residual secretion would be of about 100 ml per day while stimulated secretion would be about ten times greater. The production of saliva after each meal is essential since saliva is the only natural defense system of the body against bucco-dental pathogens. Many studies show the important role of saliva as a factor implied in the development of caries and of parodontal diseases.

The defects of the salivary function in the sense of a reduction in the salivary secretion are hyposialia and asialia. Hyposialia is a reduction in the production of saliva by the salivary glands, which causes buccal dryness. Asialia is a total lack of secretion of saliva which causes total dryness. Xerostomia defines a dryness condition of the buccal cavity and of the lips which is subjectively felt by the patient, expressing direct or indirect affection of the salivary glands and either appearing as a reduction in the salivary flow or hyposialia or by zero salivary secretion or asialia. Xerostomia is therefore a symptom.

Hyposialia has significant prevalence in about 10% of the general population and notably in elderly persons, 30% of persons having more than 65 years of age would be affected therewith. It causes pain, functional disorders (swallowing, chewing, voice), perturbations of appetite (dysphagia, dysgeusia, under nutrition with complications in elderly persons), difficulties for talking, oral infections (caries with fast progression, candidoses, ulcerations of the mucosae) responsible for multiple tooth extractions and for intolerances to prosthesis, as well as an increase in the risk of aspiration, of inhalation pneumonias and of nosocomial lung infections, notably when elderly persons are in the hospital. The absence or reduction in saliva contributes to the esophageal reflux as well as conventionally to the permanent sensation of thirst and to a modification of breath. It

may be difficult to swallow a drug with less saliva, this may cause inobservance of the medicated treatment. Dryness of the mouth may also delay the dissolution of sublingual tablets of nitroglycerine for example. Dry mouth and its consequences for both physiological and esthetical reasons profoundly affect the humor and the social behavior. Finally, consequences on nutrition causing a loss of weight and on the pleasures of orality are to be feared. All these additional problems may have a negative impact on the life quality of the patient.

Three major and well-defined causes are at the origin of hyposialia, the most common etiology is medicine-related iatrogeny. More than 500 drugs, including 42 different pharmacological groups may be at the origin of hyposialia. The drugs which induce the most intense xerostomia are those which have a direct impact on the autonomic nervous system, which regulates the secretions of glands, like anticholinergic agents, adrenergic blocking agents, those which have an indirect impact on the central nervous system like antipsychotic agents, anxiolytic agents but also drugs which increase the excretion of liquids like diuretics. Other categories like antihistaminics, anti-arrhythmics, cough suppressants are also regularly mentioned as responsible for exacerbated buccal dryness. In the case of hyposialia induced by drugs, it is important to recall that this dryness may concern all the other mucosae including those of the genital apparatus. Hyposialia also occurs in persons treated by radiotherapy during ENT cancers (mouth, tongue, tonsil, larynx, pharynx, nasal cavity cancers...). The rays destroy all the salivary glands placed on their trajectory. The third cause of hyposialia is an auto-immune disease, called « Gougerot-Sjögren syndrome ». This disease is characterized by affection of exocrine glands, in particular salivary and lacrimal glands, it affects 1 to 3% of the population and more often women than men (9/1), often after menopause. This syndrome may be associated with another auto-immune disease, disseminated erythematous

lupus, rheumatoid arthritis... Finally other causes may generate hyposialia, even a minor dehydration of the body, when the latter only loses 8% of its water, it induces an inhibition of salivary secretion. Thus, fever, excessive sedation, vomiting, diarrhoea, blood losses or burns which cause dehydration may therefore also cause dryness of the mouth. A hyposialia may also appear upon the use of drugs or the consumption of tobacco. A lesion of a nerve in the neck and head region by an injury or a surgical operation may also cause dryness of the mouth. A reduction in the chewing capacity may be at the origin of establishing a liquid food or soft food diet, which causes a reduction in the flow of saliva. Moreover, psychological factors like stress, anxiety or depressive conditions are also connected to xerostomia. However, hyposalivation is normally associated with xerostomia induced by drugs while this association is not frequent in the case of xerostomia related to psychological conditions.

All the hyposialias have to be corrected in order to avoid any risk of occurrence of bucco-dental pathologies, all the more so since modern lifestyle does no longer allow teeth to be brushed after each meal and most particularly after lunch. The lack of brushing of teeth associated with a salivary deficiency will inevitably cause the occurrence of bucco-dental pathologies and it is therefore essential to cope with this risk by stimulating salivary secretion after each meal.

