(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 July 2009 (02.07.2009)

PCT

(10) International Publication Number
WO 2009/080023 A1

(51) International Patent Classification:
A61K 9/68 (2006.01) *A61Q 11/00* (2006.01)
A61K 9/20 (2006.01) *A61K 8/64* (2006.01)
A61K 38/04 (2006.01)

(21) International Application Number:
PCT/DK2007/050198

(22) International Filing Date:
20 December 2007 (20.12.2007)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

WO 2009/080023 A1

(54) Title: COMPRESSED CHEWING GUM COMPRISING PEPTIDE

(57) Abstract: The present invention relates to compressed medicament-containing chewing gum compositions. In particular, the present invention is directed to compressed chewing gum compositions comprising a peptide, such as e.g. peptides with antimicrobial activity.

COMPRESSED CHEWING GUM COMPRISING PEPTIDE

FIELD OF THE INVENTION

The present invention is directed to compressed medicament-containing chewing gum compositions. In particular, the present invention is directed to compressed chewing gum compositions comprising peptides such as e.g. antimicrobial peptides.

BACKGROUND OF THE INVENTION

Peptidic compounds are widely used in therapy. Therapeutic peptides are often administered to patients in need thereof via injection. A number of disadvantages are however associated with such administration forms, including stability problems with aqueous formulations, storage, pain, inconvenience, poor patient compliance, a need of facilities for supplying clean needles and syringes, risk of infections, etc.

Peptides with antimicrobial effects may e.g. be used as an alternative or a as a supplement to antibiotics and other antimicrobial agents. In therapy, antimicrobial peptides are usually administered intravenously, although other modes of administration have been suggested.

AAPS PharmaSciTech 2007; 8(1) Article 26 (US Army Dental and Trauma Research Detachment) discloses chewing gum compositions with KSL-W antimicrobial peptides and CPC (cetylpyridinium chloride) produced using conventional methods employing heating of the chewing gum composition. The undesired off taste of KSL-W is masked using xylitol as sweetener. The chewing gum compositions are used as anti-plaque agents.

Compressed chewing gum tablets, including the manufacturing thereof, are described in WO 04/004479, WO 04/004480, WO 04/068964, WO 04/068965 and WO 05/063038.

The buccal membrane potentially offers advantages over other routes of administration. For example, drugs administered through the buccal route potentially has a rapid onset of action, reach high levels in the blood, avoid the first-pass effect of hepatic metabolism, and avoid exposure of the drug to the fluids of the gastrointestinal tract. Additional advantages include easy access to the membrane sites so that the drug can be applied, localized, and removed easily.

Buccal administration of peptide is disclosed in US 5,766,620. Different types of delivering vehicles have been suggested herein, such as creams, gels, ointments, tablets, patches, and troches. In example 6 it is disclosed that tablets are placed inside the cheek and removed after 4.5 hours. It follows that there is a need in the art for oral peptide compositions intended for buccal administration that are convenient to use for the patients in need thereof. Most patients will have severe problems with compliance of medical regiments if buccal administration requires that they have to rest for several hours with an oral composition tablet in the mouth.

A number of problems are however associated with buccal administration of active peptide compounds:

- Generally, peptides should not exceed a certain size in order to be able to reach and/or cross the mucosal membranes with sufficient efficiency.

- Controlled release characteristics are desirable in connection with buccal compositions in order to ensure efficient peptide uptake by the buccal membranes and to avoid that the majority of the peptides are swallowed and degraded without exerting their desired effects.

- Due care needs to be taken in connection with production of oral compositions comprising peptide compounds, since the compounds may suffer stability problems if the production methods comprise subjecting the peptides to harsh conditions such as e.g. heating, water and oxidation from the air.

- Some peptide compounds may have an undesirable off-taste which is difficult to mask in connection with oral compositions intended for uptake and/or absorption by the buccal membranes.

- Peptide compounds may be relatively unstable and it may thus be difficult to obtain compositions with good stability properties.

- Some peptides may be relatively expensive compounds. Efficient uptake by the compounds of the buccal membranes is thus essential in order to avoid preparing expensive compositions with disproportionately large peptide doses.

- Compositions with large peptide doses may increase the risk of getting overdosed since some patients may be able to take up the active compounds more efficiently than other patients.

- It is desirable that the compositions are easy and comfortable to use in order for the patients to comply with their medical regiments with sufficient efficiency.

SUMMARY OF THE INVENTION

Thus, the present invention provides a compressed chewing gum composition comprising peptides, such as e.g. antimicrobial peptides and optionally at least one absorption enhancer.

Accordingly, in a first aspect the present invention relates to a compressed chewing gum tablet comprising a first compressed module, wherein said tablet comprises at least one peptide and compressed chewing gum particles containing gum base.

In a further aspect, the present invention relates to a tablet according to the invention for use as a medicament.

Other aspects of the present invention will be apparent from the below description and the appended claims.

It will appear in the following that the present invention provides chewing gum compositions with peptides, said compositions having desirable characteristics.

One advantage of compressed chewing gum tablets containing peptide over conventional chewing gums containing peptide may be said to be that the chewing experience of patients requiring administration of peptide is more pleasant with the compressed chewing gum tablets. The normal experience is that more patients prefer the experience of chewing the compressed chewing gum tablets of the invention over conventional chewing gums.

A more pleasant chewing experience will result in better patient compliance with their medical regimens, which in turn will result in a better treatment. The compressed chewing gum tablets of the invention therefore facilitate correct and safe administration of peptide compared to prior art formulations.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and nomenclature

In the context of the present application and invention the following definitions apply:

In the present context, the expression "taste-masking agent" relates to one or more agents or compounds which, optionally together, successfully mask or cover the (potential) bitter taste of the peptide, but which simultaneously provides the chewing gum with a good palatability. In a preferred embodiment, the taste masking agent comprises a polyol sweetener.

In the present context, the term "gum base" refers in general to a commercially available gum base suitable for production of chewing gum. Such gum bases normally comprise one or more elastomeric compounds which may be of synthetic or natural origin, one or more resinous compounds which may be of synthetic or natural origin and softening compounds.

The term "gum base composition" as used herein may be a gum base as defined above comprising one or more ingredients (e.g. sweetener, flavour, colouring agents, fillers, etc.) as described below. The gum base is essentially water insoluble.

The term "chewing gum composition" is the final formulation, which constitutes at least a part of the compressed chewing gum tablets ready for sale or use by the consumer. A chewing gum composition may comprise a peptide, a taste masking agent, a pH controlling agent, sweetener and/or flavour and optionally other ingredients like colouring agents, enzymes, humectants, flavour enhancers, anti-caking agents etc.

Thus, the expression "chewing gum particles containing gum base" refers to particulated material of a chewing gum composition and is to be understood as any form of chewing gum particles containing a certain amount of gum base as described in detail below. The chewing gum particles may be in any suitable form such as pellets, granules, agglomerates or powder. Thus, in some embodiments, the particles have been particulated prior to application. Particulation may be in any form of "building up" particles from smaller primary particles into macro particles or in any form of "building down" from larger substances into macro particles. Any form of particulation may be applied, such as granulation, pelletizing, agglomeration, or any other suitable means for particulation, as described below. Thus, the particles may also to be understood as macroparticles.

Furthermore, the expression "compressed chewing gum particles containing gum base" refers to a portion of chewing gum particles which become compressed after mixed with, e.g., a taste masking agent, a pH controlling agent, sweeteners or flavours.

The expression "compressed chewing gum tablet" denotes a ready-for-use chewing gum tablet comprising at least one peptide and compressed chewing gum particles containing gum base possibly mixed with a taste masking agent, a pH controlling agent, sweeteners, flavour or other ingredients and optionally coated. As described in detail below, a compressed chewing gum tablet may be produced

by an initial conventional mixing of the gum base with e.g. water-insoluble ingredients such as elastomers and resins, followed by a granulation or the like of the obtained gum base mix. The obtained particles containing gum base may then be mixed with further chewing gum ingredients. The final mix may then be compressed under high pressure (typically when applying cooling) into to a compressed chewing gum tablet or a compressed module.

Different types of compressed chewing gum tablets

In one embodiment of the present invention, the compressed chewing gum tablet comprises one compressed module, i.e. the above-mentioned "first compressed module" is the only compressed module present in the tablet.

In the embodiment where the tablet contains only one compressed module, the compressed module also contains the compressed chewing gum particles containing gum base. The compressed module also contains the at least one peptide. The peptide may be incorporated in the compressed chewing gum particles. However, it is currently preferred that the peptide is present in the compressed module, but is located between the compressed chewing gum particles, i.e. the peptide does not form part of the compressed chewing gum particles.

Furthermore, in the embodiment where the tablet contains only one compressed module, the compressed module may further contain one or more components selected from the group consisting of tablet material, a taste masking agent, an absorption enhancer, a mucoadhesive agent, and combinations thereof. In a preferred embodiment of the invention, the compressed module contains an absorption enhancer and/or a mucoadhesive agent. A detailed description of the above-mentioned components is provided *infra*.

In another, and currently preferred, embodiment of the invention, the tablet further comprises a second compressed module. Thus, according to this embodiment of the invention, the compressed chewing gum tablet of the invention comprises a first compressed module and a second compressed module, wherein the tablet comprises at least one peptide and compressed chewing gum particles containing gum base.

According to this embodiment of the invention, the compressed chewing gum tablet is one wherein the first compressed module and the second compressed module are cohered to each other. Thus, the first compressed module is typically located on the top of the second compressed module as illustrated in Figure 1 which shows a compressed chewing gum tablet **10** containing two compressed modules, i.e. a first compressed module **11** and a second compressed module **12**. As illustrated in Figure 1, the two modules **11** and **12** are cohered (or adhered) to each other. Different processes may be applied for obtaining sufficient adhesion between the modules as described in detail below. However, according to a preferred embodiment of the invention, the mutual adhering between the two modules is obtained by the compression of one module onto the other module.

In an interesting embodiment of the invention, the second compressed module contains the at least one peptide. Thus, according to this embodiment of the invention, the peptide may be contained in the first compressed module and in the second compressed module. However, in a preferred embodiment of the invention the at least one peptide is contained in the second compressed module only, i.e. the first compressed module does not contain any peptide. As explained above, the peptide, independently of whether the peptide is contained in the second compressed module only or if contained in both the first and the second compressed module, is preferably not contained within the compressed chewing gum particles containing gum base, i.e. it is preferred that the peptide does not form part of the compressed chewing gum particles.

Thus, a preferred embodiment of the invention concerns a compressed chewing gum tablet comprising a first compressed module and a second compressed module, wherein said tablet comprises at least one peptide and compressed chewing gum particles containing gum base, and wherein the second compressed module contains the at least one peptide. Preferably, the first compressed module does not contain any peptide. Referring to Figure 1, it will be understood that this preferred embodiment corresponds to the situation where the first compressed module **11** does not contain any peptide and where the second compressed module **12** contains the at least one peptide.

The compressed chewing gum particles containing gum base may be present in the first compressed module and in the second compressed module. However, in a further, and even more preferred, embodiment of the invention, the second compressed module does not contain gum base, i.e. the second compressed module does not contain compressed chewing gum particles containing gum base.

Thus, a particularly preferred embodiment of the invention concerns a compressed chewing gum tablet comprising a first compressed module and a second compressed module, wherein the first compressed module comprises chewing gum particles containing gum base, and wherein the second compressed module contains the at least one peptide. Preferably, the first compressed module does not contain any peptide and the second compressed module does not contain any chewing gum particles containing gum base. Again, referring to Figure 1, it will be understood that this particular preferred embodiment corresponds to the situation where the first compressed module **11** does not contain any peptide, but contains compressed chewing gum particles containing gum base and where the second compressed module **12** contains the at least one peptide, but does not contain compressed chewing gum particles containing gum base.

In a further, and still more preferred embodiment of the invention, the second compressed module comprises compressed tablet material. Accordingly, it is also preferred that the first compressed module does not contain tablet material. Examples of useful tablet material are given *infra*.

