

BLISTER PACKAGING AND KIT THEREWITH

The present invention relates to an improved packaging for an active agent, e.g., peptides that need to be stored in dry form and dissolved before application, for example, self-assembling peptides such as P11-4. In particular, the present invention provides a blister packaging that can be both conveniently used and more cheaply produced than previous packaging. The invention also relates to use thereof in application of the peptide, e.g., in treatment of caries lesions. In one embodiment, the blister packaging comprises a blister sheet with at least one first cavity, a cover sheet laid over and bonded to the blister sheet, wherein the at least one first cavity comprises a porous support coated with an active agent, and, advantageously, a stabilizing cavity reducing wobbling of the blister packaging during the process of dissolving the active agent, preferably, a V-shaped stabilizing cavity.

Tooth decay, also known as dental caries, is one of the most ubiquitous bacterial infections in the world. It is a breakdown of tooth material due to bacterial metabolites, mainly acids made by bacteria when they break down food debris or sugar on the surface or in the biofilm of the teeth. This leads to an imbalance between demineralisation and remineralisation processes. Hard tooth structures, i.e., enamel, dentin and cementum, are damaged by ongoing demineralisation, which results in carious lesions and eventually in the appearance of caries cavities. The earliest sign of a new carious lesion is the appearance of a chalky white spot on the surface of the tooth, a so-called white spot lesion (also designated an incipient carious lesion), i.e. a subsurface lesion. As the demineralisation progresses, the mineralised surface of the lesion (partially) collapses and breaks and a microcavity or a cavity, a hole in the tooth, appears. This is referred to as a (partially) cavitated carious lesion or cavitated carious lesion.

Caries preventative approaches including topical fluoride therapy and application of dental sealants, also known as pit and fissure sealants, have been described. Non-invasive approaches have been suggested for non-cavitated carious lesions, i.e. subsurface lesions. For example, remineralisation is attempted by the application of topical fluoride.

Furthermore, enamel matrix derivatives or self-assembling peptides have been shown to be effective in the remineralisation of subsurface carious lesions (Ruan et al., 2013, *Acta Biomater.* 9(7):7289-97; Ruan et al., 2014, *J Vis Exp.* 10(89), doi 10.379151606; Schmidlin et al., 2016, *J Appl Oral Sci.* 24(1), 31-36; Alkilzy et al., 2018, *Adv Dent Res.* 29(1), 42-47; Brunton et al., 2013, *Br Dent J*, 215:E6; Kind et al., 2017, *J Dent Res.*, 96(7), 790-797; Kirkham et al., 2007, *J Dent Res.*, 86, 426-430). In WO 2014/027012 A1, a method for the targeted delivery of a self-assembling peptide to a subsurface tooth lesion with the aim of remineralising carious lesions is

described. Alkilzy et al. (2018, above) found an additional effect of the application of P11-4, a self-assembling peptide, to early carious lesions, in combination with fluoride, compared to the application of fluoride alone. Further, WO2021/005153 A1 teaches prevention and treatment of cavitated caries lesions with self-assembling peptides.

Amelogenin-based biomineralisation approaches for tooth repair have been described in the context of dentinal hypersensitivity, whitening or bleaching of teeth, and the treatment of caries in WO 2017/123986 A1, US 2014/0186273 A1 and US 2017/0007737 A1.

In WO 2017/168183 A1, a biomimetic mineralised apatite structure based on elastin-like peptides is described for use as dental restorative material, in particular for the reconstruction of enamel, and for use in the treatment of dental diseases such as dental caries.

Furthermore, casein-based strategies have been developed for remineralisation of enamel and prevention and/or treatment of caries or tooth erosion (e.g. WO 00/06108 A1 and WO 2010/042754 A2). Casein phosphopeptide amorphous calcium phosphate complexes (CPP-ACP) and CPP-stabilised amorphous calcium fluoride phosphate complexes have been described in combination with glass-ionomer cement as remineralising dental restorative materials, e.g., in WO 02/094204 A1. Some studies have also shown that caries progression is slowed or arrested under sealants when applied to non-cavitated carious lesions (Griffin S.O. et al., 2008, J Dent Res., 87(2), 169-174).

Thus, peptides may play an important role in prevention and treatment of caries. In particular, self-assembling peptides such as P11-4 are already successfully used for treatment of sub-surface caries lesions. However, so far, more wide-spread use is hampered by the costs of treatment. The use of self-assembling peptides in treatment of caries lesions is rendered more difficult by the fact that the peptide should to be monomeric, in particular, for treatment of sub-surface lesions, because assembled peptides cannot diffuse into the enamel and contribute to thorough remineralisation. In the presence of water, the self-assembling peptides tend to assemble. Assembly can be controlled by pH adaptation, but in clinical practice, adapting the pH before application, as e.g., done by Alkilzy et al. (above) is impractical. Therefore, on the basis of WO 2014/027012 A1, a method for producing a dry composition ready for treatment of a caries lesion upon resuspension was developed. Currently, a sponge coated with a peptide composition produced according to said method is clinically used in an applicator with a separate chamber comprising a liquid (Curodont Repair, Credentis AG, Switzerland), and for application, the liquid from said separate chamber is used to resuspend the peptide. It can then be administered with the sponge. However, production of these applicators is expensive, a lot of plastic waste is produced, and if a plurality of lesions are to be treated, it is not very comfortable to use.

It is therefore the object of the invention to at least partially overcome drawbacks mentioned above and to provide a packaging which is easy and comfortable to handle and which helps to make the day-to-day business of dentist's offices more efficient.

This object is achieved by the present invention, in particular, by the claimed subject-matter.

