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(54) **Titre : UN DISPOSITIF DE DISTRIBUTION ORALE DE GOMME A MACHER DE POLYHEXANIDE**
(54) **Title: A CHEWING GUM ORAL DELIVERY SYSTEM FOR POLYHEXANIDE**

(57) **Abrégé/Abstract:**
The present invention relates to an oral delivery system comprising polyhexanide. The oral delivery system may for example be in a solid pharmaceutical form, such as in the form of a chewing gum. The oral delivery system may be used for example for the treatment and/or prophylaxis of pathogen-induced pathological changes in the oropharyngeal cavity, such as periodontal, pen-implant and other bacterial and viral diseases or fungal diseases in the area of the mouth and throat as well as halitosis.

ABSTRACT

The present invention relates to an oral delivery system comprising polyhexanide. The oral delivery system may for example be in a solid pharmaceutical form, such as in the form of a chewing gum. The oral delivery system may be used for example for the treatment and/or prophylaxis of pathogen-induced pathological changes in the oropharyngeal cavity, such as periodontal, peri-implant and other bacterial and viral diseases or fungal diseases in the area of the mouth and throat as well as halitosis.

A CHEWING GUM ORAL DELIVERY SYSTEM FOR POLYHEXANIDE

The present invention relates to an oral delivery system for the treatment and/or prevention of periodontal, peri-implant and other bacterial and viral diseases or fungal diseases in the area of the mouth and throat as well as halitosis (hereinafter: infectious pathological changes).

Infectious pathological changes occur very often and are the main reason for tooth loss/implant loss and halitosis in humans over 35 years of age. An infectious pathological change can be understood to mean an infection or inflammation of the gingival pocket, which, in several steps, can cause loss of the bone holding the tooth/implant. There are different degrees of severity of the condition. Lighter cases relate to the clinically termed gingivitis, whereas more severe cases are clinically called periodontitis/peri-implantitis.

Gingivitis is an inflammation of the gingiva (or of the gums), which is often caused by poor oral hygiene and/or the hormonal state of the patient. It is assumed that the untreated gingivitis develops into a periodontitis/peri-implantitis. Periodontitis is a bacterial disease which attacks the gingival tissue, the teeth, implants and the bone surrounding the teeth/implants.

The oral cavity is a substantially aerobe environment through which saliva is flowing. In contrast, the periodontal/peri-implant microenvironment is rather anaerobe and plasma filtrate is flowing through it, which is called "gingival crevicular fluid". The growth of microorganisms within this microenvironment is believed to be responsible for the occurrence of an infectious pathological change. Hence, treatment of said change is directed at monitoring and influencing said growth.

Trials in treating infectious pathological changes by agents which are administered into the oral cavity, such as antibacterial agents, have generally proved ineffective because the periodontal/peri-implant pocket is

substantially inaccessible. On the other hand, the systemic administration of antibiotics has only little success in treating periodontal diseases.

Antibacterial agents, such as chlorhexidine and quaternary ammonium salts, in the form of mouth rinses have proved somewhat effective in the prophylaxis/treatment of infectious pathological changes. These agents, however, have different disadvantages. For instance, they are often accompanied by side effects, such as discoloration of the teeth, tongue, mucous membranes or of dental prostheses. Furthermore, these agents oft have a bad taste and affect the patient's sense of taste. Moreover, these agents often disturb wound healing. In addition, the agents are regularly absorbed by the mucous membranes or by the gastro-intestinal tract, which may lead to systemic effects. Further, toxic metabolites are often produced from the mentioned agents. Another disadvantage lies in the mentioned agents usually having to be used in very high concentrations in order to achieve a corresponding effect. Further, allergenic potential was observed. Additionally, the mentioned agents often have irritant effects and do not have particularly long shelf lives. Moreover, it was observed that blood and proteins influence the effects of these agents.

