



- (51) **International Patent Classification:**
A61Q 15/00 (2006.01) *A61K 8/11* (2006.01)
- (21) **International Application Number:**
PCT/EP2014/065379
- (22) **International Filing Date:**
17 July 2014 (17.07.2014)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
13178827.5 31 July 2013 (31.07.2013) EP
- (71) **Applicant** (for AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, IN, KE, KN, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SA, SC, SD, SG, SL, SZ, TT, TZ, UG, VC, ZA, ZM, ZW only): **UNILEVER PLC** [GB/GB]; a company registered in England and Wales under company no. 41424 of Unilever House, 100 Victoria Embankment, London Greater London EC4Y 0DY (GB).
- (71) **Applicant** (for all designated States except AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, IN, KE, KN, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SA, SC, SD, SG, SL, SZ, TT, TZ, UG, US, VC, ZA, ZM, ZW): **UNILEVER N.V.** [NL/NL]; Weena 455, NL-3013 AL Rotterdam (NL).
- (71) **Applicant** (for US only): **CONOPCO, INC., D/B/A UNILEVER** [US/US]; 800 Sylvan Avenue, AG West, S. Wing, Englewood Cliffs, NJ 07632 (US).
- (72) **Inventors:** **ALONSO, Coralie, Claudine**; Unilever R&D Port Sunlight, Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **BARNETT, Stuart, Anthony**; Unilever R&D Port Sunlight, Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **CROPPER, Martin, Peter**; Unilever R&D Port Sunlight, Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **PELAN, Edward, George**; Unilever R&D Vlaardingen, Olivier van Noortlaan 120, NL-3133 AT Vlaardingen (NL). **THOMPSON, Katherine, Mary**; Unilever R&D

Port Sunlight, Quarry Road East, Bebington, Wirral Merseyside CH63 3JW (GB). **ZUIDAM, Nicolaas, Jan**; Unilever R&D Vlaardingen, Olivier van Noortlaan 120, NL-3133 AT Vlaardingen (NL).

(74) **Agents:** **BRISTOW, Stephen, Robert** et al.; Unilever PLC, Unilever Patent Group, Colworth House, Sharnbrook, Bedford Bedfordshire MK44 1LQ (GB).

(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, 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))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))

(54) **Title:** COMPOSITION COMPRISING A TRIGGERED RELEASE SYSTEM

(57) **Abstract:** A composition, which is not an ethanolic based deodorant spray composition, for treating axilla skin, wherein the skin has a naturally occurring enzyme population comprising protease and/or lipase, wherein the composition comprises: - a) a particle, having a particle size of from 1 to 100 microns, comprising i) an insoluble enzymatically degradable material, preferably natural, wherein the enzymatically degradable material is degraded by a protease enzyme; and ii) a hydrophobic benefit agent selected from a fragrance, a skin care agent, an anti-oxidant, a vitamin, an anti-fungal agent, an anti-inflammatory active, a skin conditioning agent, a sunscreen and mixtures thereof; and b) an active ingredient selected from surfactants, polymers, moisturisers, humectants and emollients, antimicrobials, antiperspirant actives, deodorant actives, skin health actives, and mixtures thereof.



- 1 -

COMPOSITION COMPRISING A TRIGGERED RELEASE SYSTEMField of the Invention

5

The present invention relates to a composition, which is suitable for application to the axillary skin, comprising particles that comprise a release system that is triggered by enzymes naturally present on the skin. The invention further relates to the manufacture of said composition and its use.

10

Background and Prior Art

The release of active components and/or benefit agents from personal care products, one example being deodorants is important in delivering good performance from such products. The mechanism and timing of release can have a major impact on the benefit derived during product use.

15

Active components and benefit agents may be encapsulated in the form of particles, such that release of the encapsulated material is effected by a trigger, for example shear force, change in conditions, and so on. Particles may be prepared that comprise different release systems in order to effectively release active compounds or benefit agents at particular points in time during use.

20

The action of human skin enzymes on lipids, proteins and polyesters, as well as encapsulates comprised of these materials, is well established. This action has been exploited in skin products, cosmetics and medical applications.

25

WO 2009/126742 (Appian Labs, 15/10/2009) discloses the release of active ingredients from microcapsules by the exposure to metalloproteinase.

30

- 2 -

IN 2009DE00656 (Council of Sci & Ind Res.) discloses hybrid conjugates of a skin care molecule and perfume molecule that is cleaved by enzymes in human skin.