Because possibilities of causal treatment of xerostomia are still lacking up until now, the therapeutic goal is limited to sole symptomatic relief of buccal dryness. Such improvement may be obtained by different therapeutic means, i.e. on the one hand with solutions for buccal rinses or baths and on the other hand with salivary substitutes or saliva substitute or further artificial saliva, i.e. by systemic stimulation of salivary glands.

In the case of iatrogenic hyposialia, it is possible to stop the drug or the treatment responsible for xerostomia but this

seems to be difficult to conceive when most of them are prescribed over long periods and relate to serious pathologies. For the selection of salivary stimulants, because of the fact that chewing stimulates salivary flow, it is suitable to recommend that the patients preferably consume foodstuffs with firm consistency. Next comes the possibility of drinking a lot of water in order to maintain the mouth hydrated, of drinking fizzy beverages giving the possibility of humecting the buccal mucosa and also sometimes promoting secretion of saliva, of adding a humidification system in the bedroom in order increase humidity in the air, of breathing through the nose instead of through the mouth as far as possible or further sucking an acid sweet, or chewing a gum but without any sugar in order to avoid dental cavities. Another possibility for stimulating the salivary flow consists in the administration of saliva-stimulating drugs with a systemic or sialogogue effect, such as pilocarpine, nicotinamide. Among systemic sialogogues, pilocarpine has proved to be the most efficient substance, it is recognized in most countries as a drug for treating hyposialia. Pilocarpine is an alkaloid, extracted from leaves of pilocarpus from various varieties *jaborandi*, *pennatifolius*, *microphyllus*.

Pilocarpine, by its parasympathomimetic action stimulate secretions of exocrine glands, it therefore gives the possibility of generally obtaining a pronounced rise in the salivary flow rate and therefore an attenuation of the symptoms of buccal dryness. However, many patients having xerostomia suffer from the symptoms of buccal dryness in particular over night, consequently the substances for stimulating the salivary flow administered during the day are not able to relieve them at these instants. But these substances only give the possibility of obtaining the expected effect in patients still having some residual activity of salivary glands. To this it should be added that the administration of drugs based on pilocarpine may cause significant undesirable secondary effects such as nausea,

hyperhidrosis, dizziness, hot flushes or asthenias. Application WO2005/067924 discloses a composition for treating hyposialias based on pilocarpine associated with at least one bio-adhesive polymer so as to allow dissolution and local binding at the tissues of the bucco-pharyngeal sphere.

As varied as they may be, all these methods only compensate for the lack of saliva and do not re-establish durably the saliva function, which finally is the goal for the patient.

Until the arrival of more complex products for salivary substitution, the literature recommended the use of non-irritating mouthwashes, of solutions based on sodium bicarbonate, on saline or chlorhexidine for attenuating the symptoms in patients suffering from hyposialia. Also, solutions for buccal rinses, such as tea, fluorinated mineral waters and milk have been recommended because of their protective efficiency against dental cavities. It should be recommended to patients that they avoid consumption of all irritating substances or too spicy foodstuffs, as well as all those which contain alcohol. For reasons for protecting hard dental tissues, solutions for buccal rinses with an acid pH and containing a relatively high level of acids upon titration should by no means be used, in patients still having natural teeth, because of a potentially deleterious effect on dentin. Resorting to solutions for mouthwashes or buccal rinses, or even to water, milk or tea, for relieving the symptoms of xerostomia is however burdened with a major drawback. Indeed, the unfavorable physico-chemical properties of these solutions make it necessary to repeat very often the applications in order to ensure a sufficient and durable wetting effect.

The first salivary substitute was developed several decades ago, the base ingredient of this salivary substitute was carboxymethylcellulose and further contained calcium and phosphate. Subsequently, the manufacturers added sorbitol to the artificial salivas in order to make them more pleasant to taste and to increase the wetting effect by modifying the surface

tension, but the combination of both of these substances induces an increase in the viscosity of the preparations with respect to natural saliva. Other preparations for substituting saliva contain as an active basic substance sodium
5 carboxymethylcellulose, carboxyethylcellulose, hydroxyethylcellulose, mucins of animal origin, flax oil, sorbitol or polyethylene-oxide. The salivary substitutes are notably distinguished by the addition of various inorganic components, the presence of certain enzymes and by their pH
10 value.

Mention may notably be made as a salivary substitute, of Novasial® based on egg white selected for its rheological and physiological characteristics close to those of saliva, on xanthan gum, on bicarbonate and on sorbitol. Biotène® is a
15 medical device based on glycerol, polymers and xanthan gum.

Ideally, a salivary substitute should be capable of exerting a lubricating and wetting effect on the whole of the mucosae and of the hard dental tissues for an extended period, it should protect mucosae against dryness, while of course not exerting any
20 deleterious effect on the body in general.