The invention provides a blister packaging comprising a blister sheet with at least one cavity and a cover sheet laid over and bonded to the blister sheet surrounding the at least one cavity, wherein the at least one cavity of the blister comprises a poriferous support coated with an active agent, e.g., a peptide.

This configuration allows for an easy handling of the support that is already coated with an adequate dose of peptide sufficient for the treatment of at least one lesion. The support can be safely stored, in the absence of water. Directly before treatment, it can be, e.g., as provided herein, contacted with a desired amount of a liquid such as a buffer or, preferably, sterile water. This leads to resuspension of the peptide, which can then be applied to a caries lesion.

For treatment of caries lesions, as explained above and known in the art, it is beneficial if the peptide is a self-assembling peptide in monomeric form. Assembled (polymeric) peptide can be used for other purposes, e.g., for treatment of tooth sensitivity or for preventing tooth erosion.

Peptides that may be used in dental treatment, e.g., caries treatment or prevention, are known in the art, and, e.g., mentioned herein. For example, self-assembling peptides (SAP) are known for their excellent characteristics in treatment and prevention of caries lesions (e.g., WO 2004/007532 A1). WO 2004/007532 A1 discloses peptides that are capable of forming three-dimensional scaffolds, thereby promoting nucleation of de-novo calcium phosphate. These artificial peptides assemble in one dimension to form beta-sheet, and higher order assemblies such as tape-like assemblies. Three-dimensional supramolecular structures of SAP can be formed, which have an affinity for/ to calcium phosphate.

In the context of the present invention, self-assembling peptides taught in WO 2004/007532 A1, US10/521,628, US12/729,046, US13/551,878, US 14/062,768, or WO2014/027012 A1, which are all fully incorporated herein by reference, are preferred. In particular, self-assembling peptides having a net charge of +2 or -2 at pH 7.5, may be used in monomeric or assembled form.

Self-assembling peptides used in the present invention preferably comprise a sequence of the formula X1-X2-X1-X2-X1, wherein X1 is an amino acid with an acidic side chain and X2 is an amino acid with a hydrophobic side chain. For example, the self-assembling peptide used in the

present invention comprises the consensus sequence SEQ ID NO: 1, X1-X2-X1-X2-X1, wherein X1 is independently selected from the group consisting of glutamic acid, aspartic acid, glutamine and ornithine, and X2 is independently selected from the group consisting of alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan and glutamine, or an amino acid sequence having at least 80% identity thereto. Independently selected means that, e.g., X1 in positions 1, 3 or 5 of the sequence above can be different from each other. Of course, they can also be identical.

Preferably, self-assembling peptides used in the invention comprise SEQ ID NO: 2, X1-X2-X1-X2-X1, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine, and X2 is independently selected from the group consisting of tryptophan and phenylalanine.

In a further embodiment, self-assembling peptides used in the invention may comprise SEQ ID NO: 3, X3-F-X1-W-X1-F-X1, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine, and X3 is selected from the group consisting of arginine, glutamic acid and ornithine, wherein X3 preferably is arginine.

Furthermore, self-assembling peptides used in the invention may comprise SEQ ID NO: 4 or, preferably, consist thereof: X4-X4-X3-F-X1-W-X1-F-X1-X4-X4, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine, and wherein X3 is selected from the group consisting of arginine, glutamic acid and ornithine, and wherein X4 is independently selected from the group consisting of glutamine, glutamic acid, serine, threonine and ornithine. X3 preferably is arginine. Independently, X4 preferably is glutamine.

Self-assembling peptides of the invention may comprise SEQ ID NO: 5, or, preferably, consist thereof: Q-Q-R-F-X1-W-X1-F-X1-Q-Q, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine.

Preferably, the self-assembling peptides used in the present invention comprise or consist of a sequence selected from the consensus sequences listed in Table 1 below.

Most preferably, said peptides comprise the specific peptides listed in Table 2 or consist thereof. Of course, self-assembling peptides assembling in combination with another self-assembling peptide, e.g., as disclosed herein, may be formulated in one kit or in one composition.

Peptides of SEQ ID NO: 6, 9, 11, 12, 16 or 17 are particularly advantageous, e.g., as they can be used in relatively low concentrations, they are highly compatible with cells and have beneficial charge distribution.

Preferably, the self-assembling peptide comprises the sequence of SEQ ID NO: 6 or consists thereof. A peptide consisting of a sequence of SEQ ID NO: 6 is also designated P11-4, and is preferred throughout the invention. In another preferred embodiment, the self-assembling peptide comprises the sequence of SEQ ID NO: 9 or consists thereof (P11-8).

The kit or composition of the invention may also comprise at least one self-assembling peptide having at least 45% sequence identity to a peptide consisting of SEQ ID NO: 6. Preferably, the peptide has at least 54%, at least 63%, at least 72%, at least 81% or at least 90% sequence identity to a peptide consisting of SEQ ID NO: 6, or is said peptide. Peptides of the invention are, for example, 11 amino acids in length.

Self-assembling peptides may be modified peptides comprising an Ac-N-terminus and/or NH₂-C-Terminus, preferably, both, or non-modified peptides. As non-blocked forms tend to start a deamination reaction, the termini of all self-assembling peptides of SEQ ID NO: 1 are preferably blocked to increase stability. In particular, peptides of SEQ ID NO: 6, 9, 11, 12, 16 and 17 may comprise an Ac-N-terminus and NH₂-C-Terminus. SEQ ID NO: 18-29 correspond to modified peptides of the invention.