As will be understood by the person skilled in the art, the above-disclosed principles concerning the structure and components of a compressed chewing gum tablet may be utilised to design a variety of different chewing gum tablets.

One example of such an alternative design is a three-module chewing gum tablet as illustrated in Figure 2. The compressed chewing gum tablet **20** shown in Figure 2 contains three compressed modules **21**, **22** and **23**. Thus, according to this embodiment, the present invention concerns a compressed chewing gum tablet comprising a first, second and third compressed module, wherein said tablet comprises at least one peptide and compressed chewing gum particles containing gum base.

In one embodiment, the first and the third compressed module (i.e. modules **21** and **23**) have the properties, and contains the features, discussed above in connection with the first compressed module, whereas the second compressed module (i.e. module **22**) has the properties, and contains the features, discussed above in connection with the second compressed module. Thus, according to this particular embodiment, the present invention concerns a compressed chewing gum composition comprising a first, a second and a third compressed module, wherein the first and third compressed module comprise chewing gum particles containing gum base, and wherein the second compressed module contains the at least one peptide. Preferably, the first and/or the third compressed module do not contain any peptide and the second compressed module does not contain any chewing gum particles containing gum base. Moreover, the second compressed module preferably comprises tablet material. Referring to Figure 2, it will be understood that this particular embodiment corresponds to the situation where the first compressed module **21** does not contain any peptide, but contains compressed chewing gum particles containing gum base; the second compressed module **22** contains the at least one peptide, but does not contain compressed chewing gum particles containing gum base; and the third compressed module **23** does not contain any peptide, but contains compressed chewing gum particles containing gum base.

In another embodiment, the first and the third compressed module (i.e. modules **21** and **23**) have the properties, and contains the features, discussed above in connection with the second compressed module, whereas the second compressed module (i.e. module **22**) has the properties, and contains the features, discussed above in connection with the first compressed module. Thus, according to this particular embodiment, the present invention concerns a compressed chewing gum composition comprising a first, a second and a third compressed module, wherein the first and third compressed module contain the at least one peptide, and wherein the second compressed module comprises chewing gum particles containing gum base. Preferably, the second compressed module does not contain any peptide and the first and/or third compressed modules do not contain any chewing gum particles containing gum base. Moreover, the first and/or the third compressed module preferably contain tablet material. Referring to Figure 2, it

will be understood that this particular embodiment corresponds to the situation where the first compressed module **21** contains the at least one peptide, but does not contain compressed chewing gum particles containing gum base; the second compressed module **22** does not contain any peptide, but contains compressed chewing gum particles containing gum base; and the third compressed module **23** contains the at least one peptide, but does not contain compressed chewing gum particles containing gum base.

It will be understood that independent of the actual design of the compressed chewing gum tablet, the tablet may, in addition to conventional chewing gum components, contain one or more components selected from the group consisting of tablet material, a taste masking agent, an absorption enhancer, a mucoadhesive agent, and combinations thereof. Such components are described in more detail *infra*, and may be present in the some or all of the above-mentioned compressed modules. In a preferred embodiment of the invention, the compressed tablet contains a mucoadhesive agent and/or an absorption enhancer. While such components may be present in all or just some of the compressed modules, it is in general preferred that such components are located in the same compressed modules as the at least one peptide in order to obtain a co-release of such components.

In further embodiments, peptide, the taste masking agent, the absorption enhancer, the mucoadhesive agent, and combinations thereof may encapsulated in the manner described *infra*, the encapsulated components being present in the modules as disclosed in the preceding paragraphs.

In general, and independent of the specific design of the chewing gum tablet, the present inventors have found that a surprisingly high absorption of peptide through the buccal mucosal membrane is achieved with the compressed chewing gum tablets of the present invention compared to conventional chewing gum designs.

In general, and independent of the specific design of the chewing gum tablet, the present inventors have found that a surprisingly high buccal bioavailability is

achieved if certain well-defined release characteristics of the peptide are fulfilled. The peptides may be designed to give a controlled release.

Thus, a particular preferred chewing gum tablet is a tablet wherein at least 10%, 20%, 30%, 40%, 50% or 60% of the incretin mimetic is released within 2, 3, 4, or 5 minutes as determined by USP XXIX Paddle Method II using 500 ml simulated saliva at 37°C as the dissolution media and 50 rpm as the stirring rate.

The term "conjugate" (or interchangeably "conjugated") is intended to indicate a heterogeneous (in the sense of composite or chimeric) molecule formed by the covalent conjugation (or attachment) of one or more peptides to one or more non-peptide moieties. The term "covalently conjugated" (or "covalently attached") means that the peptide and the non-peptide moiety are either directly covalently joined to one another, or else are indirectly covalently joined to one another through an intervening moiety or moieties, such as a bridge, spacer, or linkage moiety or moieties. Preferably, a conjugated peptide is soluble at relevant concentrations and conditions, i.e. soluble in physiological fluids such as saliva. Examples of conjugated peptides of the invention include alkylated, glycosylated and/or PEGylated peptides.

In the present context, the term "derivative" (of an peptide) is used synonymous with the term "conjugate", i.e. a "derivative" (of an peptide) is intended to mean a heterogeneous molecule formed by the covalent conjugation (or attachment) of one or more peptides to one or more non-peptide moieties. The term "derivative" also covers amidated forms, acylated forms, and esterified forms of such peptides.

The term "polymer molecule" is defined as a molecule formed by covalent linkage of two or more monomers, wherein none of the monomers is an amino acid residue. The term "polymer" may be used interchangeably with the term "polymer molecule".

The term "sugar moiety" is intended to indicate a carbohydrate molecule attached by *in vivo* or *in vitro* glycosylation, such as N- or O-glycosylation.

An "N-glycosylation site" has the sequence N-X-S/T/C, wherein X is any amino acid residue except proline, N is asparagine and S/T/C is either serine, threonine or cysteine, preferably serine or threonine, and most preferably threonine. An "O-glycosylation site" is the OH-group of a serine or threonine residue.

The term "analogue" is intended to cover a peptide, which contains one or more amino acid modifications relative to the parent amino acid sequence (such as SEQ ID NOs:1-9). The analogue typically contains 1-10 amino acid modifications (such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid modifications), e.g. in 1-7 amino acid modifications, 1-5 amino acid modifications or 1-3 amino acid modifications.

Taste masking agent

The compressed chewing gum tablet may, as discussed above, comprise one or more taste masking agents such as e.g. acids, flavours, sweeteners, etc. As will be understood, the necessity of incorporating one or more taste masking agents in the chewing gum tablet is highly dependent on the chosen peptide and to what extent the peptide has an unpleasant taste when released from the chewing gum.

Since the peptides according to the invention are sometimes released faster from a compressed chewing gum tablet than from a conventionally mixed chewing gum, it may be necessary to taste mask the (potential) unpleasant taste of the chosen peptide. In any event, once the peptide is released from the chewing gum it is desirable mask this unpleasant off taste. In some embodiments, the taste masking agent and the peptide is preferably located within the same compressed module(s). In other embodiments, it is generally preferred that the taste masking agent does not form part of the compressed chewing gum particles containing gum base, i.e. the taste masking agent is located between the compressed chewing gum particles containing gum base. This has the advantage that the peptide and the taste masking agent are co-released from the compressed chewing gum tablet upon chewing. In this context, the term "co-release" means that when the peptide is released from the chewing gum during chewing, at least some taste masking agent is also released. Evidently, it is preferred that when the peptide is released from the chewing gum tablet during chewing, an amount of taste masking agent, which is sufficient to mask the unpleasant taste of the peptide, is also released.

The taste-masking agent is one or more agents or compounds which, optionally together, successfully mask or cover the (potential) unpleasant taste of the peptide, but which simultaneously provides the chewing gum with a good palatability.

In a preferred embodiment, the taste masking agent is a polyol sweetener.

A specific example of one category of polyol sweeteners include sugars, in particular a sugar selected from the group consisting of dextrose, sucrose, maltose, fructose, lactose, and combinations thereof.

Another specific example of another category of polyol sweeteners include sugar alcohols, in particular sugar alcohols selected from the group consisting of xylitol, sorbitol, mannitol, maltitol, isomaltol, isomalt, erythritol, lactitol, maltodextrin, hydrogenated starch hydrolysates, and combinations thereof.

Polyol sweetener may be added in an amount of 0-75% by weight of the tablet. Preferably, poyol is present in an amount of 5-50%, more preferably 5-40%, more preferably 5-30%, more preferably 7-25%, more preferably 7-20%, and most preferably 10-20%.

In another embodiment of the invention, the taste masking agent is a high intensity sweetener or a flavour, optionally in combination with a polyol sweetener. Useful high intensity sweeteners may be selected from the group consisting of sucralose, neotame, aspartame, salts of acesulfame in particular the potassium salt of acesulfame (acesulfame K), alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizin, dihydrochalcones e.g. NHDC, thaumatin, monellin, stevioside, Twinsweet (aspartame-acesulfame salt) and combinations thereof.

In an interesting embodiment, the tablet of the invention comprises two or more taste masking agent, such as a polyol sweetener and a high intensity sweetener. In this case, the polyol sweetener is typically present in an amount of from 90-99.99% by weight of the total amount of taste masking agent, and the high

intensity sweetener is present in an amount of from 0.01-10% by weight of the total amount of taste masking agent. Preferably, the polyol sweetener is present in an amount of from 95-99.99% by weight of the total amount of taste masking agent, and the high intensity sweetener is present in an amount of from 0.01-5% by weight of the total amount of taste masking agent. More preferably, the polyol sweetener is present in an amount of from 98-99.9% by weight of the total amount of taste masking agent, and the high intensity sweetener is present in an amount of from 0.1-2% by weight of the total amount of taste masking agent.

Still other examples of suitable taste masking agents include salts of gluconate, such as sodium gluconate.

Examples of food acids include: citric acid, tartaric acid, malic acid, fumaric acid, ascorbic acid, adipic acid and lactic acid, and mixtures thereof.

Furthermore, various flavours also aid in masking potentially unpleasant flavours from various peptidic compounds.

pH controling agent

As will be understood by the skilled person, peptide-based active compounds, such as the peptides disclosed herein, unstable in (strong) acidic and alkaline environments. Accordingly, in order to maintain a pre-defined pH environment, it may be desirable to incorporate a pH controlling agent in the chewing gum tablet of the invention. Thus, in an interesting embodiment of the invention, the chewing gum tablet further comprises a pH controlling agent.

Useful pH controlling agents include organic or mineral acids (acidulants), bases, and neutralizing agents. Specific examples of such pH controlling agents include, but is not limited to, ascorbic acid, fumaric acid, adipic acid, lactic acid, malic acid, citric acid, tartaric acid, propionic acid, phosphoric acid and combinations thereof. In general, the pH controlling agent and the peptide is preferably located within the same compressed module(s). Moreover, it is generally preferred that the pH controlling agent does not form part of the compressed chewing gum particles containing gum base, i.e. the pH controlling agent is located between the compressed chewing gum particles containing gum base. The preferred ratio of pH

controlling agents in relation to the amount of incretin mimetics is 1:6, or more preferably 2:6 and most preferably about 2:4. In other preferred embodiments, the ratio is about 1:10.

Absorption enhancer

In order to increase the buccal bioavailability of the peptide, the tablet of the invention may advantageously contain an absorption enhancer.

As used herein, the term "absorption enhancer," (or, analoguously, "penetration enhancer," "permeation enhancer," and the like) is intended to include enhancers that increase the flux of a drug across the mucosa and is limited only by functionality. Thus, absorption enhancers may be selected from the group consisting of bile salts, cetomacrogols, chelating agents, citrates, cyclodextrins, detergents including steroidal detergents, enamine derivatives, fatty acids, lecithins, phospholipids, synthetic and natural surfactants including non-ionic surfactants.