Thus, if there exist a certain number of substitute products for saliva intended for symptomatic treatment in the case of xerostomia, there always exists a real need for novel compositions easy to use with actual efficiency and for an
25 extended lapse of time and especially well tolerated by the patient.

The applicant has shown that the composition according to the invention gives the possibility of perfectly fitting this need.

30 The composition according to the invention is intended to be directly administered in the mouth. Topical administration of the composition may be accomplished by applying a solution, a suspension, a gel, a lotion, a milk, a cream. One of the possible and preferred means is the administration of the composition with

a spray. Preferably, a wide spray facilitating the application of the composition for covering the whole of the buccal cavity will be selected.

5 The frequency of use of such a spray will depend on the composition, on the dose to be administered during the daytime, on the needs of the patient, this frequency will be determined by the physician and/or the pharmacist, however, a maximum frequency of three sprayings eight times a day is recommended.

10 The present disclosure therefore relates to a pharmaceutical composition comprising at least one humectant, one gelling agent and one film-forming agent for its use in the treatment of hyposialia or asialia.

15 In one aspect, the invention relates to the use of the pharmaceutical composition comprising at least one humectant in an amount from 15 % to 65 % by weight based on the total weight of the composition, one gelling agent and a derivative of polyvinyl alcohols as a film-forming agent in the manufacture of a medicament for treatment of hyposialia or asialia, wherein the film-forming agent is a mixture of polyvinylpyrrolidone and of
20 copolyvidone.

In another aspect, there is provided the pharmaceutical composition as disclosed herein for use as a medicament.

25 An object of the present invention therefore appears as a medical device which, according to article L.5211-1 of the Public Health Code (France) is defined as any instrument, device, piece of equipment, material or other article, intended to be used in humans for diagnostic, prevention, control, treatment or attenuation purposes for a pathology, and the main action of which in or on the human body is not obtained by pharmacological
30 or immunological means or by metabolism, but the function of which may be assisted with such means.

By humectant in the sense of the present invention is meant a small molecule capable of attracting and/or retaining water in proximity to or available to cells by means of its hygroscopic properties.

5 The humectant may advantageously be selected from pidolic acid and its derivatives, butylene glycol, calcium gluconate, fructose, glucose, isomalt, lactose, maltitol, mannitol, polydextrose, sorbitol, saccharose, xylitol, glycerol, glycyrrhizic acid and its derivatives, histidine, hyaluronic acid
10 and its salts, silk, keratin or soja hydrolyzates, PEGs (-7, -8, -10, -12, -14...), phytantriol, propylene glycol, silk, urea. Preferably, the humectant is glycerol.

By gelling agent is meant in the sense of the present invention, a substance which gives the possibility of transforming a more or less fluid composition into a more or less viscous composition.

5 The gelling agent may advantageously be selected from among polysaccharides of plant origin, such as xanthan gum and its derivatives, copolymers of alkylacrylates and of acrylic and methacrylic acids, notably obtained via a synthesis route, and
10 silicates, notably silicates of mineral origin more commonly called under the name of Veegum® or Bentones®. Preferably, the gelling agent is xanthan gum.

Thus, according to a preferred embodiment of the invention, the pharmaceutical composition comprises glycerol, xanthan gum and a film-forming agent.

15 By film-forming agent is meant in the sense of the present invention, a substance which gives the possibility of producing a continuous film on a mucosa.

 The film-forming agent may advantageously be selected from among hydrophobic film-forming agents, such as mineral oils,
20 silicones and synthetic or natural waxes, mention will be made as an example, as an illustration, of Vaseline oil; but also hydrophilic film-forming agents, such as proteins (collagens, elastin...), complex carbohydrates such as glucosaminoglycans (hyaluronic acid, chondroitin sulfate), chitosan, hydrophilic
25 polymers of plant origin (galactomannans, xyloglucans, polysaccharides, mucopolysaccharides...), synthetic polymers, derivatives of polyvinyl alcohols, carbopol... As an example, polyvinylpyrrolidone will be mentioned, with notably the various Kollidon®.

30 Preferably, the composition will comprise two film-forming agents, notably derivatives of polyvinyl alcohols.

 In a still preferred way, the film-forming agent of the composition is a mixture of polyvinylpyrrolidone and of copolyvidone.

According to an embodiment of the invention, the composition comprises at least one humectant, one gelling agent and one film-forming agent in a pharmaceutically acceptable carrier.

5 In the present invention, referring to as "pharmaceutically acceptable" or "acceptable pharmaceutically" is meant to refer to what is useful in the preparation of a pharmaceutical composition which is generally safe, non-toxic and neither biologically or otherwise undesirable and which is acceptable for veterinary use
10 as well as human pharmaceutical use.