Pharmaceutical compositions which exhibit a release of agents and which can be introduced into the periodontal cavity and slowly release an antimicrobial agent have been developed. For example, US 4,764,377 and US 4,892,736 disclose the introduction of tetracycline into non-degradable polymeric fibers which can be wound around the teeth and release the antibiotic in the periodontal cavity over several days. However, the fibers must be fixed in their place with an adhesive and be removed again at the end of the treatment method.

US 4,569,837 discloses the use of water-soluble polymeric substances (e.g. methyl cellulose, gelatin, etc.) as a polymeric matrix for a periodontal implant.

US 5,002,769 discloses a biodegradable system for oral administration with delayed release for treating periodontal diseases. The agent is embedded into a matrix of hydrolyzed gelatin which is cross-linked with glutaraldehyde.

The above-described compositions show varying effectiveness in reducing the bacterial load in the periodontal pocket and in reducing the depth of the pocket. Moreover, these compositions often have the above-mentioned disadvantages.

It is the object of the present invention to provide an effective delivery system for the treatment and/or prevention of infectious pathological changes which is easy to use and effective at the same time.

The object is attained by an oral delivery system of the kind mentioned in the introduction, which comprises polyhexanide.

Polyhexanide has been found to be particularly effective in the use of oral delivery systems for treating and/or preventing periodontal diseases. Polyhexanide can in particular be used in the kind of delivery systems by means of which a slow release in the area of the gingival pockets is to be achieved so that a prolonged contact time is accomplished.

In a preferred version of the oral delivery system, the latter is in a solid pharmaceutical form. A solid pharmaceutical form is particularly advantageous in the use of the system.

In a preferred embodiment of the oral delivery system, the latter is in the form of a chewing gum. Among other advantages, chewing gums counteract the delayed effect observed in polyhexanide because they can be easily used by the patient over a longer period of time, which would be a problem with mouth rinses, for example.

Chewing gum is generally composed of the following groups of raw materials: gum base or gum mass, plasticizers, filler materials, lubricants, fats,

emulsifiers, aromas, dyes, antioxidants, and edible acids for flavoring. As gum mass, either natural materials such as chicle, gutta-percha, latex, benzoin resins or gum arabic or consistency-providing, synthetic thermoplastics, such as polyvinyl acetate in amounts of up to 65 % of the gum mass, polybutadiene styrene, polyisobutylene, isoprene, polyvinyl ether, and polyethylene can be used.

Typical plasticizers are emulsifiers, resins, waxes or glucitol. Typical filler materials are magnesium stearates, chalk, calcium carbonate, silicate or celluloses. The filler materials and technical auxiliary substances maintain flowability and prevent clumping of the particles at low pressure. Mineral oils, microcrystalline waxes or herbal oils are typically used as lubricants, fats or emulsifiers. These auxiliary substances prevent clumping of the instruments and to the instruments.

Traditional chewing gums can be highly cariogenic because of their high sugar content, but they also massage the gingiva and the salivary glands in case of dry mouth. Chewing gums are also refreshing, vitalizing and/or thirst-quenching owing to the added flavorings.

To avoid the above-mentioned cariogenic effect of sugar in chewing gums, sugar-free chewing gums have been on the market for a long time. Instead of sugar, they contain sugar substitutes, which are mainly sorbitol and xylitol.

The chewing gum according to the invention is intended to support teeth and mouth hygiene and for the treatment/prevention of infectious pathological changes. It is particularly suited for on the go, when there is no opportunity to brush the teeth. The chewing gum according to the invention is usually sugar-free and, similarly to tooth paste, contains traces of minerals for the regeneration of the teeth. The chewing gum according to the invention can also comprise at least one abrasive, in particular calcium carbonate, calcium phosphates, metaphosphates, silicic acid, aluminum oxides, silicates and/or talcum.

Further, the chewing gum according to the invention can comprise at least one suspending agent or a humectant, in particular water, glycerin, propylene glycol and/or sorbitol syrup, and at least one thickening agent, stabilizer and/or binder, in particular gels, starches, alginates, oils and/or cellulose gum.