Absorption enhancers according to the present invention may be selected from one or more of the following groups and sub-groups:

- solubilization agents;
- charge modifying agents;
- pH control agents;
- degradative enzyme inhibitors;
- mucolytic or mucus clearing agents;
- membrane penetration-enhancing agents (e.g.,
    - (i) a surfactant,
    - (ii) a bile salt,
    - (iii) a phospholipid or fatty acid additive, mixed micelle, liposome, or carrier,
    - (iv) an alcohol, (v) an enamine,
    - (iv) an NO donor compound,
    - (vii) a long-chain amphipathic molecule,
    - (viii) a small hydrophobic penetration enhancer,
    - (ix) sodium or a salicylic acid derivative,
    - (x) a glycerol ester of acetoacetic acid,
    - (xi) a cyclodextrin or beta-cyclodextrin derivative,
    - (xii) a medium-chain fatty acid,
    - (xiii) a chelating agent,
    - (xiv) an amino acid or salt thereof,
    - (xv) an N-acetylamino acid or salt thereof,
    - (xvi) an enzyme degradative to a selected membrane component,

- (xvii) an inhibitor of fatty acid synthesis,
- (xviii) an inhibitor of cholesterol synthesis; or
- (xiv) any combination of the membrane penetration enhancing agents of (i)-(xviii));

- modulatory agents of epithelial junction physiology, such as
  - nitric oxide (NO) stimulators,
  - chitosan, and chitosan derivatives;
- vasodilator agents;
- selective transport-enhancing agents; and
- stabilizing delivery vehicles, carriers, supports or complex- forming species with which the peptide(s) is/are effectively combined, associated, contained, encapsulated or bound to stabilize the active agent for enhanced mucosal delivery.
- small hydrophilic penetration enhancers,
- Emulsifiers:

Examples of compounds that can be used as enhancers according to the present invention include but are not limited to: CPC (Cetylpyridinium Chloride), Benzalkonium chloride, Sodium lauryl sulfate, Polysorbate 80, Cetyltrimethylammonium bromide, Laureth 9, Sodium salicylate, Sodium EDTA, EDTA, Aprotinin, Sodium taurocholate, Saponins, Bile salt derivatives, Fatty acids, Sucrose esters, Azone emulsion, Dextran sulphate, Linoleic acid, Labrafil, Transcutol, Urea, Azone, Nonionic surfactants, Sulfoxides, Lauric acid/PG, POE 23 lauryl ether, Methoxysalicylate, Dextran sukfate, Methanol, Ethanol, Sodium cholate, Sodium taurocholate, Lysophosphatidyl choline, Cyclodextrin, Alkylglycosides, Polysorbates, Sorbitan esters, Poloxamer block copolymers, PEG-35 castor oil, PEG-40 hydrogenated castor oil, Caprocaproyl macrogol-8 glycerides, PEG-8 caprylic/capric glycerides, Dioctyl sulfosuccinate, Polyethylene lauryl ether, Ethoxydiglycol, Propylene glycol mono-di-caprylate, Glycerol monocaprylate, Glyceryl fatty acids (C.sub.8-C.sub.18) ethoxylated, Oleic acid, Linoleic acid, Glyceryl caprylate/caprate, Glyceryl monooleate, Glyceryl monolaurate, Caprylliccapric triglycerides, Ethoxylated nonylphenols, PEG-(8-50) stearates, Olive oil PEG-6 esters, Triolein PEG-6 esters, Lecithin, d-alpha tocopherol polyethylene glycol 1,000 succinate, Citric acid, Sodium citrate, BRIJ, Sodium laurate, 5-methoxysalicylic acid, Bile salts, Acetyl salicylate, ZOT, Docosahexaenoic acid, Alkylglycosides, Sodium glycocholate (GC-Na), Sodium taurocholate (TC-Na), EDTA, Choline salicylate, Sodium caprate (Cap-Na), N-lauryl-beta-D-maltopyranoside (LM), Diethyl maleate, Labrasol, Sodium salicylate, Mentol, Alkali metal alkyl sulphate, Sodium lauryl sulphate, Glycerin, Bile acid,

Lecithin, phosphatidylcholine, phosphatidylserine, sphingomyelin, phophatidylethanolamine, cephalin, lysolecithin, Hyaluronic acid: alkalimetal salts, sodium, alkaline earth and aluminium, Octylphenoxypolyethoxyethanol, Glycolic acid, Lactic acid, Chamomile extract, Cucumber extract, Borage oil (Danish: "Hjulkrone olie"), Evening primrose oil, Polyglycerin, Lysine, Polylysine, Triolein, Monoolein, Monooleates, Monolaurates, Polydocanol alkyl ethers, Chenodeoxycholate, Deoxycholate, Glycocholic acid, Taurocholic acid, Glycodeoxycholic acid, Taurodeoxycholic acid, Sodium glycocholate, Phosphatidylcholine, Phosphatidylserine, Sphingomyelin, Phosphatidylethanolamine, Cephalin, Lysolecithin, Alkali metal hyaluronates, Chitosan, Poly-L-arginine, Alkyl glucoside, Saccharide alkyl ester, Fusidic acid derivatives, Sodium taurdihydrofusidate (STDHF), L-α-phosphatidylcholine Didecanoyl (DDPC), Polysorbate 20, Nitroglycerine, nitropruside, NOC5 [3-(2-hydroxy-l-(methyl-ethyl)-2-nitrosohydrazino)-l- propanamine], NOC12 [iV-ethyl-2-(l-ethyl-hydroxy-2-nitrosohydrazino)-ethanamine, SNAP [S-nitroso-N-acetyl-DL-penicillamine, NORI, NOR4, deacylmethyl sulfoxide, azone, salicylamide, glyceryl-l,3-diacetoacetate or l,2-isopropylideneglycerine-3-acetoacetate), Amino acids, Amino acid salts, monoaminocarboxlic acids, Glycine, alanine, phenylalanine, praline, hydroxyproline, hydroxyamino acids, serine, acidic amino acids,, aspartic acid, Glutamic acid, Basic amino acids, Lysine, N-acetylamino acids, N-acetylalanine, N-acetylphenylalanine, TM-acetylserine, N-acetylglycine, N-acetyllysine, N-acetylglutamic acid, N-acetylproline, N-acetylhydroxyproline, lactic acid, malic acid and citric acid and alkali metal salts thereof, pyrrolidonecarboxylic acids, alkylpyrrolidonecarboxylic acid esters, N-alkylpyrrolidones, proline acyl esters, sodium lauryl phosphate, sodium lauryl sulphate, sodium oleyl phosphate, sodium myristyl sulphate, polyoxyethylene alkyl ethers, polyoxyethylene alkyl esters, caproic acid, alkylsaccharide, Fusidic acid, Polyethylene glycol, Cetyl alcohol, Polyvinylpyrolidone, Polyvinyl alcohol, Lanolin alcohol, Sorbitan monooleate, Ethylene glycol tetraacetic acid, Bile acid conjugate with taurine, Cholanic acid and salts, Cyclodextran, Cyclodextrin (beta), Hydroxypropyl-β-cyclodetran, Sulfobutylether-β-cyclodextran, Methyl-β-cyclodextrin, Chitosan glutamate, Chitosan acetate, Chitosan hydrochloride, Chitosan hydrolactate, 1-O-alkyl-2-hydroxy-sn-glycero-3-phosphocholine, 3-O-alkyl-2-acetoyl-sn-glycero-1-phosphocholine, 1-O-alkyl-2-O-acetyl-sn-glycero-3-phospho(N,N,N-

trimethyl)hexanolamine, Propylene glycol, Tetradecylmaltoside (TDM), sodium lauryl sulfate og sodium glycocholate and Sucrose dedecanoate.

Particularly preferred enahncers include: Polysorbate 80, Polysorbate 20, L-α-phosphatidylcholine Didecanoyl (DDPC), Polyethylene glycol, Cetyl alcohol, Polyvinylpyrolidone, Polyvinyl alcohol, Lanolin alcohol, Sorbitan monooleate, Methyl-β-cylodextrin.

isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and sorbitan esters

C_2 or C_3 alcohol, and C_3 or C_4 diol, DMSO, DMA, DMF, 1-n-dodecyl-cyclazacyclo-heptan-2-one, N-methyl pyrrolidone, N-(2-hydroxyethyl) pyrrolidone, triacetin, propylene carbonate and dimethyl isosorbide

Tetradecylmaltoside (TDM), Sucrose dedecanoate

1-O-alkyl-2-hydroxy-sn-glycero-3-phosphocholine,

3-O-alkyl-2-acetoyl-sn-glycero-1-phosphocholine

1-O-alkyl-2-O-acetyl-sn-glycero-3-phospho(N,N,N-trimethyl)hexanolamine.

1-O-hexadecyl-2-hydroxy-sn-glycero-3-phosphocholine;; and

1-O-octadecyl-2-hydroxy-sn-glycero-3-phosphocholine

3-O-hexadecyl-2-acetoyl-sn-glycero-1-phosphocholine

1-O-hexadecyl-2-O-acetyl-sn-glycero-3-phospho(N,N,N-trimethyl)hexanolamin- e and a bile salt comprising a steroidal detergent consisting of a member of the group consisting of natural and synthetic salts of cholanic acid and mixtures

Furthermore, pH control agents may also function as enhancers and/or pH control agents in tablets according to the present invention. Examples of such compounds include but are not limited to: Acetic acid, Adipic acid, Citric acid, Fumaric acid, Glucono-δ-lactone, Gluconsyre, Lactic acid, Malic acid, Maleic acid, Tartaric acid, Succinic acid, Propionic acid, Ascorbic acid, Phosphoric acid, Sodium orthophosphate, Potassium orthophosphate, Calcium orthophosphate, Sodium diphosphate, Potassium diphosphate, Calcium diphosphate, Pentasodium triphosphate, Pentapotassium triphosphate, Sodium polyphosphate, Potassium polyphosphate, Carbonic acid, Sodium carbonate, Sodium bicarbonate, Potasium carbonate, Calcium carbonate, Magnesium carbonate, and Magnesium oxide.

Finally, mucoadhesive agents may also function as enhancers and/or mucoadhesives in tablets according to the present invention. Exampls of such mucoadhesive compounds include but are not limited to: Carbopol 934+HPC, Maize + Carbopol 907, HPC (hydroxypropyl cellulose), Na-CMC, HPMC (hydroxypropylmethylcellulose), HEMA hydroxyethyl metacrylate, Carbopol 907 crosslinked with sucrose, Polyacrylic acids (PAA), Chitosans, Lectins, Polymetacrylate derivatives, Hyaluronic acid, P(AA-co-PEG) monomethylether monomethacrylate, PAA-PVP (Poly acrylic acid-poly vinyl pyrrilidone), PVP-PEG, methylcellulose, N-Trimethyl, Chitosans, PDMAEMA (poly(dimethyl-aminoethyl methacrylate), HEC Hydroxethyl Cellulose, Carbomer 940, Carbomer 971, Polyethylene Oxide, Dextrin, Poly(Methyl Vinyl Ether/Maleic Anhydride), Polycarbophil (Polymers of acrylic acid crosslinked with divinyl glycol), Poly vinyl pyrrilidone (PVP), Agar, Tragacanth, Sodium Alginate, Karaya gum, MEC, HPC Hydroxy propyl cellulose, Lectins, AB Block copolymer of oligo (methyl methacrylate) and PAA, Polymers with thiol groups, Spheromers, Thiomers, Alginic acid sodium salt, Carbopol 974P (Carbomer), Etylcellulose EC), Carboxymethyl cellulose (CMC), Dextran, Guar Gum, Pectins, Starch, Gelatin, Casein, Acrylic acid polymers, Polymers of acrylic acid esters, Acrylic acid copolymers, Vinyl polymers, Vinyl copolymers, Polymers of Vinyl alcohols, Alcoxy polymers, Polyethylene oxide polymers, Polyethylene glycol, Cetyl alcohol, Polyvinylpyrolidone, Polyethylene glycol, Polyethylene glycol, Cetyl alcohol, Polyvinylpyrolidone, Polyvinyl alcohol, Lanolin alcohol, Sorbitan monooleate, Ethylene glycol tetraacetic acid.