Table 1: Consensus sequences of preferred self-assembling peptides

SEQ ID NO	Peptide name	Sequence	Exemplary SAP
SEQ ID NO: 1	Consensus sequence 1	X1-X2-X1-X2-X1, wherein X1 is independently selected from the group consisting of glutamic acid, aspartic acid, glutamine and ornithine, and X2 is independently selected from the group consisting of alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan and glutamine	P11-2, P11-4, P11-5, P11-8, P11-12, P11-13, P11-14, P11-17, P11-19, P11-20, P11-28, P11-29
SEQ ID NO: 2	Consensus sequence 2	X1-X2-X1-X2-X1, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine, and X2 is independently selected from the group consisting of tryptophan and phenylalanine	P11-4, P11-8, P11-12, P11-13, P11-14, P11-17, P11-28, P11-29

SEQ ID NO: 3	Consensus sequence 3	X3-F-X1-W-X1-F-X1, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine, and X3 is selected from the group consisting of arginine, glutamic acid and ornithine, wherein X3 preferably is arginine	P11-4, P11-8, P11-12, P11-13, P11-14, P11-17, P11-28, P11-29
SEQ ID NO: 4	Consensus sequence 4	X4-X4-X3-F-X1-W-X1-F-X1-X4-X4, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine, and wherein X3 is selected from the group consisting of arginine, glutamic acid and ornithine, and wherein X4 is independently selected from the group consisting of glutamine, glutamic acid, serine, threonine and ornithine. X3 preferably is arginine. Independently, X4 preferably is glutamine.	P11-4, P11-8, P11-12, P11-13, P11-14, P11-17, P11-28, P11-29
SEQ ID NO: 5	Consensus sequence 5	Q-Q-R-F-X1-W-X1-F-X1-Q-Q, wherein X1 is independently selected from the group consisting of glutamic acid and ornithine.	P11-4, P11-8

Table 2: Preferred self-assembling peptides. Positions X1 are underlined

SEQ ID NO	Peptide name	Sequence (One letter code)	% amino acid identity to P11-4 (ClustalW (2.1, standard parameters))
SEQ ID NO: 6	P11-4	QQRFE <u>W</u> FE <u>W</u> EQQ	100
SEQ ID NO: 7	P11-2	QQRFQ <u>W</u> Q <u>W</u> FE <u>W</u> EQQ	81.8
SEQ ID NO: 8	P11-5	QQRFQ <u>W</u> Q <u>W</u> FQQQ	72.7
SEQ ID NO: 9	P11-8	QQRFQ <u>W</u> Q <u>W</u> FE <u>W</u> EQQ	81.8
SEQ ID NO: 10	P11-12	SSRFQ <u>W</u> Q <u>W</u> FE <u>W</u> ESS	45.4
SEQ ID NO: 11	P11-13	EQFE <u>W</u> FE <u>W</u> FEQE	72.7

SEQ ID NO: 12	P11-14	QQOFQWQFQQ	63.6
SEQ ID NO: 13	P11-17	TTRFEWFEETT	63.6
SEQ ID NO: 14	P11-19	QQRQQQQEQQ	54.5
SEQ ID NO: 15	P11-20	QQRQEQQEQQ	72.7
SEQ ID NO: 16	P11-28	OQOFQWQFQQ	45.4
SEQ ID NO: 17	P11-29	QQEFEWFEQQ	90.9
SEQ ID NO: 30	P11-16	NNRFQWQFNN	45.4
SEQ ID NO: 31	P11-18	TTRFQWQFETT	45.4
SEQ ID NO: 32	P11-26	QQOQQQQQQQ	36.4
SEQ ID NO: 33	P11-31	SSOFQWQFSS	27.3

The self-assembling peptides preferably do not have restriction sites for the subject's endopeptidases. They also do not need to comprise a special recognition motif for cells.

In a preferred embodiment, the peptide is a P11-4 self-assembling peptide having SEQ ID NO: 6.

The peptide in monomeric form is preferably prepared as disclosed in WO 2014/027012 A1, so that it can be directly used after being resuspended in water. In the context of the invention, the resuspended peptide solution can be transferred from the packaging to the tooth surface using the poriferous support. The support can, e.g., be held with a pincer, and the tooth surface contacted with the support. The tooth surface is advantageously pretreated to remove plaque and biofilm, e.g., as disclosed by Alkilzy et al (above) or in the instructions for use of Cu-rodont Repair.

The amount of peptide coated on the support may vary, e.g., depending on the number of cavities for treatment of which it is intended. For example, 0.1 to 10 mg of peptide (preferably, self-assembling peptide, e.g., P11-4) may be coated on one support, such as 0.5 to 5 mg, preferably, 1-2 mg or 1.4 to 1.6 mg.

The active agent can also be a protein, e.g., a growth factor, or a peptide that is not a self-assembling peptide, or a non-peptide active agent such as a small molecule (e.g., an organic compound having a molecular weight of 800 or less kDa) which can be used for any pharmaceutical purpose. The advantages of the inventive blister packaging are particularly relevant if the active agent is in dry form and needs to be resuspended in a liquid before use. A plurality of active agents can also be present, e.g., an antibiotic in combination with a self-assembling peptide or with a growth factor.

In an advantageous embodiment the blister packaging comprises a plurality of cavities comprising a poriferous support coated with a peptide. Such cavities are designated first cavities. In this way the poriferous supports can be packaged by known in the art packaging machines in large quantities, which reduces costs of the inventive blister package. The blister sheet can also be referred to as a blister for short.

For example, one blister sheet can comprise one first cavity. The at least one first cavity in the blister sheet comprises a bottom and at least one surrounding side wall. While the bottom of the cavity can also be rounded, typically, the bottom of the cavity and the surrounding side wall(s) have an angle of about 90° to each other. Optionally, the side wall is linked to the bottom by at least one corner, optionally, by two corners, for example, each formed by walls having an angle of about 45° to each other. The shape of the first cavity, seen from above (i.e., from the side at which the blister sheet is bonded to the cover sheet, which is opposite to the bottom of the cavity, can e.g., be round, square or hexagonal. Corners may help a person using the blister packaging to get good hold of the support, e.g., with tweezers.