 In an embodiment of the invention, the pharmaceutical composition further comprises at least one solubilizing agent, these agents are well known to one skilled in the art. A particularly suitable solubilizer adapted to the pharmaceutical
15 composition according to the invention is macrogolglycerol 40 hydroxystearate.

 In an embodiment of the invention, the pharmaceutical composition further comprises at least one mucilage. Preferably the mucilage stems from an extract of marshmallow root. By
20 mucilage is meant a plant substance consisting of polysaccharides of a pectic nature (polygalacturonic acid) which swells upon contact with water and which has viscous consistency. The primary roots of most plants secrete mucilages. Marshmallow roots are particularly rich in mucilage. The latter are particularly
25 suitable for being incorporated into a composition according to the invention.

 In an embodiment of the invention, the pharmaceutical composition further comprises at least one auxiliary substance selected from sweeteners, antioxidants, colouring agents, aromas.

30 One or several sweeteners may be selected from the group formed with: acesulfame, aspartame, cyclamic acid and its salts, isomalt, saccharin and its salts, sucralose, alitame, thaumatin, glycyrrhizic acid and its salts, neohesperidin dihydrochalcone, steviol glucosides, neotame, aspartame-acesulfame salt, tagatose,

brazzein, curculin, hydrogenated starch hydrolysate, mabinlin, miraculin, monellin, pentadin, polyglycitol syrup, maltitol, maltitol syrup, lactitol, xylitol, erythritol, trehalose.

One or several antioxidants may be selected from the group
 5 formed with: ascorbic acid, sodium ascorbate, calcium ascorbate, ascorbyl diacetate, ascorbyl palmitate, ascorbyl stearate, alpha tocopherol, beta tocopherol, gamma tocopherol, delta tocopherol, gallates, compounds releasing sulfur dioxide such as sodium metabisulfite, gaiac resin, erythorbic acid, sodium erythorbate,
 10 potassium or calcium isoascorbate, butylhydroquinone, butylhydroxyanisole, butylhydroxytoluene, derivatives of ethylenediamine tetracetic acid and combinations thereof.

The colouring agents and the aromas may either be natural and/or artificial, they are well known to one skilled in the art.

15 In an embodiment of the invention, the pharmaceutical composition may further comprise antimicrobial agents such as preservatives or antifungal agents selected from 2-hydroxybiphenyl, imidazolidinyl urea, diazolidinyl urea, sodium hydroxymethylglycinate, halogenated derivatives such as
 20 iodopropynyl butylcarbamate, 2-bromo-2-nitropropane-1,3-diol, 2,4,4'-trichloro-2'-hydroxydiphenylether (triclosan), 3,4,4'-trichlorocarbanilide (triclocarban), chlorbutanulum, 2,4-dichlorobenzyl alcohol, N-4-chlorophenyl-N'-3,4-dichlorophenyl urea, 1,2-dibromo-2,4-dicyanobutane, chloroxylenol, ketoconazole,
 25 oxiconazole, butoconazole, clotrimazole, econazole, enilconazole, fenticonazole, miconazole, sulconazole, tioconazole, fluconazole, itraconazole, terconazole, actives containing one or several cationic nitrogens such as cetyltrimethylammonium chloride, cetylpyridinium chloride, benzethonium chloride,
 30 diisobutylethoxyethyl-dimethylbenzylammonium chloride, diisobutyl-phenoxy-ethoxyethyl-dimethyl-benzyl-ammonium chloride, N-alkyl-N,N-dimethylbenzylammonium chloride, bromide saccharinate, trimethylammonium chloride, sodium aluminiumchlorohydroxyacetate, tricetylmethylammonium chloride,

diaminoalkylamide, unsaturated antimicrobial agents such as farnesol, terbinafine or naftifine, heterocyclic aromatic agents such as bifonazole, cloconazole, isoconazole, compounds from the family of parabens, notably methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, benzylparaben, of any other antimicrobial or antifungal agent known to one skilled in the art and mixtures thereof.

In an embodiment of the invention, the pharmaceutical composition may also comprise compounds allowing adjustment of the pH range of said composition by avoiding acid pH's favourable to demineralization of hard tissues, these are referred to as pH adjusting agents. This comprises neutralizing agents or else buffer agents. The commonly used acid salts are sodium citrate, sodium phosphate, potassium lactate, potassium phosphate or further potassium malate. By sodium phosphate is meant the whole of sodium and phosphate salts, sodium dihydrogenphosphate or monosodium phosphate, sodium hydrogenphosphate or disodium phosphate, sodium phosphate or trisodium phosphate. By potassium phosphate are meant the salts formed of phosphate and potassium ions resulting from the attack of potassium hydroxide by phosphoric acid, monopotassium potassium dihydrogenphosphate, dipotassium potassium hydrogenphosphate, potassium phosphate, dipotassium and tripotassium phosphate.