It thus appears that the term "enhancer" encompasses a wide range of different compounds, and it even encompasses compounds that can also be grouped as mucoadhesive agents as well as pH control agents. This means that in some cases a mucoadhesive agent is used as an enhancer and sometimes as a mucoadhesive agent and in some cases a pH control agent is used as an enhancer and sometimes as a pH control agent.

Furthermore, absorption enhancers may also help peptides to adhere to the mucosa and/or penetrate bacterial cell walls, which may be desirable in connection with e.g. use of antimicrobial peptides. Examples of such enhancers include CPC. In a preferred aspect, tablets according to the present invention

comprising antimicrobial peptide thus also comprises at leas tone mucoadhesive agent.

Furthermore, other examples of suitable absorption enhancers can be found in *inter alia* Rowe et al., Handbook of Pharmaceutical Excipients, Fourth Ed. Pharmaceutical Press, London, 2003, and in US 5,766,620. The absorption enhancers disclosed from column 9, line 46, to column 11, line 4, of US 5,766,620 are hereby incorporated by reference.

In general, the absorption enhancer and the peptide is preferably located within the same compressed module(s). Moreover, it is generally preferred that the absorption enhancer does not form part of the compressed chewing gum particles containing gum base, i.e. the absorption enhancer is located between the compressed chewing gum particles containing gum base.

Mucoadhesive agent

In order to facilitate mucoadhesion, and hence buccal absorption, of the peptide, the tablet of the invention may advantageously contain a mucoadhesive agent. Mucoadhesive agents are well-known to the person skilled in the art and may, preferably, be a hydrophilic polymer or a hydrogel, in particular a hydrophilic polymer.

One particular class of hydrophilic polymers includes the cellulose derivatives. Thus, in one embodiment of the invention the mucoadhesive agent is a cellulose derivative, in particular a cellulose derivative selected from the group consisting of hydroxypropylcellulose (HPC), sodium carboxy methylcellulose (Na-CMC), hydroxypropylmethylcellulose (HPMC), methylcellulose (MC), ethylcellulose (EC), hydroxyethylcellulose (HEC), and combinations thereof.

Other examples of suitable mucoadhesive agents include, for example, cross-linked acrylic acid-based polymers, such as the Carbopols and Carbomers, e.g. Carbopol 934, Carbopol 907, Carbomer 940 and Carbomer 971; acrylic-acid based polymers, such as hydroxyethyl methacrylate, polyacrylic acid (PAA), polymethacrylate derivatives; monomethylether monomethacrylate (P(AA-co-PEG), poly acrylic acid-poly vinyl pyrrolidone (PAA-PVP); poly(dimethyl-

aminoethyl methacrylate) (PDMAEMA); polymers of acrylic acid cross-linked with di-vinyl groups, such as Polycarbophil; AB block polymers of methyl methacrylate and PAA. Still other examples include chitosan and its derivatives, such as N-trimethyl chitosans; pectins; lectin and its derivatives; hyaluronic acid; polyethylene oxide; polyethers; vinyl polymers; polymers of vinyl alcohols; dextrin; dextran; poly(methyl vinyl ether/maleic anhydride); polyvinylpyrrolidone (PVP); PVP-PEG; agar; gaur gum; tragacanth; sodium alginate; karaya gum; MEC and thiol group-containing polymers.

In general, the mucoadhesive agent and the peptide is preferably located within the same compressed module(s). Moreover, it is generally preferred that the mucoadhesive agent does not form part of the compressed chewing gum particles containing gum base, i.e. the mucoadhesive agent is located between the compressed chewing gum particles containing gum base.

Tablet material

It is well known to the man skilled in the art that the chewing gum tablet material comprises water soluble ingredients as well as water insoluble ingredients – and it follows that the particular mixture of ingredients can be compressed into a tablet. In some embodiments, most or all of the water soluble ingredients form one separate module of the tablet and the water insoluble components form another separate module. In other embodiments, some or all of the water soluble material is mixed with the insoluble material.

Generally, the water soluble ingredients comprise conventional pharmaceutically acceptable excipients, such as glidants, lubricants, fillers, dry or wet binders, etc., used in the pharmaceutical industry in the manufacturing of standard tablets. Examples of useful glidants and lubricants are stearic acid, metallic stearates, talc, colloidal silica, sodium stearyl fumarate and alkyl sulphates. Likewise, a dry binder such as e.g. sorbitol, isomalt, or mixtures thereof may be used. The dry binder provides the effect of binding a material and thereby providing a powder that can be compressed into a tablet. A wet binder is an excipient that in combination with water facilitates a powder to be compressed into tablets. A wet binder must, at least to some extent, be soluble in water. Examples of wet binders are PVP (polyvinylpyrrolidone), HPMC (hydroxymethylpropylcellulose) or gelatine.

A filler substance may be any pharmaceutically acceptable substance that does not interact with the peptide or with other excipients. Useful filler substances include sorbitol, mannitol, dextrins, maltodextrins, inositol, erythritol, isomalt, lactitol, maltitol, mannitol, xylitol, low-substituted hydroxypropylcellulose, starches or modified starches (e.g. potato starch, maize starch, rice starch, pre-gelatinised starch), polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, agar (e.g. sodium alginate), carboxyalkylcellulose, dextrates, gelatine, gummi arabicum, hydroxypropyl cellulose, hydroxypropylmethylcellulose, methylcellulose, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysaccharides e.g. dextran, soy polysaccharide, sodium carbonate, and sodium chloride.

In addition, ingredients such as peptides, enhancers, mucoadhesive agents, pH controlling agents, emulsifiers, taste masking agents, etc. usually also form part of the "water soluble ingredients".

Other commonly used tablet materials are *inter alia* discussed in Remington's Pharmaceutical Sciences, 18. Ed. 1990

Chewing gum particles containing gum base

The gum base contained in the compressed modules of the chewing gum tablet is typically present in the form of compressed gum base particles. Gum base is essentially insoluble in water. The manufacturing of gum base particles is described below. However, the particles may be manufactured according to conventional methods or e.g. those described in the EP 1 474 993, EP 1 474 994 and EP 1 474 995, hereby incorporated by reference.

As indicated above, the chewing gum particles contain gum base. The content of gum base in the particles may vary. In some embodiments, the amount of gum base in the chewing gum particles is rather high, such in the range of 40-99% by weight of the chewing gum particles. In some embodiments, the amount of gum base in the chewing gum particles is in the range of 40-90% by weight of the chewing gum particles, such as in the range of 40-80% by weight, including in the range of 40-70% by weight, e.g. in the range of 40-50% by weight, such as in the

range of 50-85% by weight, including in the range of 50-75% by weight, e.g. in the range of 50-55% by weight of the chewing gum particles.

In some other embodiments, the amount of gum base in the chewing gum particles is lower, such as in the range of 15-60% by weight of the chewing gum particles. Other useful amounts may vary in the range of 20-60% by weight of the chewing gum particles, such as in the range of 20-50%, including in the range of 20-40% by weight, e.g. in the range of 30-55% by weight, such as in the range of 30-45% by weight of the chewing gum particles. The remaining content of the chewing gum particles may comprise one or more of the below described chewing gum ingredients.

In some embodiments, the particles are made entirely of gum base, substantially without conventional chewing gum ingredients. In this case, the chewing gum ingredients may be applied in the compression process, such as by adding the chewing gum ingredients together with the gum base particles for compression.

In some other embodiments, the particles are made of chewing gum, substantially without further needs for chewing gum ingredients in the compression process. Of course, intermediate solutions may be applicable, such as a varying amount of chewing gum ingredients in the chewing gum particles or in the compression process.

It may be preferred to apply at least a certain amount of high intensity sweetener and/or flavour and/or colour to the chewing gum particles in some embodiments of the invention, such as in case the chewing gum particles substantially consist of gum base.

In preferred embodiments, the average particle size of the particles is in the range of 50-2000 μm measured as the longest dimension of the particle, preferably in the range of 100-1500 μm, and even more preferred in the range of 200-1300 μm.

In even more preferred embodiments, the chewing gum tablet is one wherein at least 70%, such as at least 80% or at least 90%, of the particles have a particle

size in the range of 50-2000 μm measured as the longest dimension of the particle, preferably in the range of 100-1500 μm, and even more preferred in the range of 200-1300 μm.

Gum base

The chewing gum tablet of the invention comprises a gum base. A useful gum base composition typically comprises one or more elastomeric compounds which may be of synthetic or natural origin, one or more resinous compounds which may be of synthetic or natural origin, fillers, softening compounds and minor amounts of miscellaneous ingredients such as antioxidants and colorants, etc. One advantage of the present invention is that there is no need to adjust the content of other chewing gum ingredients in order to maintain the desired texture. Furthermore, a very interesting observation is that no disintegration of the chewing gum occurs upon chewing.

The compressed module containing gum base may typically be made on the basis of gum base particles. The gum base particles are made on the basis of a gum base. In addition to the above definition of the expression "gum base", the expression further refers to the water-insoluble part of the chewing gum tablet which typically constitutes 10 to 99% by weight, including the range of 20-99% by weight of the total chewing gum composition, such as the range of 30-99% by weight of the total chewing gum tablet. In preferred embodiments, the chewing gum tablet comprises gum base in the range of 10-80% by weight of the chewing gum tablet, preferably in the range 20-70% by weight, and even more preferably in the range 30-60% by weight of the chewing gum tablet.

The gum base, which is admixed with chewing gum ingredients *(infra)*, can vary substantially depending on the particular product to be prepared and on the desired masticatory and other sensory characteristics of the final product. However, typical ranges (weight %) of the above gum base components are: 5 to 50% by weight elastomeric compounds, 5 to 55% by weight elastomer plasticizers, 0 to 50% by weight filler/texturiser, 5 to 35% by weight softener and 0 to 1% by weight of miscellaneous ingredients such as antioxidants, colorants, etc.

In a preferred embodiment, the gum base comprises an elastomer. Natural elastomers may include natural rubber such as smoked or liquid latex and guayule as well as natural gums such as jelutong, lechi caspi, massaranduba balata, sorva, perillo, rosindinha, massaranduba chocolate, chicle, nispero, gutta hang kang, and combinations thereof. Useful synthetic elastomers include, but are not limited to, synthetic elastomers listed in U.S. Food and Drug Administration, CFR, Title 21, Section 172,615, the Masticatory Substances, Synthetic, the contents of which are incorporated herein by reference for all purposes, such as polyisobutylene. e.g. having an average molecular weight in the range of about 10,000 to 1,000,000 including the range of 50,000 to 80,000, isobutylene-isoprene copolymer (butyl elastomer), styrene- butadiene copolymers e.g. having styrene-butadiene ratios of about 1:3 to 3:1, polyvinyl acetate (PVA), e.g. having a average molecular weight in the range of 2,000 to 90,000 such as the range of 3,000 to 80,000 including the range of 30,000 to 50,000, where the higher molecular weight polyvinyl acetates are typically used in bubble gum base, polyisoprene, polyethylene, vinyl acetate-vinyl laurate copolymer e.g. having a vinyl laurate content of about 5 to 50% by weight such as 10 to 45% by weight of the copolymer and combinations hereof.

It is possible to combine a synthetic elastomer having a high molecular weight and a synthetic elastomer having a low molecular weight elastomer in a gum base. Presently preferred combinations of synthetic elastomers include, but are not limited to, polyisobutylene and styrene-butadiene, polyisobutylene and polyisoprene, polyisobutylene and isobutylene-isoprene copolymer (butyl rubber) and a combination of polyisobutylene, styrene-butadiene copolymer and isobutylene isoprene copolymer, and all of the above individual synthetic polymers in admixture with polyvinyl acetate, vinyl acetate-vinyl laurate copolymers, respectively and mixtures thereof.

Typically, the gum base comprises at least one elastomer in an amount in the range of 3-80% by weight of the gum base, preferably in an amount in the range of 4-60% by weight of the gum base, and even more preferred in the range of 5-40% by weight of the gum base, such as in the range of 8-20% by weight of the gum base.