Further, the blister packaging might comprise at least one second cavity, optionally, a plurality of second cavities comprising a liquid, wherein such cavities are designated second cavities. Therewith, the already dosed liquid for activating the peptide coating can be provided by the same blister packaging. This reduces preparation workings for the poriferous peptide coated support, as both components for the treatment of the tooth surfaces can be provided simultaneously.

The packaging may alternatively contain a liquid in another container, e.g., in a single use ampoule, for example as used for eyedrops.

The liquid is a water-based liquid. It can be a buffer, but, preferably, it is water, such as sterile water.

In an advantageous embodiment, the liquid is an aqueous solution which preferably comprises a fluoride salt, e.g., sodium fluoride, stannous fluoride or ammonium fluoride.

The amount of liquid is chosen based on the amount of peptide on the support, e.g., to yield a peptide concentration of about 0.1-100 mg/mL, such as 1-50 mg/mL, preferably, 5-20 mg/mL or about 10 mg/mL. For example, the volume of the liquid can be 10 µL to 1 mL, e.g., 16 µL to 500 µL, 50 µL to 200 µL or 100 to 150 µL, preferably, about 100 µL.

In one embodiment of the blister packaging, adjacent to each first cavity, a second cavity is arranged. Optionally, each blister packaging, in particular, each blister sheet, only comprises

one first and one second cavity, but it may also comprise a plurality of first and second cavities.

In another advantageous embodiment of the blister packaging, the blister sheet comprises, in addition to the first cavity and, optionally, the second cavity, at least one stabilizing cavity. Optionally, the stabilizing cavity does not comprise any solid or liquid substance. It may comprise a gas, e.g., air or nitrogen, typically the same as other cavities.

The at least one stabilizing cavity is located at least at three points, a first point, a second point, and a third point, each arranged in a predetermined distance from the centre of the first cavity, wherein the first and the third points are on opposite sides of the centre of the first cavity on a first line intersecting the first cavity, and the second point is arranged on a second line intersecting the first line between the first and the third points at an angle of about 90°, preferably, 90°C.

Said blister packaging is comfortable to handle during dental therapy, as the stabilizing cavity supports the blister packaging, in particular the blister sheet and the first cavity, when set on a plane surface. It prevents wobbling of the blister sheet during handling, in particular, while the liquid is added to the first cavity with the poriferous support and while the active agent is being dissolved. Because of the arrangement of the stabilizing cavity and its extension through said three points the stabilizing cavity surrounds the first cavity at least partly (seen from above), and thereby prevents wobbling of the blister sheet and potential spillage of the liquid.

The at least one stabilizing cavity and the at least one first cavity do not overlap each other. Accordingly, the at least one stabilizing cavity and the at least one first cavity are independently formed within the blister sheet.

The first, second and third points are arranged in a predetermined distance from the centre of the one first cavity. The centre of the at least one first cavity is the geometric centre of the shape of the at least one first cavity. The predetermined distances of the three points can be individually predetermined, i.e., they can be different from each other. Preferably, they are the same. The predetermined distances may be 1 cm or more, e.g. 1 cm to 5 cm, optionally, about 2 cm. The distance is limited by the edge of the blister sheets and the extension of the first cavity. However, the larger the distance, the more stable the blister sheet.

The angle between the first and second lines is measured as the smaller angle between these two lines. "About", in the context of the present invention, should be understood as +/- 10%. In

one embodiment, the first and the second line intersect in the first cavity, e.g., in the centre of the first cavity.

While the three points P1, P2 and P3 of the at least one stabilizing cavity can be formed as individual cavities, in a preferred embodiment, the stabilizing cavity links said three points with each other. Preferably, the stabilizing cavity is formed between the first point, the second point and the third point in this particular order. It can thus be (viewed from the top), a V-shaped cavity, wherein the first cavity with the poriferous support is located between the arms of the V, optionally, between the endpoints of the arms of the V. This shape gives good stability and allows for easy access to the first cavity for removing the cover sheet and handling the poriferous support.

The shape of the at least one stabilizing cavity is not limited by said three points. It may also extend over one or more of these, e.g., it may also be defined by more points not specified herein. For example, the shape of the at least one stabilizing cavity may be U-formed, rectangular, hexagonal or circular.

Preferably, the blister packaging only comprises one first cavity and one stabilizing cavity. The only one first cavity can be favourably arranged in relation to the stabilizing cavity, in particular between limbs of a V-shaped stabilizing cavity.

Preferably, the blister package has a total length between 40 and 70 mm and a total width of 30 to 60 mm. Due to these dimensions of the blister package, the blister package can be easily picked up and handled, e.g. by two fingers. The preferred dimensions also improve the overall handling of the blister package in general, e.g. during packaging, transport and storage.

The depth of the stabilizing cavity is at least equal or greater relative to depth of the first cavity. Optionally, the depth of the stabilizing cavities is 4 to 8 mm, e.g. 5 to 6 mm. The depth is measured perpendicular to the length and width direction of the blister sheet, from the top side of the blister sheet, where it is bonded to the cover sheet, to the bottom side of the bottom of the cavities, i.e. on the outer side.

A width of the at least one stabilizing cavity may be between 2 to 8 mm, more preferably between 3 to 5 mm. Preferably, the stabilizing cavity has a constant width. Thereby a compact design of the blister packaging can be achieved, comprising favourable flexural rigidity in the length direction of the blister sheet. This facilitates removal of the cover sheet.