The compositions may further comprise one or several other ingredients such as pH buffers, vitamins, fragrances, and any other useful compound well known to one skilled in the art.

In an embodiment of the invention, the pharmaceutical composition may also comprise one or several mineralizing agents, for example mention may be made of potassium chloride, sodium chloride, magnesium chloride, calcium chloride, these agents are well known to one skilled in the art.

In a particular embodiment of the invention, the amount of humectant is comprised from 15% to 65% of the total weight of the pharmaceutical composition. Preferably, the amount of humectant

is comprised from 20% to 50% of the total weight of the pharmaceutical composition. Still more preferably, the amount of humectant is comprised from 30% to 40% of the total weight of the pharmaceutical composition. In another preferred way, the amount of humectant is equal to 35% of the total weight of the pharmaceutical composition.

In a particular embodiment of the invention, the amount of gelling agent is comprised from 0.05% to 1% of the total weight of the pharmaceutical composition. Preferably, the amount of the gelling agent is comprised from 0.1% to 0.5% of the total weight of the pharmaceutical composition. In another preferred way, the amount of the gelling agent is equal to 0.2% of the total weight of the pharmaceutical composition.

In a particular embodiment of the invention, the amount of film-forming agent is comprised from 0.1% to 10% of the total weight of the pharmaceutical composition. Preferably, the amount of film-forming agent is comprised from 0.1% to 5% of the total weight of the pharmaceutical composition. In another preferred way, the amount of film-forming agent is comprised from 0.5% to 3% of the total weight of the pharmaceutical composition. In another preferred way, the amount of film-forming agent is equal to 2% of the total weight of the pharmaceutical composition.

According to a preferred embodiment of the invention, the pharmaceutical composition may be administered as a spray. A wide spray is particularly suitable so that the application of the composition covers the whole of the buccal cavity.

According to another preferred embodiment of the invention, the pharmaceutical composition is in the form of a pharmaceutical presentation of the single dose type or further described as unidose or monodose. Mention may be made as examples of sachets which may contain the pharmaceutical composition according to the invention as a powder or granules or even as a solution, suspension or gel; glass ampoule with two tips or with one tip may contain the pharmaceutical composition according to the

invention as a liquid; tubes in plastic material which may contain the pharmaceutical composition according to the invention as a liquid or as a gel. These monodose pharmaceutical presentations are well known to one skilled in the art.

5 The following examples illustrate the invention without limiting the scope thereof.

Example 1: tribological characterization of salivary products

10 The purpose of this study is to characterize the lubricating effect of various salivary products on pig tongues.

Equipment and methods

 The whole of the tests is carried out under controlled temperature and humidity in an enclosure specifically adapted for the study.

15 - Preparation of tongue samples

 The tongues are selected from a slaughter house, they are conditioned, i.e. the non-used areas are destroyed. They are then cleaned with neutral saline. They are then cut out in order to produce homogenous and standard samples. The samples are again
20 cleaned with neutral saline, they are placed in an individual package and frozen.

 - Measurement of friction

 Friction is measured by means of a bio-tribometer (Zahouani et al., Skin Research and Technology, 15: 68-76, 2009), this
25 device was specifically designed for carrying out experiments on biological tissues. This technology allows measurement, in a stabilized friction phase, of the normal and tangential forces. By the ratio between both of these quantities, the friction coefficient τ is calculated. Three measurements are made for each
30 salivary substitute before and after lubrication. The effects of the products before and after lubrication are analysed as regards the significance of the lubricating effect on the one hand and as regards their lubricating effect on the other hand as compared with that provided by human saliva.

In this test, 17 different compositions were tested, 4 of which are used as references (table 1), human saliva, the Aequasyl® substitute, the Biotène® substitute and the Oasis® substitute. A composition (composition no. 1) was evaluated twice
5 in order to test the reproducibility of the test.