Particularly interesting elastomeric or resinous polymer compounds which advantageously can be used in accordance with the present invention include polymers which, in contrast to currently used elastomers and resins, can be degraded physically, chemically or enzymatically in the environment after use of the chewing gum, thereby giving rise to less environmental pollution than chewing gums based on non-degradable polymers, as the used degradable chewing gum remnants will eventually disintegrate and/or can be removed more readily by physical or chemical means from the site where it has been dumped.

In preferred embodiments, the gum base of the chewing gum tablet comprises one or more resins contributing to obtain the desired masticatory properties and acting as plasticizers for the elastomers of the gum base. The resin may be a natural resin and/or it may be a synthetic resin. In the present context, useful resins include, but are not limited to, natural rosin esters, often referred to as ester gums including as examples glycerol esters of partially hydrogenated rosins, glycerol esters of polymerised rosins, glycerol esters of partially dimerised rosins, glycerol esters of tally oil rosins, pentaerythritol esters of partially hydrogenated rosins, methyl esters of rosins, partially hydrogenated methyl esters of rosins and pentaerythritol esters of rosins. Other useful resinous compounds include synthetic resins such as terpene resins derived from alpha-pinene, beta-pinene, and/or d-limonene, natural terpene resins; and any suitable combinations of the foregoing. The choice of resins will vary depending on the specific application, and on the type of elastomer(s) being used. It should be noted that the resin may also form part of a matrix encapsulating various ingredients, in particular taste masking ingredients such as e.g. acids, sweeteners, flavours, as well as other constituents such as peptides, enhancers, mucoadhesive agents, etc.

Usually, the gum base comprises at least one resin in an amount in the range of 10-90% by weight of the gum base, preferably in the range of 20-80% by weight, even more preferred in the range of 30-70% by weight of the gum base, such as in the range of 40-60% by weight of the gum base. In preferred embodiments, the gum base comprises at least one resin in the range of 3-80% by weight of the gum base, preferably in an amount in the range of 4-60% by weight of the gum base, and even more preferred in the range of 5-40% by weight of the gum base, such as in the range of 8-20% by weight of the gum base.

The gum base may furthermore comprise one or more softeners. In the present context, the term "softener" may be used interchangeably with term like "plasticizer" and "plasticizing agent", and is used for ingredients, which softens the gum or chewing gum formulation and encompass wax, fat, oil, emulsifiers, surfactants, solubilizers etc. The softeners may also include sucrose polyesters, such as glycerin, lecithin, and combinations thereof. Aqueous sweetener solutions such as those containing sorbitol, hydrogenated starch hydrolysates, corn syrup and combinations thereof, may also be used as softeners and binding agents in the chewing gum according to the invention.

In a preferred embodiment, the gum base comprises an emulsifier, which aid in dispersing any immiscible components into a single stable system. The emulsifiers useful in this invention include glyceryl monostearate, lecithin, fatty acid monoglycerides, diglycerides, propylene glycol monostearate, and the like, and mixtures thereof. The emulsifier may be employed in an amount in the range of 1-15% by weight of the gum base, and preferably in the range 5-10% by weight of the gum base.

Further examples of useful emulsifier include anionic, cationic, amphoteric or non-ionic emulsifiers can be used. Suitable emulsifiers include lecithins, polyoxyethylene stearate, polyoxyethylene sorbitan fatty acid esters, fatty acid salts, mono and diacetyl tartaric acid esters of mono and diglycerides of edible fatty acids, citric acid esters of mono and diglycerides of edible fatty acids, saccharose esters of fatty acids, polyglycerol esters of fatty acids, polyglycerol esters ofinteresterified castor oil acid (E476), sodium stearoyllatylate, sodium lauryl sulfate and sorbitan esters of fatty acids and polyoxyethylated hydrogenated castor oil (e.g. the product sold under the trade name CREMOPHOR), block copolymers of ethylene oxide and propylene oxide (e.g. products sold under trade names PLURONIC and POLOXAMER), polyoxyethylene fatty alcohol ethers, polyoxyethylene sorbitan fatty acid esters, sorbitan esters of fatty acids and polyoxyethylene steraric acid esters.

Particularly suitable emulsifiers are polyoxyethylene stearates, such as for instance polyoxyethylene (8) stearate and polyoxyethylene (40) stearate, the

polyoxyethylene sorbitan fatty acid esters sold under the trade name TWEEN, for instance TWEEN 20 (monolaurate), TWEEN 80 (monooleate), TWEEN 40 (monopalmitate), TWEEN 60 (monostearate) or TWEEN 65 (tristearate), mono and diacetyl tartaric acid esters of mono and diglycerides of edible fatty acids, citric acid esters of mono and diglycerides of edible fatty acids, sodium stearoyllactylate, sodium laurylsulfate, polyoxyethylated hydrogenated castor oil, blockcopolymers of ethylene oxide and propyleneoxide and polyoxyethylene fatty alcohol ether. The emulsifiers may either be a single compound or a combination of several compounds.

Some emulsifiers may also be considered to be plasticizers, and provide a variety of desirable textures and consistency properties. Because of the low molecular weight of these components, the plasticizers are able to penetrate the fundamental structure of the gum base making it plastic and less viscous. Useful plasticizers include lanolin, palmitic acid, oleic acid, stearic acid, sodium stearate, potassium stearate, glyceryl triacetate, glyceryl lecithin, glyceryl monostearate, propylene glycol monostearate, acetylated monoglyceride, glycerine, and the like, and mixtures thereof.

In preferred embodiments, the softener used in the gum base of the chewing gum of the invention is a fat. The fat may e.g. include partially or fully hydrogenated vegetable or animal fats, such as partially or fully hydrogenated coconut oil, partially or fully hydrogenated palm oil, partially or fully hydrogenated palm kernel oil, partially or fully hydrogenated rapeseed oil, partially or fully hydrogenated castor oil, partially or fully hydrogenated maize oil, partially or fully hydrogenated cottonseed oil, partially or fully hydrogenated olive oil, partially or fully hydrogenated sunflower oil, partially or fully hydrogenated safflower oil, partially or fully hydrogenated sesame oil, partially or fully hydrogenated soybean oil, partially or fully hydrogenated beef tallow, and partially or fully hydrogenated lard, and any mixture thereof and any derivative thereof. In useful embodiments, the gum base comprises a fat in an amount in the range of 1-15% by weight of the gum base, and preferably in the range 5-10% by weight of the gum base.

The gum base may furthermore comprise a wax. When a wax is present in the gum base, it softens the polymeric elastomer mixture and improves the elasticity

of the gum base. The waxes employed will have a melting point below about 60°C, and preferably between about 45°C and about 55°C. The low melting wax may be a paraffin wax. The wax may be present in the gum base in an amount from about 6% to about 10%, and preferably from about 7% to about 9.5% by weight of the gum base.

In addition to the low melting point waxes, waxes having a higher melting point may be used in the gum base in amounts up to about 5%, by weight of the gum base. Such high melting waxes include beeswax, vegetable wax, candelilla wax, canauba wax, most petroleum waxes, and the like, and mixtures thereof.

Further useful waxes include natural and synthetic waxes, hydrogenated vegetable oils, petroleum waxes such as polyurethane waxes, polyethylene waxes, paraffin waxes, microcrystalline waxes, fatty waxes, sorbitan monostearate, tallow, propylene glycol, mixtures thereof, and the like, may also be incorporated into the gum base.

Anhydrous glycerin may also be employed as a softening agent, such as the commercially available United States Pharmacopeia (USP) grade. Glycerin is a syrupy liquid with a sweet warm taste and has a sweetness of about 60% of that of cane sugar. Because glycerin is hygroscopic, the anhydrous glycerin may be maintained under anhydrous conditions throughout the preparation of the chewing gum composition.

In an embodiment of the invention, the gum base comprises at least one resin in an amount in the range of 10-90% by weight of the gum base, at least one elastomer in an amount in the range of 4-60% by weight of the gum base, and an emulsifier in an amount in the range of 1-15% by weight. Preferably, the gum base comprises at least one resin in an amount in the range of 30-70% by weight of the gum base, at least one elastomer in an amount in the range of 5-40% by weight of the gum base, and an emulsifier in an amount in the range of 5-10% by weight of the gum base.

In a preferred embodiment, the gum base of the chewing gum according to the invention comprises a filler. The fillers/texturizers may include magnesium and

calcium carbonate, sodium sulphate, ground limestone, silicate types such as magnesium and aluminium silicate, kaolin, clay, aluminium oxide, silicium oxide, talc, titanium oxide, mono-, di- and tri-calcium phosphates, cellulose polymers, such as wood, and combinations thereof.

The fillers/texturizers may also include natural organic fibres such as fruit vegetable fibres, grain, rice, cellulose and combinations thereof.

Chewing gum ingredients

The chewing gum tablet typically comprises further chewing gum ingredients. Examples of such chewing gum ingredients include, but is not limited to, bulk sweeteners, high intensity sweeteners, flavouring agents, cooling agents, warming agents, and combinations thereof.

In a useful embodiment of the present invention, the at least one chewing gum ingredient is a bulk sweetener. The bulk sweetener may be selected from the group consisting of monosaccharides, disaccharides, polysaccharides, sugar alcohols, and mixtures thereof; randomly bonded glucose polymers such as those polymers distributed under the tradename POLYDEXTROSE by Pfizer, Inc., Groton, Conn.; isomalt (a racemic mixture of alpha-D-glucopyranosyl-1,6-mannitol and alpha-D-glucopyranosyl-1,6-sorbitol manufactured under the tradename PALATINIT by Süddeutsche Zucker), maltodextrins; hydrogenated starch hydrolysates; hydrogenated hexoses; and hydrogenated disaccharides.

Furthermore, the bulk sweetener may be selected from the group consisting of dextrose, sucrose, lactose, xylitol, mannitol, sorbitol, mannitol, maltitol, isomaltol or isomalt, erythritol, lactitol, and cyclodextrin.

In a preferred embodiment of the invention, the bulk sweetener is present in amount ranging from 10-70% by weight of the chewing gum tablet. Preferably, the bulk sweetener may be present in amount ranging from 30-70% by weight of the chewing gum tablet, such as in the range 35-65% by weight of the chewing gum tablet, e.g. in the range 40-60% by weight of the chewing gum tablet. For example, the bulk sweetener may be present in amount ranging from 20-55% by

weight of the chewing gum tablet, such as in amount ranging from 30-50% by weight of the chewing gum tablet.

In an interesting embodiment, the chewing gum tablet further comprises a high intensity sweetener. Useful high intensity sweetener may be selected from the group consisting of sucralose, neotame, aspartame, salts of acesulfame, alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizin, dihydrochalcones e.g. NHDC, thaumatin, monellin, stevioside, Twinsweet (aspartame-acesulfame salt) and combinations thereof.

In order to provide longer lasting sweetness and flavour perception, it may be desirable to encapsulate or otherwise control the release of at least a portion of the high intensity sweetener. Likewise, encapsulation may be applied for the purpose of stabilizing the ingredients. Techniques such as wet granulation, wax granulation, spray drying, spray chilling, fluid bed coating, coascervation, encapsulation in yeast cells and fiber extrusion may be used to achieve the desired release characteristics. Encapsulation of high intensity sweeteners can also be provided e.g. using another chewing gum component, such as a resinous compound, as the encapsulation agent. These encapsulation methods (spray drying, etc.) may also be employed in order to encapsulate e.g. peptides and/or enhancer.

The concentration of the high intensity sweetener will vary considerably depending e.g. on factors such as potency of the sweetener, rate of release, desired sweetness of the product, level and type of flavour used and cost considerations. Thus, the level of high intensity sweetener will typically vary from about 0.02% to 8% by weight of the chewing gum tablet. When carriers used for encapsulation are included, the usage level of the encapsulated high intensity sweetener will be proportionally higher. Combinations of sugar and/or non-sugar sweeteners can be used in the chewing gum formulation processed in accordance with the invention. Additionally, the softener may also provide additional sweetness such as with aqueous sugar or alditol solutions.

If a low calorie chewing gum tablet is desired, a low calorie bulking agent can be used. Examples of low calorie bulking agents include polydextrose, Raftilose,

Raftilin, Inuline, fructooligosaccharides (NutraFlora®), palatinose oligosaccharided; guar gum hydrolysates (e.g. Sun Fiber®) or indigestible dextrins (e.g. Fibersol®). However, other low calorie-bulking agents can be used.