The packaging therefore solves in reliable manner the problem of conveniently handling and providing two components simultaneously, which otherwise may have to be prepared or pH adapted shortly before a treatment or provided in a complicated applicator. This reduces the preparation workings of professional dental stuff or cost and is beneficial for the day-to-day business at a dentist's offices.

The bonding of the cover sheet to the blister sheet in the blister packaging of the invention maintains in dry environment in the cavities of the blister that comprise the peptide-coated poriferous supports. The bonding is thus airtight and water-tight. This can be carried out by hot sealing or gluing the cover sheet onto the blister sheet which contributes to a sterile airtight enclosure of the coated support.

The cover sheet may be firmly attached to the blister sheet, e.g., to provide a push-through pack. A push-through pack comprises a cover sheet that is brittle, making it possible to press the support out while breaking the cover sheet, and/or by a semi-rigid formed cavity being sufficiently collapsible to be able to dispense the poriferous support by means of pressing it out with the thumb. Additionally, breaking the cover sheet with an object like a tweezer or a fingernail may make the pressing out easier.

Alternatively, and preferably, the cover sheet may be removably attached to the blister sheet. Removably attached in the context of the invention means that it is easily possible to remove the cover sheet from the blister sheet by hand and without undue force. In particular, the force should not lead to shaking of the packaging that may lead to the support falling out. Preferably, removal is possible with one hand. A flap of the cover sheet, e.g., at the edge of the blister packaging may be loose to simplify holding and removing the sheet. Thus, the user can easily access the support lying in the cavity.

Further, the cover sheet may be removably attached, as described herein, and the blister packaging comprises a plurality of cavities. In this case, preferably, the cover sheet may be individually removable for each cavity comprising a poriferous support coated with a peptide. If second cavities comprising a liquid are present, the cover sheet over these may, optionally, similarly be individually removable. If stabilizing cavities are present, the cover sheet over these may, optionally, similarly be individually removable.

Optionally, the cover sheet is individually removable for each pair of first and second cavities together, i.e., the cover sheet for both first and second cavity of an adjacent pair of cavities is removable together without disturbing the cover sheet over other cavities. In a preferred embodiment, the blister sheet only comprises first cavities and stabilizing cavities, and the cover sheet is individually removable for each pair of first and stabilizing cavities together, i.e., the

cover sheet for both first and stabilizing cavity of an adjacent pair of cavities is removable together. If there are more than one pair of first and stabilizing cavities, this is possible without disturbing the cover sheet over other cavities. This enables a comfortable handling of the respective cavities.

To allow for individually removing (or individually removing together) certain regions of cover sheet, the cover sheet, when bonded to the blister sheet, may comprise a perforation, which enables the user to individually remove the cover sheet from a certain cavity or pair of cavities. Alternatively, the cover sheet of each individual cavity may be individualized during or after the bonding of the cover sheet.

The cover sheet of each individual cavity may additionally comprise a section which is not bonded with the blister sheet, i.e., a flap, that enables the user to grip the not bonded flap of the cover sheet in order to tear off the latter from the blister sheet.

Additionally, or alternatively, the blister sheet may comprise predetermined breaking lines, which enable the user to individualize single cavities or pairs of first and second cavities from the blister sheet according to the actual needs during the treatment. In this case the cavity is still closed during breaking. In an alternative embodiment, multiple blister packages are connected by predetermined breaking or cutting lines to provide a band of blister packages. E.g., three to six blister packages can be connected by breaking or cutting lines. This band of multiple blister packages may be flexible in a length direction of the blister band by the breaking or cutting lines, which take effect as joints. In result, the blister band may be rolled up on a reel providing favourable removal of individual blister packages. Before use, only the cover sheet over the desired part of the sheet is removed so that the rest of the packaged support and/or liquid remains sterile during the handling of the individual cavity.

These features contribute to a quick and easy handling of the poriferous support and minimizes the preparations for dental treatments requiring a sterile poriferous support.

In one embodiment, the second cavities are configured to, at least partly, preferably, completely, receive the support so that the support can absorb the liquid within the second cavity. In this manner, a container is provided, in which the support can absorb and, if required, briefly rest during its preparation. More preferably, the first and second cavities are dimensioned equally. This ensures that the support can be received by the second cavity and this provision also lowers the production costs of the blister sheet, as the blister sheet can be uniformly produced.

In another embodiment, the blister packaging is configured such that the removal of the cover sheet also removes a barrier between the first and the second cavity of the pair and allows for the liquid contacting the peptide coated support. Therewith, the liquid of the second cavity is able to flow into the first cavity holding the peptide coated support, e.g., when inclining the blister packaging towards the first cavity. This also results in a comfortable and fast preparation of the peptide coated support without handling of the latter.

Throughout the invention, the poriferous support can be, e.g., a sponge, a swab, a fleece or wool, e.g., cotton wool. The poriferous support is not explicitly limited to the before named examples. The poriferous support may also be a tampon, a plug, a dapper or any other pharmaceutically acceptable liquid absorbing product for medical use.

Medical sponges, swabs and cotton wools are well known in the art. They are individualizable in size which can be mechanized manufactured at low costs and in great quantity.

The poriferous support may e.g., comprise or consist of polyvinyl alcohol (PVA), cotton wool, polyethylene (PE), polyethylene terephthalate (PET), polypropylene (PP), or cyclic olefin copolymers (COC). These listed materials are widely used and well suited for the absorption of liquids when processed to nonwovens or foams. The poriferous support may also be configured to comprise one or more materials listed above so that optimal absorption characteristics can be achieved and medical requirements can be fulfilled.

Preferably, the active agent, e.g., the peptide is coated on the poriferous support together with an excipient, optionally, together with a cellulose-based excipient that improves binding to the support. Preferably, carboxymethylcellulose may be used as excipient. Coating the poriferous support together with the excipient results in more reliable results, and the coating can be uniformly applied to the poriferous support.