Table: Tested compositions

Composition No.	Description
Composition 1	Flax extract + 15% glycerol + 0.2% xanthan + cremophor 40
Composition 2	Yam extract + 5% glycerol
Composition 3	Flax extract + 30% glycerol + 0.2% xanthan + cremophor 40
Composition 4	35% glycerol + 0.2% xanthan + cremophor 60 + copolyvidone
Composition 5	Flax extract + 5% glycerol
Composition 6	Bovine mucin + 5% glycerol
Composition 7	Commercial reference Aequasyl®
Composition 8	Commercial reference Biotène®
Composition 9	Bovine mucin + 63% glycerol + blanose + carrageenate
Composition 10	Commercial reference Oasis®
Composition 11	Lecithin + 5% glycerol + 0.2% xanthan
Composition 12	35% glycerol
Composition 13	85% silicone + 15% paraffin oil
Composition 14	Lecithin + 15% glycerol + 0.4% xanthan
Composition 15	Lecithin + 5% glycerol + 0.4% xanthan
Composition 16	95% silicone + 5% paraffin oil
Composition 17	Human saliva

Aequasyl®: oxidized glycerol triesters, silicon dioxide;
Biotène®: glycerol, xylitol, PEG 60, VP/VA copolymer, castor oil,
10 xanthan;
Oasis®: glycerol, sorbitol, poloxamer 338, PEG 60, castor oil, xanthan.

Results

The basal measurements carried out after lubrication reveal some variability. As these measurements were made on different substrates, this variability is easily explained. Thus, the overall average of the measured friction coefficients is of 1.12 including a standard deviation of 0.18. The maximum value is 1.51 and the minimum value is 0.73. The dispersion of the results is non-negligible which therefore induces the requirement of reasoning with absolute values of the friction coefficients and not with their variations expressed as percentages.

Fig. 1 illustrates the lubricating effect of the different tested compositions, i.e. the variation of the obtained friction coefficient after and before lubrication with a given composition. Composition 17 (human saliva) is obviously used as a reference, (black column). From this analysis it emerges that two groups may be distinguished. Ten compositions (white columns of Fig. 1) have a significantly lower effect than human saliva, three compositions of which (2, 13 and 16) prove to be anti-lubricating. Six compositions (shaded columns) have a lubricating effect comparable with human saliva. From among these efficient compositions, two commercial references are found, which validates the reliability of the test. However, a third commercial reference has a less significant lubricating effect, it even proves to be significantly lower than that of human saliva, this test is therefore quite restrictive. It appears to be interesting to correlate the lubricating effects with the components of each salivary composition. The three salivary substitutes of reference 1, 3 and 5 which have a strong composition similarity in flax extract, glycerol and xanthan gum and of cremophor 40 for references 1 and 3, do not seem to be convincing in terms of lubricating effect. The absence of flax extract and the addition of copolyvidone in reference 4 as compared with reference 3, tends to improve the lubricating

power. This comparison gives the possibility of setting aside the flax extract as a fundamental component of the substitutes. By observing the compositions and results associated with references 13 and 16, it is possible to draw the conclusion that the use of a silicone base does not seem to be appropriate for this problem. Both of these products have a reverse effect to the expected one and proportional to the amount of silicone used for the formulation. The flow properties of this viscoelastic constituent and its physico-chemical properties, surface tension relatively to the adhesive capabilities may be questioned. Also, the addition of yam extract in the composition of reference 2 seems to induce a negative effect on the lubricating power. By observing the composition of reference 6, it would seem that bovine mucin does not exert any influence on the lubricating power. However, reference 9 manages to satisfactorily mimick the operation of human saliva. Blanose and the carrageenate, both playing a role of thickeners probably participate in the good performances of this product, unless the high glycerol level is responsible for this good activity or performance. The results of reference 12 seem to show the opposite, but glycerol alone certainly does not give the possibility of attaining a sufficient effect. The comparison of both substitutes 14 and 15 is also in favour of a high glycerol content for good activity. If both of these references have a lubricating power comparable with that of human saliva, the best result is found for reference 14, containing 15% of glycerol versus 5% in the composition 15. The xanthan gum proportion may also be analysed by comparing references 11 and 15, where the only difference is the xanthan gum content, 0.4% versus 0.2%. The reference having the best lubricating power, it would seem that a xanthan gum level of 0.2% is sufficient. Finally only four compositions (references 9, 11, 14 and 15) manage to mimic satisfactorily the operation of human saliva. If lecithin is present in three of these compositions, glycerol is present in all these performing compositions. It

therefore seems to be tempting to build a composition on this fundamental constituent.

The commercial references are represented by the reference products 7, 8 and 10. These three compositions contain glycerol. But from among these three substitutes, only the products 8 and 10 seem to be satisfactory substitutes. It is interesting to note that in the commercial reference Aequasyl® which proves to be significantly less active than human saliva, glycerol is found as oxidized glycerol triesters. During this test, a composition was tested twice in order to check the reproducibility of the test. This is the case of reference 1. The gross variations (difference of the friction coefficient before and after lubrication) are 0.19 and 0.16, which demonstrates good reproducibility of this test.