Flavouring agents may also be useful for the organoleptic properties of the chewing gum tablet. The flavouring agents which may be used include those flavouring agents known to the skilled artisan, such as natural and artificial flavouring agents. These flavouring agents may be chosen from synthetic flavour oils and flavouring aromatics and/or oils, oleoresins and extracts derived from plants, leaves, flowers, fruits, and so forth, and combinations thereof. Non-limiting representative flavour oils include spearmint oil, cinnamon oil, oil of wintergreen (methyl salicylate), peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil, thyme oil, cedar leaf oil, oil of nutmeg, allspice, oil of sage, mace, oil of bitter almonds, and cassia oil. Also useful flavouring agents are artificial, natural and synthetic fruit flavours such as vanilla, and citrus oils including lemon, orange, lime, grapefruit, and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. These flavouring agents may be used in liquid or solid form and may be used individually or in admixture. Commonly used flavouring agents include mints such as peppermint, menthol, spearmint, artificial vanilla, cinnamon derivatives, and various fruit flavouring agents, whether employed individually or in admixture.

Other useful flavouring agents include aldehydes and esters such as cinnamyl acetate, cinnamaldehyde, citral diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylamisol, and so forth may be used. Generally any flavouring agent or food additive such as those described in Chemicals Used in Food Processing, publication 1274, pages 63-258, by the National Academy of Sciences, may be used. This publication is incorporated herein by reference.

Further examples of aldehyde flavouring agents include, but are not limited to, acetaldehyde (apple), benzaldehyde (cherry, almond), anisic aldehyde (licorice, anise), cinnamic aldehyde (cinnamon), citral, i.e., alpha-citral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), ethyl vanillin (vanilla, cream), heliotrope, i.e., piperonal (vanilla, cream), vanillin (vanilla, cream), alpha-amyl cinnamaldehyde (spicy fruity flavours), butyraldehyde (butter,

cheese), valeraldehyde (butter, cheese), citronellal (modifies, many types), decanal (citrus fruits), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), 2-ethyl butyraldehyde (berry fruits), hexenal, i.e., trans-2 (berry fruits), tolyl aldehyde (cherry, almond), veratraldehyde (vanilla), 2,6-dimethyl-5-heptenal, i.e., melonal (melon), 2,6-dimethyloctanal (green fruit), and 2-dodecenal (citrus, mandarin), cherry, grape, strawberry shortcake, and mixtures thereof.

In some embodiments, the flavouring agent may be employed in either liquid form and/or dried form. When employed in the latter form, suitable drying means such as spray drying the oil may be used. Alternatively, the flavouring agent may be absorbed onto water soluble materials, such as cellulose, starch, sugar, maltodextrin, gum arabic and so forth or may be encapsulated. The actual techniques for preparing such dried forms are well-known.

In some embodiments, the flavouring agents may be used in many distinct physical forms well-known in the art to provide an initial burst of flavour and/or a prolonged sensation of flavour. Without being limited thereto, such physical forms include free forms, such as spray dried, powdered, beaded forms, encapsulated forms, and mixtures thereof.

The amount of flavouring agent employed herein may be a matter of preference subject to such factors as the type of final chewing gum, the individual flavour, the gum base employed, and the strength of flavour desired. Thus, the amount of flavouring may be varied in order to obtain the result desired in the final product and such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In chewing gum compositions, the flavouring agent is generally present in amounts from about 0.02% to about 5% by weight, and more specifically from about 0.1% to about 2% by weight, and even more specifically, from about 0.8% to about 1.8%, by weight of the chewing gum tablet.

Encapsulated flavours may be added to the final blend prior to compression. Different methods of encapsulating flavours mixed into the gum base and flavours compressed into the chewing gum may e.g. include spray drying, spray cooling,

film coating, coascervation, double emulsion method (extrusion technology) or prilling. Materials to be used for the above-mentioned encapsulation methods may e.g. include gelatine, wheat protein, soya protein, sodium caseinate, caseine, gum arabic, modified starch, hydrolyzed starches (maltodextrines), alginates, pectin, carregeenan, xanthan gum, locus bean gum, chitosan, bees wax, candelilla wax, camauba wax, hydrogenated vegetable oils, zein and/or sucrose.

Useful cooling agents are mentioned in US 6,627,233, the contents of which are incorporated herein by reference for all purposes. Particular examples of cooling agents include: menthol, xylitol, menthane, menthone, menthyl acetate, menthyl salicylate, N,2,3-trimethyl-2-isopropyl butanamide (WS-23), substituted p-menthanes, substituted p-menthane-carboxamides (e.g., N-ethyl-p-menthane-3-carboxamide (FEMA 3455)), acyclic carboxamides, substituted cyclohexanamides, substituted cyclohexane carboxamides, substituted ureas and sulphonamides, and substituted menthanols (all from Wilkinson Sword); hydroxymethyl and hydroxyethyl derivatives of p-menthane (from Lever Bros.); menthyl succinate; 2-mercapto-cyclo-decanone (from International Flavors and Fragrances); 2-isopropanyl-5-methylcyclohexanol (from Hisamitsu Pharmaceuticals, hereinafter "isopregol"); hydroxycarboxylic acids with 2-6 carbon atoms; menthone glycerol ketals (FEMA 3807, tradename FRESCOLAT(TM) type MGA); 3-l-menthoxypropane-1,2-diol (from Takasago, FEMA 3784, (hereinafter "TCA")); menthyl lactate; (from Haarman & Reimer, FEMA 3748, tradename FRESCOLAT(TM) type ML). These and other suitable cooling agents are further described in the following US patents, all of which are incorporated in their entirety by reference hereto: US 4,230,688; US 4,032,661; US 4,459,425; US 4,136,163; and US 5,266,592. The cooling agents are typically present in amounts from about 0.001& to about 10% by weight of the chewing gum tablet.

Useful warming agents may be selected from a wide variety of compounds known to provide the sensory signal of warming to the user. These compounds offer the perceived sensation of warmth, particularly in the oral cavity, and often enhance the perception of flavours, sweeteners and other organoleptic components. Among the useful warming compounds included are vanillyl alcohol n-butylether (TK-1000) supplied by Takasago Perfumary Company Limited, Tokyo, Japan, vanillyl alcohol n-propylether, vanillyl alcohol isopropylether, vanillyl alcohol

isobutylether, vanillyl alcohol n-aminoether, vanillyl alcohol isoamyleather, vanillyl alcohol n-hexyleather, vanillyl alcohol methylether, vanillyl alcohol ethyleather, gingerol, shogaol, paradol, zingerone, capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, homodihydrocapsaicin, ethanol, isopropol alcohol, iso-amylalcohol, benzyl alcohol, glycerine, and combinations thereof. Furthermore, useful warming agents include capsicum and nicotinate esters, such as benzyl nicotinate.

Whiteners and colouring agents may be used in amounts effective to produce the desired colour. The colouring agents may include pigments which may be incorporated in amounts up to about 6%, by weight of the chewing gum tablet. For example, titanium dioxide may be incorporated in amounts up to about 2%, but preferably less than about 1%, by weight of the chewing gum tablet. Colouring agents may also include natural food colours and dyes suitable for food, drug and cosmetic applications. These colouring agent are known as F.D.& C. dyes and lakes. The materials acceptable for the foregoing uses are preferably water-insoluble. Illustrative non-limiting examples include the indigoid dye known as F.D.& C. Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as F.D.& C. Green No. 1 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-(N-ethyl-p-sulfoniumbenzylamino) diphenylmethylene]-[1-(N-ethyl-N-p-- sulfoniumbenzyl)-delta-2,5-cyclohexadieneimine]. A full recitation of all F.D.& C. colourants and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition, in volume 5 at pages 857-884, which text is incorporated herein by reference.

Encapsulation of taste masking agents, peptides and absorption enhancers

Food acids may enhance the perception of other ingredients in the compressed chewing gum tablet. If the taste masking agents comprise e.g. both food acids and flavouring agents, the perception of the flavouring agents may thus be enhanced by the presence of food acids.

However, in relation to various chewable chewing gums, the release of taste masking agents such as e.g. food acids and flavouring agents do not always follow

the same release profile upon chewing. Usually food acids tend to release rather quickly from the chewing gum upon chewing, while e.g. flavouring agents tend to remain in the chewing gum for a longer period. Consequently, if food acids are released from the chewing gum rather quickly, the perception of the other ingredients in the confectionary base may be significantly reduced, and the effects of the taste masking agents may thus be impaired.

Delayed release of food acids and flavouring agents may be accomplished by a method of encapsulating one or more food acids into an encapsulation material, and subsequently incorporating the encapsulation material in the compressed chewing gum tablet as discrete encapsulations for delivery of the taste masking agents upon chewing.

Another advantage of encapsulating food acids is that it may buffer food acids from other ingredients, and vice versa, which may be helpful in situations where the food acids and said ingredients may interact or react together in a manner that degrades the product if the food acid is not encapsulated.

The one or more flavouring agents may also be encapsulated separate from the one or more food acids, optionally with a different encapsulation material than the one or more food acids.

For some food acids and flavouring agents it may however also be an advantage to encapsulate one or more food acids and one or more flavouring agents together in order to ensure their simultaneous release. Alternatively, the one or more food acids and the one or more flavouring agents are encapsulated separately in encapsulation material having substantially the same release characteristics, optionally being encapsulated in identical encapsulation material.

Another interesting option is to encapsulate peptides together with the one or more food acids. The peptides may however also be encapsulated separately, optionally in encapsulation material having substantially the same release characteristics as the encapsulation material of the one or more food acids, optionally being encapsulated in identical encapsulation material. It is also envisioned that peptides may be encapsulated together with one or more flavouring agents as well as one or more food acids. Alternatively, peptides, the

one or more flavouring agents, and the one or more food acids are encapsulated separately in encapsulation materials having substantially the same release characteristics, optionally identical release characteristics.

Encapsulating peptides and/or absorption enhancers together or separately may also be advantageous for obtaining desired release characteristics. Encapsulation of peptides may in particular achieve slow or controlled release of peptides in order to avoid excessive ingestion of peptides via the gastrointestinal route. Encapsulation of peptides and one or more absorption enhancers together may help to ensure better absorption through the buccal membrane since the two components are released simultaneously. Alternatively, peptides and one or more absorption enhancers are encapsulated separately in encapsulation material having substantially the same release characteristics, optionally being encapsulated in identical encapsulation material.

Another interesting option is to encapsulate one or more mucoadhesive agents together with the one or more absorption enhancers. The one or more mucoadhesive agents may however also be encapsulated separately, optionally in encapsulation material having substantially the same release characteristics as the encapsulation material of the one or more absorption enhancers, optionally being encapsulated in identical encapsulation material. It is also envisioned that peptides may be encapsulated together with one or more absorption enhancers as well as one or more mucoadhesive agents. Alternatively, peptides, the one or more absorption enhancers, and the one or more mucoadhesive agents are encapsulated separately in encapsulation materials having substantially the same release characteristics, optionally identical release characteristics.

It may also be envisioned encapsulating peptides, one or more flavouring agents, and one or more absorption enhancers together. Alternatively, they are encapsulated separately in encapsulation material having substantially the same release characteristics, optionally being encapsulated in identical encapsulation material. A particularly interesting option may be to encapsulate peptides and the one or more absorption enhancers together, while the one or more flavouring agents are encapsulated separately from peptides and the one or more absorption enhancers. The encapsulation material of peptides and the one or more absorption

enhancers may have substantially the same release characteristics as the encapsulation material of the one or more flavouring agents.