The active agent, e.g., the peptide may be lyophilized. It may be coated on the poriferous support by a method selected from spray drying, fluidized bed coating, dip coating or mixing. These methods lead to reliable reproductive results, whereas the coating can be uniformly applied to the poriferous support.

Preferably, the blister sheet and/or cover sheet comprise polyethylene (PE), polyethylene terephthalate (PET), polypropylene (PP), cyclic olefin copolymers (COC), polyurethane (PU), polystyrene (PS), or polyvinyl chloride (PVC), and/or a metal foil, preferably an aluminium foil or a plastic-laminated metal foil therefrom. These materials ensure that the concentration of the peptide coating remains constant when stored within the cavity and prevents contact of the

support with water which further contributes to an optimal dental treatment as originally intended.

Of note it is not required that the liquid, e.g., water, is also stored in the blister packaging. It should however be preferably provided together in a kit with the blister packaging of the invention, advantageously, in a form that allows easily measuring out and adding the desired amount of liquid.

Thus, in another aspect, the invention provides a kit that in addition to the blister packaging comprises a container comprising a sterile liquid, preferably water. The liquid may also contain a buffer and/or a fluoride salt, e.g., stannous fluoride or ammonium fluoride. Optionally, the container allows for providing a measured amount of said liquid to the cavity comprising a porous support. The container may be a multi-dose container, but it preferably is an ampoule, e.g., a break-off ampoule containing one dose of the liquid, (e.g., as described above, such as about 100 μL) which can then be dispensed into the cavity comprising the porous support.

It is particularly preferred to use the blister packaging or the kit in treatment of a caries lesion, optionally, a non-cavitated (or subsurface) caries lesion. As described in the art and discussed above, treatment of cavitated caries lesions is also possible, e.g., for preventing secondary caries. The peptide can also be applied, e.g., to a bone lesion.

The invention also provides a method of treating a tooth, e.g., a subsurface caries lesion, using the blister packaging and support as provided herein, e.g., comprising steps as laid out below, in particular, in Fig. 3.

All references cited herein are herewith fully incorporated.

Without intending to limit the invention, preferred embodiments and advantages of the blister packaging and the kit according to the invention will now be described with reference to the attached drawings in which:

Fig. 1 is a top view on the blister packaging according to a first embodiment;

Fig. 2 is a top view on the blister packaging according to a second embodiment;

Fig. 3 is a schematic process flow describing the method of preparation of the coated porous support;

Fig. 4 is a top view of the blister packaging according to a third embodiment;

Fig. 5 is a top view of the blister packaging according to a fourth embodiment; and

Fig. 6 is a side view of the blister packaging of Fig. 5.

Fig. 7 is a perspective view of the blister packaging according to a fifth embodiment.

- 1. Blister packaging
- 2. Cavity
- 3. Cover sheet
- 4. Support
- 5. Transversal perforation
- 6. Longitudinal perforation
- 7. Liquid
- 8. Liquid container
- 9. Single-use-ampoule
- 10. Stabilizing cavity
- 11. Bottom
- 12. Side wall
- 13. Corner
- 14. First line
- 15. Second line
- 16. Wall section
- α Angle
- P1. First point
- P2. Second point
- P3. Third point
- C. Centre of first cavity

Fig. 1 shows a first preferred embodiment of the blister packaging 1 according to the invention. In this embodiment, the blister packaging 1 comprises eight first cavities 2 each comprising a porous support 4 coated with a peptide. The cover sheet 3 is bonded to the blister sheet by thermal sealing. The cover sheet 3 is in this embodiment made of aluminium, whereas the blister sheet is made of a non-peptide absorbing plastics such as polyethylene (PE) but is not

limited thereto. Other suited above-mentioned non-peptide plastic materials may also be used. In one embodiment the cover sheet 3 is made of a transparent PE plastic, which enables the user to observe the quantity and condition of the poriferous supports 4 within the cavities 2. The cavities 2 are dimensioned in such way that they are able to fully receive the poriferous support 4.

The poriferous support 4 is in this embodiment, e.g., a cotton wool coated with a self-assembling peptide in monomeric form of SEQ ID NO: 6. The peptide coating is sufficiently dry so that the poriferous support 4 has long shelf live. The peptide is coated on the poriferous support together with an excipient or filler, e.g. by dip coating. Other suitable mentioned coating methods can be used.

In one embodiment, the cover sheet 3 is made of aluminium and is sufficiently rigid so that the blister packaging 1 configured as a push-through pack making it possible to press the poriferous support 4 out while breaking the cover sheet 3. Additionally, breaking the cover sheet 3 with an object like a tweezer makes the pressing out easier. Alternatively, the cover sheet 3 is manually removable, in particular, individually.

Further, the blister packaging shown in Fig. 1 comprises multiple transversal perforations 5 which are configured as predetermined breaking lines to separate at least one or a pair of cavities 2 in a transversal direction from the blister packaging 1. The transversal perforations 5 are arranged between a pair of two cavities 2. The blister packaging 1 of Fig. 1 also comprises a longitudinal perforation 6, which is configured as a predetermined breaking line to separate at least one cavity 2 in the longitudinal direction from the blister packaging 1.

The embodiment is not limited to the quantity of cavities 2 or poriferous supports 4. Other not shown embodiments might comprise more or less cavities 2 and poriferous supports 4 as well as transversal and longitudinal perforations 5, 6.