Conclusions

It emerges from this test that the references 9, 11, 14 and 15 have a lubricating power close to that of human saliva. The component common to all these compositions seems to be glycerol, a high glycerol level may even prove to be fundamental.

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Example 2: sensorial test

The purpose of this study is to evaluate the sensorial characteristic "dry mouth sensation" during the use of a spray containing a composition according to the invention as compared with a competitive spray of the market.

A survey carried out on about 60 persons belonging to a sensorial analysis panel, was conducted in order to detect healthy subjects having a dry mouth sensation. A questionnaire, inspired from European criteria for detecting the Gougerot-Sjögren syndrome was used in order to detect subjects having subjective xerostomia. Thus, six subjects were identified and participated in the sensorial test. The dry mouth sensation was evaluated on an analogue visual scale from 0 to 100. During two successive sessions, the subjects test according to a

randomization plan, both sprays (a single use per session). The sprays are shown anonymously, the subjects carry out either four sprayings for the spray containing the composition according to the invention, corresponding all in all to 0.52 g of administered product, or two sprayings for the Aequasyl® spray corresponding all in all to 0.20 g of administered product.

- The comparator is the Aequasyl® spray, in a commercial conditioning made to be anonymous.
- The composition according to the invention was sprayed by means of a spray adapted to the composition, described below:

Ingredients	Amount (%)
Glycerol	35
Kollidon VA64	0.5
Macrogolglycerol 40 hydroxystearate	1.0
Xanthan gum	0.2
Xylitol	0.5
Benzyl alcohol	0.8
Potassium sorbate	0.4
Aroma	0.02
¼ diluted lactic acid	qs pH 6.25
Water	qs 100

A computer questionnaire shows the analogue measurement scales at the different phases of the experiment. The study consists in 6 successive phases, phase 1 is the dry mouth sensation before spraying, phase 2, immediately after spraying, phase 3 is the dry mouth sensation 5 minutes after spraying, phase 4, 10 minutes after spraying, phase 5, 15 minutes later, phase 6, 20 minutes after spraying, phase 7, 25 minutes later on, phase 8, 30 minutes later on, phase 9, 35 minutes later on and phase 10, 40 minutes after spraying. Each subject tests the imposed product by the randomization order, he/she moves a cursor

on a scale from 0 to 100 depending on the intensity felt at each of the phases.

The results of this sensorial study are summarized in Fig. 2. In a time-based analysis, the composition according to the invention administered with a spray gives the possibility of significantly reducing the dry mouth sensation for all the studied instants, 40 minutes after the four sprayings, the dry mouth sensation is still significantly attenuated. The commercial composition Aequasyal® substantially reduces in the same way the dry mouth sensation as the composition according to the invention.

Example 3: composition according to the invention

As an illustration of the object of the present invention, another exemplary composition will be mentioned.

Ingredients	Amount (%)
Macrogolglycerol 40 hydroxystearate	1.00
Glycerol	35.00
Xanthan gum	0.20
Xylitol	0.25
Kollidon VA64	0.50
Kollidon 30	1.50
Hydroglycerin marshmallow	1.00
Potassium sorbate	0.40
Benzyl alcohol	0.80
Potassium chloride	0.12
Disodium phosphate	0.56
Potassium phosphate	0.54
Water	58.13

Example 4: clinical study

The purpose is to evaluate the clinical efficiency and the safety of a composition according to the invention in relieving

xerostomia in patients having iatrogenic hyposialia, a commercial reference Aequasyal® was also tested as a comparison.

Methodology

5 The study was conducted in patients having xerostomia induced by drugs, iatrogenic hyposialia was objectified by a standard saliva test before their inclusion in the study. This study was carried out in a single centre, 24 patients were included, the efficiency which has to be very rapid is tested in a single day. Two
10 compositions are evaluated:

- the composition according to the invention, the composition of Example 3,
- the commercial reference, Aequasyal®.

Half an hour after breakfast, the product is administered with a
15 spray, three sprayings for the composition according to the invention, which corresponds to 0.6 g of administered product, and two sprayings for the commercial reference, corresponding to 0.2 g of administered product.

A second administration of the products is carried out 4 hours
20 later (three or two sprayings depending on the compositions) half an hour before the mid-day meal. The dry mouth sensation is evaluated by a computer questionnaire which shows scales of analogue measurements (same evaluation as for Example 2) ranging from 0 to 100, 0 being no dry mouth sensation and 100 being the
25 worst conceivable sensation of a dry mouth. The evaluation is made over at least 6 hours. After this test day, a "wash out" period from one to three days is left to the patients which then come back for a second evaluation, the patients which tested the composition according to the invention then test the commercial
30 reference and vice versa.