It may further be envisioned encapsulating peptides, one or more food acids, one or more flavouring agents, one or more absorption enhancers, and one or more mucoadhesive agents separately or together. It may e.g. be envisioned encapsulating peptides, one or more food acids, one or more flavouring agents, and one or more absorption enhancers together. Alternatively, they are encapsulated separately in encapsulation material having substantially the same release characteristics, optionally being encapsulated in identical encapsulation material. A particularly interesting option may be to encapsulate peptides and the one or more absorption enhancers together, while the one or more flavouring agents and the one or more food acids are encapsulated together, separate from peptides and the one or more absorption enhancers. The encapsulation material of peptides and the one or more absorption enhancers may have substantially the same release characteristics as the encapsulation material of the one or more flavouring agents and the one or more food acids.

It may even be desirable to include one or more components in the compressed chewing gum tablet in both an encapsulated form as well as in a non-encapsulated form in order to ensure that a fraction of the compound is released relatively fast, whereas the remaining (encapsulated) part is released relatively slowly.

The encapsulation material may comprise at least one natural resin, such as at least one polyterpene resin, at least one hydrogenated resin, or at least one polymerised resin, or mixtures thereof.

The at least one polyterpene resin may comprise polymerised monoterpenes. It is envisioned that the at least one polyterpene resin may consist essentially of polymerised monoterpenes.

The at least one polyterpene resin may also comprise polymerised cyclic monoterpenes, and it envisioned that the at least one polyterpene resin may consist essentially of polymerised cyclic monoterpenes.

The at least one polyterpene resin may further comprise polymerised limonene. The at least one polyterpene resin may consist essentially of polymerised limonene.

The at least one polyterpene resin may also comprise polymerised alpha-pinene. The at least one polyterpene resin may consist essentially of polymerised alpha-pinene.

The at least one polyterpene resin may further comprise polymerised beta-pinene. The at least one polyterpene resin may consist essentially of polymerised beta-pinene.

Also, the at least one polyterpene resin may comprise styrenated polyterpene resin.

The encapsulation material may comprise a combination of two or more polyterpene resins. For example the encapsulation material may comprise a combination of polymerised alpha-pinene and polymerised beta-pinene; a combination of polymerised alpha-pinene and polymerised limonene; a combination of polymerised alpha-pinene and styrenated polyterpene resin.

In an embodiment of the invention, the at least one polyterpene resin comprises at least 50% by weight polymerised monoterpenes, preferably at least 75% by weight polymerised monoterpenes, even more preferably at least 95% by weight polymerised monoterpenes.

In another embodiment of the invention, the at least one polyterpene resin comprises at least 50% by weight polymerised cyclic monoterpenes, preferably at least 75% by weight polymerised cyclic monoterpenes, even more preferably at least 95% by weight polymerised cyclic monoterpenes.

Natural resins comprised in the encapsulation delivery system may include, but are not limited to, natural rosin esters, often referred to as ester gums including as examples glycerol esters of partially hydrogenated rosins, glycerol esters of

polymerised rosins, glycerol esters of partially dimerised rosins, glycerol esters of tally oil rosins, pentaerythritol esters of partially hydrogenated rosins, methyl esters of rosins, partially hydrogenated methyl esters of rosins and pentaerythritol esters of rosins.

The compressed chewing gum tablet of the invention may comprise two or more different encapsulation materials, such as three or more different encapsulation materials. The different encapsulation materials may have different release characteristics.

In one embodiment, the encapsulation material may comprise at least one polyvinyl acetate. For example, the encapsulation material used to encapsulate one of the components discussed above as suitably being encapsulated may comprise at least one polyterpene resin and a second encapsulation material used to encapsulate another of the components discussed above as suitably being encapsulated may comprise at least one polyvinyl acetate.

Also, the encapsulation material used to encapsulate one of the components discussed above as suitably being encapsulated may comprise at least one hydrogenated resin and a second encapsulation material used to encapsulate another of the components discussed above as suitably being encapsulated may comprise at least one polyvinyl acetate.

Alternatively, the encapsulation material used to encapsulate one of the components discussed above as suitably being encapsulated may comprise at least one polymerised resin and a second encapsulation material used to encapsulate another of the components discussed above as suitably being encapsulated may comprise at least one polyvinyl acetate.

Useful encapsulation materials comprising polyvinyl acetate are disclosed in the U.S. patent application with the publication No. 2005/0 260 266, the contents of which are incorporated herein by reference in its entirety.

The encapsulation component, e.g. food acids, may be encapsulated by first melting the encapsulation material, e.g. a natural resin, in e.g. a high shear

mixer. A softening system may then be added to the molten polymer. The encapsulation component, e.g. food acids, may then be added to the resulting mixture and mixed, e.g. under high shear.

The resulting filled polymer melt is then cooled and formed to a suitable size, e.g. by means such as chopping, pulverizing, milling or grinding. The encapsulated component may be stored in an air tight container with low humidity until it is to be employed in a compressed chewing gum tablet.

In other words, the method comprising the step of:

a) mixing the at least one encapsulation component, e.g. food acids with at least one encapsulation material, e.g. a natural resin,

b) converting the mixture of step a) to particles, thus obtaining the encapsulated component.

Step a) may also involve mixing components such as a softening system and/or at least one elastomer with the at least one encapsulation component and the at least one encapsulation material.

Further details on encapsulating food acids and other components for chewing gums etc. may be found inter alia in WO 2007/095939, U.S. patent application with the publication No. 2005/0 260 266, and U.S. patent No. 5,789,002, all of which are incorporated herein by reference.

Useful encapsulation materials comprising polyvinyl acetate are disclosed in the U.S. patent application with the publication No. 2005/0 260 266, the contents of which are incorporated herein by reference in its entirety.

Compression adjuvants may also be added. These compounds facilitate compression of the gum into tablets. Suitable compression adjuvants include, but are not limited to, glidants, lubricants, wetting agents, diluents, humectants. More specifically, useful compression adjuvants include silicon dioxide, magnesium stearate, calcium stearate, behenic acid, talc and similar substances which can be used to limit the tendency of the gum tablets to stick to the presses.

The above mentioned chewing gum ingredients may be pre-mixed into the gum base or be added to a portion of the chewing gum comprising no or a low amount of gum base.

In an embodiment of the invention, the chewing gum comprises a center filling. Furthermore, the chewing gum tablet may be processed into in a number of different shapes such as a stick, a core, a tablet, a slab, a bead, a pellet, a tape, or a ball.

Coating

The chewing gum tablet may comprise a coating applied onto the chewing gum tablet. A suitable coating is preferably a coating that results in extended storage stability of the compressed chewing gum products as defined above, relative to a chewing gum of the same composition that is not coated. Thus, suitable coating types include hard coatings, soft coatings, film coatings and sealing coatings of any composition including those currently used in coating of chewing gum, pharmaceutical products and confectioneries.

The chewing gum tablet comprises the coating in an amount in the range of 1-80% by weight of the tablet, such as in an amount in the range of 10-50%, or 15-45% by weight of the tablet. Preferably, the chewing gum tablet comprises the coating in an amount in the range of 20-40% by weight of the chewing gum tablet.

The coating may be a hard coating, which term is used in the conventional meaning of that term including sugar coatings and sugar-free (or sugarless) coatings and combinations thereof. The objects of hard coating are to obtain a sweet, crunchy layer, which is appreciated by the consumer, and to protect the composition for various reasons. In a typical process of providing the composition with a protective sugar coating the gum tablets are successively treated in suitable coating equipment with aqueous solutions of crystallizable sugar and/or polyols such as sucrose or dextrose, which, depending on the stage of coating reached, may contain other functional ingredients, e.g. fillers, colours, etc. In the present context, the sugar coating may contain further functional or active

compounds including flavour compounds, peptides and/or other therapeutically active compounds.

In the production of chewing gums it may, however, be preferred to replace the cariogenic sugar compounds in the coating by other, preferably crystallizable, sweetening compounds that do not have a cariogenic effect. In the art such coating is generally referred to as sugarless or sugar-free coatings. Preferred non-cariogenic hard coating substances include polyols, e.g. sorbitol, maltitol, mannitol, xylitol, erythritol, lactitol, isomalt and tagatose which are obtained by industrial methods by hydrogenation of D-glucose, maltose, fructose or levulose, xylose, erythrose, lactose, isomaltulose and D-galactose, respectively. One advantage of using polyols in the coating is that they may act simultaneously as a sweetener and as a taste masking agent.

The coating, in general, typically comprises one or more layers. For example the number of layers of the coating may be in the range of 1-100 layers, such as 3-75 layers, 10-60 layers, and 20-40 layers.

A compressed chewing gum tablet according to the present invention, has typically a weight in the range of 0.1-10 g, such as in the range of 0.5-5 g or in the range of 0.75-2.5 g, preferably in the range of 0.8-2 g, and even more preferred in the range of 1-1.5 g. Compressed center-filled chewing gum tabletss normally have weights in the range of 0.5-5 g, preferably in the range of 1-4 g, and even more preferred in the range of 2-3 g. Typical weights for bead shaped chewing gum tablets are in the range of 0.1-0.6 g, preferably in the range of 0.2-0.5 g, and even more preferred in the range of 0.3-0.4 g.

Additional therapeutically active compounds

In one embodiment of the invention, the compressed chewing gum tablet comprises, in addition to the at least one peptide, at least one additional therapeutically active compound. One example of such compounds include e.g. antimicrobial peptides such as e.g. KSL and/or KSL-W.

In general, the additional therapeutically active compound and the peptide is preferably located within the same compressed module(s). Moreover, it is

generally preferred that the additional therapeutically active compound does not form part of the compressed chewing gum particles containing gum base, i.e. the additional therapeutically active compound is located between the compressed chewing gum particles containing gum base.

Peptides:

Examples of peptides suitable for use in connection with the present invention include any peptidic compound with a therapeutic potential.

Examples of such peptides include: incretin mimetics, exendins, Liraglutide (Novo Nordisk), ZP-10 (Zealand Pharma), MC-4 Antagonists, PYY (3-36), Tesofensine (Neurosearch), Obinepitide (7TM Pharma), TM30339 (7TM Pharma), RHS08 (Rheoscience), vasopressin, a vasopressin polypeptide analog, desmopressin, glucagon, corticotropin, gonadotropin, C- peptide of insulin, parathyroid hormone, human growth hormone, growth hormone, growth hormone releasing hormone, oxytocin, corticotropin releasing hormone, somatostatin, a somatostatin polypeptide analog, gonadotropin agonist, a gonadotropin agonist polypeptide analog, atrial natriuretic peptide, thyroxine releasing hormone, follicle stimulating ho[pi]none, prolactin, growth factors, interleukin, polypeptide vaccine, enzyme, endorphin, glycoprotein, lipoprotein, a polypeptide involved in the blood coagulation cascade, peptide YY (PYY), parathyroid hormone (PTH), interferon-alpha (INF-.alpha.), interferon-beta (INF-.beta.), interferon-gamma (INF-.gamma.), human growth hormone (hGH), exenatide, glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), glucagon-like peptide-1 derivatives, oxytocin, insulin and carbetocin.

Particularly preferred peptides according to the present invention include: KSL (KKVVFKVKFK – corresponding to SEQ ID NO 1), and KSL-W (H_2N-Lys-Lys-Val-Val-Phe-Try-Val-Lys-Phe-Lys-COOH – corresponding to SEQ ID NO 2). In connection with use of KSL and KSL-W as anti-plaque agents, KSL-W is most preferred since this peptide is more resistant to peptidase digestion compared to KSL.

In connection with chewing gum compositions comprising antibacterial compounds and wherein said compositions are used anti-plague agents, it may be desirable to select enhancers that promote absorption to bacterial cell walls, and/or absorption to tooth enamel and/or buccal membranes rather than selecting enhancers that promote buccal absoption. A particularly preferred enhancer for use in an anti-plaque composition is CPC.

In connection with the present invention the terms "peptide", "peptidic compound", "polypeptide", "protein", etc. are used interchangeably. Chemically, peptides are polymers formed from the linking, in a defined order, of α-amino acids, although other covalent modifications of the amino acid chain may also occur. It may also be that two or more peptide chains are linked to each other via e.g. disulphide bridges. The peptides according to the present invention may in theory be of any length from 6 to 6000 amino acids. However, as the efficiency of buccal absorption of peptides is thought to decrease with increasing peptide lengths, the peptides are preferably of a length of about 6-4000 amino acids, more preferably about 8-2000 amino acids, more preferably about 8-1000 amino acids, more preferably about 8-500 amino acids, more preferably about 8-250 amino acids, more preferably about 8-200 amino acids, more preferably about 8-175 amino acids, more preferably about 8-150 amino acids, more preferably about 8-125 amino acids, more preferably about 8-100 amino acids, more preferably about 8-75 amino acids, and most preferably about 8-50 amino acids, and most preferably about 8-30 amino acids.