The shown second embodiment of the inventive blister packaging 1 in Fig. 2 is structurally equal to the first embodiment described above. The difference between the first and second embodiment lies in that the cavities on the right side of the blister packaging 1, the first cavities 2, comprise the poriferous support 4 and the cavities on the left side of the blister packaging 1, the second cavities 2, comprise a liquid 7 to be soaked into the poriferous support 4. In particular, the liquid 7 is sterile water sufficiently dosed relative to the peptide coating of the poriferous support 4. The liquid can also be an aqueous solvent which comprises fluoride salt, e.g., stannous fluoride, ammonium fluoride or sodium fluoride

The second cavities 2 are adjacent arranged to the first cavities 2 and equally sized so that they can fully receive the poriferous support 4. A first cavity 2 and a second cavity 2 forms a pair. Further, the first and second cavities 2 are configured in such way, that they can rest on a plane. With this configuration, when the cavities 2, especially the second cavity 2 is opened, the first cavity 2 can be used as a container holding the poriferous support 4 which can soak the liquid 7 comprised in the second cavity 2.

A third embodiment of the inventive blister packaging 1 is disclosed in Fig. 4. The blister packaging 1 of the third embodiment is structurally identical to that already described in the first embodiment of Fig. 1. The third embodiment illustrates an inventive kit comprising a separate sterile liquid container 8 that provides a measured amount of said liquid 7, e.g., sterile water. In this embodiment, the liquid container 8 comprises multiple unit dose packagings 9, more particularly, single-use ampoules, e.g., of about 0.3 mL of sterile water. They can also contain about 0.3 mL of aqueous solvent which comprises fluoride salt, e.g., stannous fluoride, ammonium fluoride or sodium fluoride. The unit dose packagings 9 are interconnected with each other, which simplifies the handling of the kit. The unit dose packagings 9 can be manually separated by tearing them off by hand or cutting them through at an interconnection section. The interconnection section is configured as a predetermined breaking line.

Fig. 3 discloses a method of preparing the poriferous support 4. The embodiment of the method is carried out by use of the inventive blister packaging 1 according to the second embodiment with reference to Fig. 2.

The first step comprises unpacking of the peptide coated poriferous support 4. The poriferous support 4 can be unpacked by pushing it through the cover layer 3 with the thumb, whereby the cover sheet 3 brakes and releases the poriferous support 4.

The following step comprises soaking the poriferous support 4 within the second cavity 2 holding the sterile water. The poriferous support 4 is inserted into the second cavity 2, which receives it completely. Optionally, the poriferous support 4 may be left to rest until it has absorbed at least partly, preferably fully, the liquid 7 of the second cavity 2. During the soaking step, the second and/or first cavity 2 can be placed on a plane, while the poriferous support 4 soaks the liquid 7.

The final third step comprises applying the poriferous support 4 soaked in liquid 7 onto teeth surfaces of the subject. The poriferous support 4 can be simply handled by tweezers. Slightly pressing the poriferous support 4 with the tweezers or against a tooth surface helps to release the liquid 7.

In Fig. 5 a top view of the blister packaging 1 according to the fourth embodiment is displayed. The fourth embodiment of Fig. 5 is a modification of the kit of the third embodiment of Fig. 3. The unit dose packaging 9 of the liquid described in association with the third embodiment is also used in the kit of the fourth embodiment. The blister packaging 1 comprises one first cavity 2 containing a porous support 4 and an empty (i.e., not containing solid or liquid substances) stabilizing cavity 10. The stabilizing cavity 10 is sealed by the cover sheet 3 and improves stability of the blister packaging 1 during handling.

In the top view of Fig. 5, first and third points P1, P3 are arranged on the first line 14 which intersects the centre C of the first cavity 2. The second line 15 is arranged in an angle α of 90° regarding the first line 14. In the embodiment of Fig. 5, the second line 15 also intersects the centre C of the first cavity. The second point P2 is arranged on the second line 15 in a predetermined distance to the centre C and the first line 14. Said points P1, P2, P3 form the corners of a triangle, wherein the points P1, P2, P3 are physically linked by the V-shaped stabilizing cavity 10. Here, said points P1, P2, P3 also define corners 13 of the stabilizing cavity 10. Of note, points P1, P2 and P3 as well as the centre C of the first cavity 2 and the two lines 14, 15 are not physically embodiments or marked in the blister package of the invention, but they define its construction.

The stabilizing cavity 10 extends over a large part of the length of the blister packaging 1 in length direction and comprises two limbs inclined to each other. The stabilizing cavity 2 may also comprise multiple limb portions inclined towards each other, e.g. x-, m-, n-, triangular, or rectangular shape. In particular, the stabilizing cavity 10 partly surrounds the first cavity 2 in the length and width direction of the blister sheet.

The first cavity 2 containing the porous support 4 may be structurally identical to that described in the first, second and third embodiment. Hence, features of the first cavity 2 described in association with one of the foregoing embodiments can also be applicable to the fourth embodiment. The same applies to the porous support 4, the cover sheet 3 and the blister sheet in general. However, alternatively, the form of the first cavity 2, as seen from the top, can be hexagonal instead of circular.

Fig. 6 is a side view of the blister packaging of Fig. 5, wherein it can be seen that the stabilizing cavity 10 has at least the same depth as the first cavity 2. It is further recognizable that the stabilizing cavity 10 extends over a large part of the width of the blister sheet seen in top view. The bottom 11 of the stabilizing cavity is parallel to the coversheet 3 and the bottom 11 comprises a planar surface. The sidewalls 12 are perpendicular to the cover sheet and the bottom 11, typically, with corners having angle of about 90° . Alternatively, the sidewalls 12 may be inclined in a predetermined inclination angle to the coversheet 3. Fig. 7 shows a fifth

embodiment of a blister packaging of the invention in a perspective view. Said embodiment largely corresponds to the fourth embodiment shown in Fig. 5 and 6. However, the form of the first cavity 2, as seen from the top, is hexagonal instead of circular. The sidewalls 12 are perpendicular to the cover sheet and the bottom 11, and they are linked to the bottom by two corners each having an angle of about 45°C, which are linked by a wall section 16 having a length between said 45° angles that is smaller than the length of the sidewalls 2. This can apply to both first cavity 2 and stabilizing cavity 10. The side walls can also be linked to the top of the blister sheet (i.e., the side covered by the cover sheet 3) by two corners each having an angle of about 45°C, which are linked by a wall section 16 having a length between said 45° angles that is smaller than the length of the sidewalls 2.