For improving the taste properties, at least one aromatic substance, at least one sweetener and/or at least one sugar substitute, in particular menthol, peppermint oil, sodium saccharin, aspartame, acesulfame, sorbitol, maltitol, xylitol and/or fructose, may be added to the chewing gum.

Moreover, the chewing gum according to the invention may comprise further chemical additives, dyes and/or ph regulators, in particular fluorides, astringents, inflammation inhibitors, desensitizers, vitamins, panthenol, white pigments and/or sodium hydroxide.

By way of the oral delivery system according to the invention in the form of a chewing gum, the polyhexanide can reach the site of action, in particular the gingival pockets, in a particularly effective manner. The chewing process presses the chewing gum into the gingival pocket, where the polyhexanide is then released.

In another embodiment of the delivery system according to the invention, the latter is in the form of a chip or film, comprising a biodegradable or bioerodible pharmaceutically acceptable polymer.

The chip or film according to the invention is suitable for being implanted into a periodontal pocket and is capable of treating infectious pathological changes in which a delayed release of polyhexanide is desired. The pocket can be a natural pocket, it can be related to a state of disease or it can be intentionally opened as part of the treatment. After implantation, the chip or film softens, swells up and changes into a soft paste, which adheres to the inside of the pocket.

Preferably, the chip or film can comprise at least one cross-linking agent, which is present in an amount sufficient to make the polymer water-insoluble while permitting the release of the polyhexanide from the delivery system.

The film or chip according to the invention preferably comprises a surfactant, which is preferably selected from anionic, cationic and non-ionic surfactants. The non-ionic surfactants can be selected from polyoxyethylene sorbitan fatty acid esters (polysorbate) and sorbitan fatty acid esters.

The chip or film according to the invention is preferably adapted to be administered into a periodontal pocket with in-vivo releasing properties which are aimed at reducing the depth of a periodontal pocket of a patient.

Advantageously, the chip or film according to the invention is in such a form that it is biodegraded within the periodontal pocket, wherein it becomes soft and adheres to the periodontal pocket and wherein, once inserted in a periodontal pocket, it gradually releases the polyhexanide over a period of at least about 24 hours, during which the chip or film converts into a soft material. The chip thus serves as a medium of delivery of polyhexanide as antimicrobial agent for application into the sulcus or gingival pocket. The size of a chip/film according to the invention is generally 3x3 – 10x10 mm. In general, the base of the chip/film is a gelatin cross-linked with glutaraldehyde. Cross-linked gelatin has proved particularly suitable for the delayed release of polyhexanide.

Advantageously, the polymer is selected from water-soluble protein, cellulose or a cellulose derivative, starch or a starch derivative, glyceryl monostearate, carbomer, PVP (polyvinyl pyrrolidone), gum, acacia gum, guar gum, polyvinyl alcohol, polyhydroxyethyl methacrylate, polyhydroxymethyl methacrylate acrylic acid, polyacrylamide, polyethyleneglycolene, polyacetic acid, polyglycolic acid, copolymers of polyacetic acid and polyglycolic acid, polyanhydrides and polyorthoesters. The water-

soluble protein is preferably selected from the group consisting of gelatin, collagen, albumin, an enzyme and fibrinogen.

In another embodiment of the system according to the invention, the latter is in the form of a gel or salve. In this form, it is usually introduced into the gingival pockets, where it releases polyhexanide to the surroundings.

The gel or salve according to the invention is for intraoral application, in particular for application into the sulcus or into a gingival pocket. The polyhexanide here again serves as an antimicrobial agent. The gel/salve according to the invention can be based on a conventional ethanol/glycerol/macrogol compound.

The gel according to the invention or the salve according to the invention can be both a ready-to-use preparation and a mixing system. In case of a mixing system, certain components are mixed only shortly prior to the application and brought to the diseased site. This has the advantage, among others, that a mixing system is easy to process after mixing. For instance, in one embodiment, a viscous mass may at first be present after mixing which hardens only after it has been introduced into the mouth. This significantly simplifies the application. The mixing system can be in the form of a mixing capsule, for example.