In a first aspect the present invention thus relates to a compressed chewing gum tablet comprising a first compressed module, wherein said tablet comprises at least one peptide and compressed chewing gum particles containing gum base.

In one embodiment, the tablet according to the invention comprises only one compressed module. In another embodiment, said tablet comprises a second compressed module. In yet another embodiments, the tablet according to the invention may even comprise a third and a fourth compressed module.

According to a particularly preferred embodiment, a first compressed module and a second compressed module are cohered to each other. According to another

preferred embodiment, the second compressed module does not contain gum base. According to yet another preferred embodiment, said first compressed module does not contain any peptide. In yet another particularly preferred embodiment, the tablet according to the invention comprises a second compressed module that comprises compressed tablet material. In yet another preferred embodiment, the first compressed module does not contain compressed tablet material.

According to another preferred embodiment, the tablet according to the present invention comprises one or more taste masking agent. Such taste masking agents typically comprise food, acids, flavours, and sweeteners as well as mixtures thereof. In a preferred embodiment one or more of such taste masking agents are encapsulated in a matrix comprising resin. Such resins may be synthetic or derived from natural resins as well as mixtures thereof.

According to yet another preferred embodiment, the tablet according to the invention comprises an absorption enhancer.

According to yet another preferred embodiment, the tablet according to the present invention comprises at least one antimicrobial peptide. According to a particularly preferred embodiment, the tablet according to the present invention comprises KSL-W or a derivative or variation thereof with antibacterial activity. In yet other preferred embodiments, the tablet according to the present invention comprises a peptide selected from the group consisting of di-peptides, tri-peptides, oligo-peptides, deca-peptides, deca-peptide KSL, deca-peptide KSL-W, amino acids, proteins, or any combination thereof.

In another aspect, the present invention relates to use of a tablet according to the present invention for use as a medicament.

In a third aspect, the present invention relates to use of a tablet according to the present invention for the manufacture of a chewing gum tablet for prevention and/or amelioration of dental plaque.

In a fourth aspect, the present invention relates to a method for the treatment of, or ameliorating the symptoms of, dental plaques, said method comprising administering a tablet according to the present invention to a patient in need thereof.

A final aspect relates to a method of making a chewing gum tablet according to the present invention, wherein said method comprises compression of chewing gum particles and peptides into a tablet.

Upon chewing the tablets according to the present invention, the amount of incretin mimetic being transferred from the tablet to the blood stream is about 1-25% of the amount in the tablet. The remaining 75-99% of the peptide in the tablet is either retained in the chewing gum and/or swallowed and digested. Preferably about 2-15% of the peptide is transferred to the blood stream, more preferably 3-10%, and most preferably 5-8%.

EXAMPLES

Example I

Preparation of compressed chewing gum tablets comprising KSL-W

Mixture I (Layer 1)		%	g/1000 g *)
Gum base		40	400
Sweetener - Xylitol		52,7	520
High intense sweetener acesulfame		1	10
Peppermint flavour		6	60
Magnesium stearate		1	10
Total		100,7	1000
mixture II (Layer 2)		%	g/500g
Premixture.			
	KSL-W	0,80	4
	Cetylpyridinium Chloride (CPC)	0,16	0,8
	Sorbitol	20,00	100
Sorbitol		72,74	364
Acesulfame		1,00	5
Peppermint flavour		5,00	25
Magnesium stearate		0,30	1,5
Total		100	500

1000 tablets á 1500 mg.

*) lab production

The premixture is mixed dry in a conventional dry mixer.

The ingredients for each layer including the premixture are mixed dry in a conventional dry mixer and formed into a tablet in a tablet machine:

Chewing gum mixture I is passed to a standard tablet pressing machine comprising dosing apparatus (e.g. P 3200 C, available from Fette GmbH, Germany) and compressed to form a first compressed module. Subsequent, mixture II is filed into the tablet pressing machine and compressed onto the first module to form a chewing gum tablet having two compressed modules.

The mixtures gave a total of 1000 tablets where each tablet is made op of layer 1 = 1000 mg and layer 2 = 500 mg. The content of KSL-W is 4 mg per piece and CPC 0,8 mg per piece. If a tablet with a higher or lower content af KSL-W and CPC is desired, the amounts of KSL-W, CPC and sorbitol are adjusted correspondingly.

Example 2

In vitro release of KSL-W of the chewing gum tablets obtained in Example 1

The in vitro release of KSL-W and CPC from the tablet was performed with the chewing apparatus described in the European Pharmacopea.
The apparatus is composed of a temperature controlled chewing chamber with two horizontal pistons and one vertical piston.
A chewing gum tablet is placed in the chamber and 20 ml of a phosphate buffer equilibrated to 37 º C is added. During the chewing cycle the two horizontal pistons move towards each other and press the chewing gum between them before returning to the starting point. Before the next cycle the vertical piston move down and press the chewing gum down, resulting in a better and reproducible chewing of the gum. The cycle rate is set to 60 per minute.

At 2, 5, 10, 20 and 30 minutes a sample is removed from the reservoir and the content of exenatide is determined.

Example 3

Stability of KSL-W in chewing gum tablets.

The chewing gum tablets obtained in example 1 are packed in commercial packages (blister packs, Duma bottles and/or aluminium bags) and stored for up to 3 months at conditions 40°C/75% RH and 21°C/55% RH.
The amount of exenatide is measured at the beginning of the storage (initial amount) and after 1, 2 and 3 months.

Example 4

The chewing gum tablets obtained in example 1 and corresponding placebo tablets are distributed to 2x24 healthy volunteers. The volunteers are chewing the tablets for ten minutes two time a day for a 1-month period.
Dental plaque is assessed at entry, 2 weeks and 4 weeks
Plaque scores for each group of subjects participating in the test is calculated and analysed by mean of a statistical program.

CLAIMS

1. A compressed chewing gum tablet comprising a first compressed module, wherein said tablet comprises at least one peptide and compressed chewing gum particles containing gum base.

2. The tablet according to claim 1, wherein said first compressed module is the only compressed module present in said tablet.

3. The tablet according to any one of claims 1-2, wherein said tablet comprises a second compressed module.

4. The tablet according to any one of the preceding claims, wherein said tablet comprises one or more taste masking agent.

5. The tablet according to any one of claims 1-4, wherein said tablet comprises an encapsulation delivery system.

6. The tablet according to any one of the preceding claims, wherein said tablet comprises an absorption enhancer selected from the group consisting of: solubilization agents, charge modifying agents, pH control agents, degradative enzyme inhibitors, mucolytic or mucus clearing agents, membrane penetration-enhancing agents, modulatory agents of epithelial junction physiology, vasodilator agents, selective transport-enhancing agents, stabilizing delivery vehicles, small hydrophilic penetration enhancers and emulsifiers.

7. The tablet according to any one of the preceding claims, wherein said tablet comprises a mucoadhesive agent.

8. The tablet according to any one of the preceding claims, wherein said tablet comprises an absorption enhancer and a mucoadhesive agent.

9. The tablet according to any one of the preceding claims, wherein said tablet comprises at least one antimicrobial peptide.

10. The tablet according to any of the preceding claims, wherein said tablet comprises a peptide selected from the group consisting of di-peptides, tri-peptides, oligo-peptides, deca-peptides, deca-peptide KSL, deca-peptide KSL-W, amino acids, proteins, or any combination thereof.

11. The tablet according to claim 10, wherein said tablet comprises KSL-W.

12. The tablet according to any of the preceding claims for use as a medicament.

13. Use of a tablet according to any one of claims 1-11 for the manufacture of a chewing gum tablet for prevention and/or amelioration of dental plaque.

14. A method for the treatment of, or ameliorating the symptoms of, dental plaques, said method comprising administering a tablet according to any one of claims 1-11 to a patient in need thereof.

15. A method of making a chewing gum tablet according to any one of claims 1-11, wherein said method comprises compression of chewing gum particles and peptides into a tablet.

16. A chewing gum tablet obtained by or obtainable by a method according to claim 15.

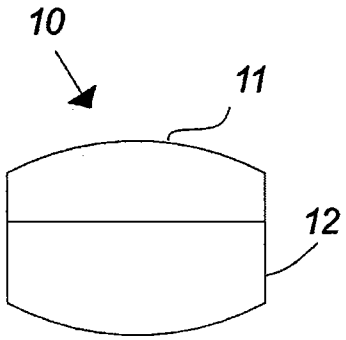

Fig.1a

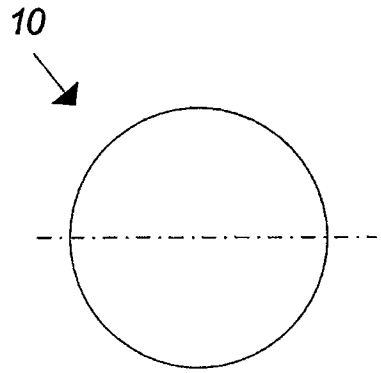

Fig.1b

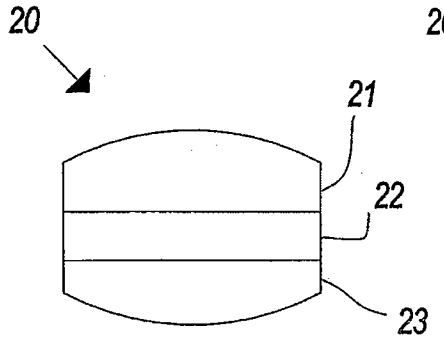

Fig.2a

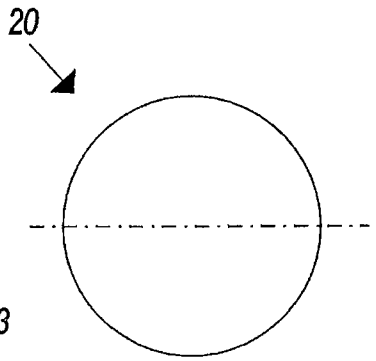

Fig.2b

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2007/050198

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/68 A61K9/20 A61K38/04 A61Q11/00 A61K8/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/140286 A (WRIGLEY W M JUN CO [US]; HAAS MICHAEL S [US]) 6 December 2007 (2007-12-06) paragraph [0046] pages 55-57; examples 26-34 claims 1,11,28	1-16
X	WO 2006/079343 A (GUMLINK AS [DK]; KRISTIANSEN TOVE NORDESTGAARD [DK]; GYLDENVANG LARS [ ]) 3 August 2006 (2006-08-03) page 14, line 18 - line 22 page 18, line 3 - line 6 page 23, line 1 - line 23 page 62 - page 63; example 13 claims 1-30	1-16

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2008	19/09/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hedegaard, Anette

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2007/050198

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/002622 A (GUMLINK AS [DK]; NISSEN VIBEKE [DK]) 12 January 2006 (2006-01-12) page 27, lines 4-6,12; figures 1a,2a page 28, line 4 - line 5 page 36, line 9 - page 38, line 29 claims 1,21,35	1-16
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A	NA ET AL: "Chewing gum of antimicrobial decapeptide (KSL) as a sustained antiplaque agent: Preformulation study" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 107, no. 1, 20 September 2005 (2005-09-20), pages 122-130, XP005064066 ISSN: 0168-3659 the whole document	1-16
A	FARAJ ET AL.: "Development of a Peptide-containing Chewing Gum as a Sustained Release Antiplaque Antimicrobial Delivery System" AAPS PHARMSCITECH, vol. 8, no. 1, 30 March 2007 (2007-03-30), pages E1-E9, XP002494327 cited in the application the whole document	1-16

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Information on patent family members

International application No
PCT/DK2007/050198

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