With the present invention a blister packaging has been provided which has a simple design, is easy to manufacture and ensures an enhanced handling and usability when used in the day-to-day business of a dentist's office.

Claims

1. A blister packaging (1) comprising a blister sheet with at least one first cavity (2) and a cover sheet (3) laid over and bonded to the blister sheet surrounding the at least one first cavity (2), wherein the at least one first cavity (2) of the blister comprises a porous support (4) coated with an active agent, optionally, a peptide.
2. The blister packaging (1) of claim 1, the blister sheet further comprising at least one stabilizing cavity (10), optionally, not comprising any solid or liquid substance, wherein the depth of the stabilizing cavity (10) is at least equal or greater relative to depth of the first cavity (2),

wherein the at least one stabilizing cavity (10) is located at least at three points, a first point (P1), a second point (P2), and a third point (P3) each arranged in a predetermined distance from the centre (C) of the first cavity (2), wherein the first and the third points (P1, P3) are on opposite sides of the centre (C) of the first cavity (2) on a first line intersecting the first cavity (2), and the second point (P2) is arranged on a second line intersecting the first line between the first and the third points (P1, P3) at an angle (α) of about 90°.
3. The blister packaging (1) of claim 2, wherein the blister packaging (1) comprises only one stabilizing cavity (10) extending through said three points (P1, P2, P3).
4. The blister packaging (1) of any of the claims 2 to 3, wherein the stabilizing cavity (10) has a V-shape and the at least one first cavity (2) is located at least partly between limbs of the V.
5. The blister packaging (1) of any of the preceding claims, wherein the blister packaging (1) only comprises one first cavity (2) and one stabilizing cavity (10).
6. The blister packaging (1) of any of claims 2-5, wherein the cover sheet (3) is removable together for a pair of one first cavity (2) and one stabilizing cavity (10), wherein, if more than one pair of first cavities (2) and stabilizing cavities (10) is present, the cover sheet (3) is individually removable together for each pair.
7. The blister packaging (1) of any of the preceding claims, wherein the active agent is a peptide.

8. The blister packaging (1) of claim 7, wherein the peptide is a self-assembling peptide in monomeric form.
9. The blister packaging (1) of any of claims 7 or 8, wherein the peptide is a self-assembling peptide having SEQ ID NO: 1, preferably, wherein the peptide is a self-assembling peptide having SEQ ID NO: 6.
10. The blister packaging (1) of any of claims 1-4 and 6-9, further comprising at least one second cavity (2) comprising a liquid, optionally, sterile water.
11. The blister packaging (1) of any of the preceding claims, wherein the cover sheet (3) is manually removable, wherein, if the blister packaging (1) comprises several cavities (2) comprising a poriferous support (4) coated with a peptide, the cover sheet (3) is individually removable for each cavity (2) comprising a poriferous support (4) coated with a peptide and, if present, optionally, for each cavity comprising a liquid and each stabilizing cavity (10).
12. The blister packaging (1) of claims 10 to 11, wherein adjacent to each first cavity (2), the second cavity (2) is arranged,

optionally,
 - a) wherein the cover sheet (3) is individually removable for each pair of first and second cavities (2) together, and/or
 - b) wherein removal of the cover sheet (3) removes a barrier between the first and the second cavity (2) of the pair and allows for the liquid (7) contacting the peptide-coated poriferous support.
13. The blister packaging (1) of any of the preceding claims, wherein the blister packaging (1) is a push-through pack.
14. The blister packaging (1) of any of the preceding claims, wherein the poriferous support (4) is a sponge, a swab, a fleece or cotton wool.
15. The blister packaging (1) of any of the preceding claims, wherein the poriferous support (4) comprises polyvinyl alcohol (PVA), cotton wool, polyethylene (PE), polyethylene terephthalate (PET), polypropylene (PP), or cyclic olefin copolymers (COC).

16. The blister packaging (1) of any of the preceding claims, wherein the peptide is coated on the poriferous support (4) together with a filler, optionally, together with carboxymethylcellulose.
17. The blister packaging (1) of any of the preceding claims, wherein the active agent, optionally, the peptide, is coated on the poriferous support (4) by a method selected from spray drying, fluidized bed coating, dip coating, or mixing.
18. The blister packaging (1) of any of the preceding claims, wherein the blister sheet and/or cover sheet (3) comprise polyethylene (PE), polyethylene terephthalate (PET), polypropylene (PP), cyclic olefin copolymers (COC), polyurethane (PU), polystyrene (PS), or polyvinyl chloride (PVC), and/or a metal foil, preferably an aluminium foil or a plastic-laminated metal foil therefrom.
19. A kit comprising the first blister packaging (1) of claim 1 to 9 and 13 to 18, wherein the kit further comprises a container (8) comprising a sterile liquid (7), preferably water, optionally, wherein the container (8) allows for providing a measured amount of said liquid (7) to the cavity (2) comprising the poriferous support (4).
20. The blister packaging (1) of any of claims 1-18 or the kit of claim 19 for use in treatment of a caries lesion, optionally, a non-cavitated caries lesion.