As compared to the known antibacterial agents, such as chlorhexidine, the oral delivery system according to the invention has decisive advantages. For instance, the polyhexanide used in the oral delivery system according to the invention is not cytotoxic. Additionally, no side effects, such as discoloration of the teeth, tongue, mucous membranes or of dental prostheses can be observed. The used polyhexanide is tasteless and does not compromise the sense of taste. Further, it does not disturb wound healing and reduces fibrin formation. Furthermore, it is not known to be absorbed by the mucous membranes or via the gastro-intestinal tract. Further, no toxic metabolites form during use. Another significant advantage lies in the fact that the effective concentration of polyhexanide is many times

lower than that of chlorhexidine, for example. Further, polyhexanide has no allergenic potential and no irritant effect. As far as is known, polyhexanide is not sensitizing. The shelf life of polyhexanide is also longer than in conventional agents. Moreover, no delevopement of resistance has been observed. Polyhexanide has a broad effective spectrum and shows very little protein and blood interference (effect is hardly influenced by proteins or blood).

Claims

1. An oral delivery system for the treatment and/or prevention of infectious pathological changes in the area of the mouth and throat, comprising polyhexanide, wherein the system is in the form of a chewing gum.

2. The oral delivery system according to claim 1, further comprising at least one suspending agent or a humectant.

3. The oral delivery system according to claim 2, wherein the at least one suspending agent or humectant is water, glycerin, propylene glycol and/or sorbitol syrup.

4. The oral delivery system according to any one of claims 1 to 3, further comprising at least one thickening agent, stabilizer and/or binder.

5. The oral delivery system according to claim 4, wherein the at least one thickening agent, stabilizer and/or binder is a gel, a starch, an alginate, an oil and/or a cellulose gum.

6. The oral delivery system according to any one of claims 1 to 5, further comprising at least one aromatic substance, sweetener and/or sugar substitute.

7. The oral delivery system according to claim 6, wherein the at least one aromatic substance, sweetener and/or sugar substitute is menthol, peppermint oil, sodium saccharin, aspartame, acesulfame, sorbitol, maltitol, xylitol and/or fructose.

8. The oral delivery system according to any one of claims 1 to 7, further comprising further chemical additives, dyes and/or pH regulators.

9. The oral delivery system according to claim 8, wherein the further chemical additives, dyes and/or pH regulators are fluorides, astringents, desensitizers, vitamins, panthenol, white pigments and/or sodium hydroxide.

10. An oral delivery system comprising polyhexanide, wherein the system is in the form of a chewing gum.

11. The oral delivery system according to claim 10, further comprising at least one suspending agent or a humectant.

12. The oral delivery system according to claim 11, wherein the at least one suspending agent or humectant is water, glycerin, propylene glycol and/or sorbitol syrup.

13. The oral delivery system according to any one of claims 10 to 12, further comprising at least one thickening agent, stabilizer and/or binder.

14. The oral delivery system according to claim 13, wherein the at least one thickening agent, stabilizer and/or binder is a gel, a starch, an alginate, an oil and/or a cellulose gum.

15. The oral delivery system according to any one of claims 10 to 14, further comprising at least one aromatic substance, sweetener and/or sugar substitute.

16. The oral delivery system according to claim 15, wherein the at least one aromatic substance, sweetener and/or sugar substitute is menthol, peppermint oil, sodium saccharin, aspartame, acesulfame, sorbitol, maltitol, xylitol and/or fructose.

17. The oral delivery system according to any one of claims 10 to 16, further comprising further chemical additives, dyes and/or pH regulators.

18. The oral delivery system according to claim 17, wherein the further chemical additives, dyes and/or pH regulators are fluorides, astringents, desensitizers, vitamins, panthenol, white pigments and/or sodium hydroxide.