During the test period, other criteria were evaluated, such as for example the difficulty of talking, the difficulty of swallowing, but also the acceptance of the composition, potential secondary effects were also evaluated.

Results

- Dry mouth sensation

Before the first administration of the product, all the subjects
 5 complained of moderate buccal dryness, i.e. with a response equal
 to or greater than 40 mm on the analogue measurement scale
 ranging from 0 to 100 mm. Hyposalivation had been confirmed by a
 measurement of the salivary flow rate (under non-stimulation
 conditions) and which had to be less than or equal to 0.5 ml/min.
 10 The results illustrated in Fig. 3 show a similar reduction on
 this measurement scale between the composition according to the
 invention and the commercial reference. Fast reduction of the
 buccal dryness sensation is observed as soon as the first 5
 minutes after applying the compounds, with a slightly better
 15 response with the composition according to the invention and this
 up to 90 minutes. The effect of the second application made
 before the meal had the purpose of facilitating the intake of the
 meal and notably the ease for swallowing. The reduction level of
 the buccal dryness is substantial for both evaluated products.
 20 The table below shows the duration of action of the effect which
 is defined as a reduction of 20% of the buccal dryness sensation
 after the first and the second application.

Buccal dryness		Composition according to the invention	Commercial reference
First administration	Average	1 h 29 mins	1 h 08 mins
Second administration	Average	33 mins	33 mins

25 The composition according to the invention proves to have a
 longer period of action than that of the commercial reference.
 After the meal, this period of action is shortened for both

formulations, probably upon fast ingestion of the products during the meal.

- Other evaluation criteria

5 Other symptoms such as difficulty in talking, difficulty in swallowing, dryness of the throat and dryness of the lips are also evaluated. The composition according to the invention has a very interesting efficiency profile.

- Tolerance

10 No major secondary effect was reported during the study. Minor events notably at a digestive level were reported (one in each group), the composition according to the invention is therefore very well tolerated.

- Acceptance

15 Fig. 4 summarizes the estimation made by the patients of both tested products with different items like the taste of the product, its after taste, its texture or the overall evaluation of the product. The composition according to the invention is favourably received for the whole of the examined criteria. Very few bad sensations in the mouth like tinglings, irritations are
20 thus reported. The composition according to the invention is even better rated than the commercial reference for several very important criteria, such as the taste of the product, its aftertaste, its texture, its lubricating effect and even on the overall evaluation of the product. It appears to be slightly
25 setback only on one criterion which is the ease in spreading the product.

As a conclusion, this clinical study clearly demonstrates that the composition according to the invention has real efficiency in
30 reducing the dry mouth sensation at least in an equivalent way to the commercial reference and even has a longer period of action. It is very well tolerated and the patients consider it highly positively as regards acceptance.

Claims

1. Use of a pharmaceutical composition comprising at least one humectant in an amount from 15 % to 65 % by weight based on the total weight of the composition, one gelling agent and a derivative of polyvinyl alcohols as a film-forming agent, in the manufacture of a medicament for the treatment of hyposialia or asialia, and wherein the film-forming agent is a mixture of polyvinylpyrrolidone and of copolyvidone.
2. The use according to claim 1, characterized in that the humectant is glycerol.
3. The use according to any one of claims 1 or 2, characterized in that the gelling agent is xanthan gum.
4. The use according to any one of claims 1 to 3, characterized in that the amount of the gelling agent is comprised from 0.05 % to 1 %, preferably from 0.1% to 0.5% of the total weight of the composition.
5. The use according to any one of claims 1 to 4, characterized in that the amount of film-forming agent is comprised from 0.1% to 5%, preferably from 0.5% to 3% of the total weight of the composition.
6. The use according to any one of claims 1 to 5, characterized in that the composition further comprises a mucilage.
7. The use according to claim 6, characterized in that the mucilage comes from a marshmallow root extract.

8. The use according to any one of claims 1 to 7, characterized in that the composition further comprises one or several pH adjusters.
- 5 9. The use according to any one of claims 1 to 8, characterized in that the composition further comprises a mineralizing agent.
- 10 10. The use according to any one of claims 1 to 9, characterized in that the composition appears in an administrable form as a spray.
- 15 11. The use according to any one of claims 1 to 10, characterized in that the composition is in the form of a pharmaceutical presentation of the monodose type.
- 20 12. A pharmaceutical composition comprising at least one humectant in an amount from 15 % to 65 % by weight based on the total weight of the composition, one gelling agent and a derivative of polyvinyl alcohols as a film-forming agent, for use as a medicament, wherein said film-forming agent is a mixture of polyvinylpyrrolidone and of copolyvidone.