5 US 2006/0088489 (Estee Lauder) describes the sustained release of fragrance molecules by enzymatic cleavage of the end groups on polycaprolactone-polydecalactone copolymers by skin enzymes. The activity occurs when the polymers are applied topically to hair or skin.

10 US 2008/0274149 (Evonik Degussa) describes the use of ester linked hyperbranched polymer microencapsulates containing cosmetic/dermatological ingredients that are degraded by skin enzymes.

15 US7456147 B2 (Dow Corning) discloses the use of repeat sequence protein polymers that are susceptible to the action of natural skin proteases for encapsulation and topical application to skin or hair.

20 L Kromidas, E Perrier, J Flanagan, R Rivero and I Bonnet (Coty Inc and Coletica, *International Journal of Cosmetic Science*, 2006, **28**, 103) describe the release of antimicrobial actives from protein based microcapsules whose walls are "selected for their ability to be digested by microbial activity". This is exemplified by *in vitro* degradation of farnesol loaded "polymerised hydrolysed wheat protein" by the action of cultured axillary bacteria.

25 Additionally, the use of pro-fragrances to mask microbially driven malodour is known.

30 *Coryne* bacteria found in the axilla region express lipase (esterase) activity and this has been reported as a trigger for fragrance release from ester based pro-fragrances (F Flachsmann, M Gautschi, J-P Bachmann and G Brunner [Givaudan], *Chemistry & Biodiversity*, 2008 (5), 1115.

- 3 -

EP 0 887 338 B1 (Givaudan) also discloses enzyme cleavable carbonate esters as precursors for fragrance aldehydes and ketones and (in a supplementary claim) antibacterial agents. Fragrance release was demonstrated as result of the action of cultured axillary bacteria.

5

However, the pro-fragrance approach suffers the disadvantage that only single fragrance notes are released. In contrast, the encapsulation of the present invention allows the release of a fully balanced and hedonically pleasing fragrance composition. In fact, the targeted systems of the present invention can be used to effectively mask microbially driven malodour ensuring that fragrance payload is not released and lost through volatility at times before the bacterial growth and malodour is most pronounced.

10

We have now found that release of a benefit agent from a particle can be obtained, *in vivo*, by the action of enzymes naturally present on human skin.

15

Definition of the Invention

In a first aspect, the invention provides a composition, which is not an ethanolic based deodorant spray composition, for treating axilla skin, wherein the skin has a naturally occurring enzyme population comprising protease and/or lipase, wherein the composition comprises:-

20

- a) a particle, having a particle size of from 1 to 100 microns, comprising
 - i) an insoluble enzymatically degradable material, preferably natural, wherein the enzymatically degradable material is degraded by a protease enzyme; and
 - ii) a hydrophobic benefit agent selected from a fragrance, a skin care agent, an anti-oxidant, a vitamin, an anti-fungal agent, an anti-inflammatory active, a skin conditioning agent, a sunscreen and mixtures thereof; and

25

30

- 4 -

- b) an active ingredient selected from surfactants, polymers, moisturisers, humectants and emollients, antimicrobials, antiperspirant actives, deodorant actives, skin health actives, and mixtures thereof.

5 In a second aspect of the invention there is provided a method of treating axilla skin wherein the skin has a naturally occurring enzyme population comprising protease, said method comprising applying to the skin a composition, which is not an ethanolic based deodorant spray composition, wherein the composition comprises:-

10

- a) a particle, having a particle size of from 0.1 to 100 microns, comprising
 - i) an insoluble enzymatically degradable material, preferably natural, wherein the enzymatically degradable material is degraded by protease enzyme; and
 - 15 ii) a hydrophobic benefit agent selected from a fragrance, an skin care agent, an anti-oxidant, a vitamin, an anti-fungal agent, an anti-inflammatory active, a skin conditioning agent, a sunscreen and mixtures thereof; and

- 20 b) an active ingredient selected from surfactants, polymers, moisturisers, humectants and emollients, antimicrobials, antiperspirant actives, deodorant actives, skin health actives, and mixtures thereof such that release of the hydrophobic benefit agent is delayed.

25 A third aspect of the invention provides a process for treating an axilla surface; said surface producing protease enzymes; wherein the process comprises the step of treating the surface with a composition as defined by the first aspect of the invention.

- 5 -

Detailed Description of the Invention

The Particle

- 5 Preferred particles are encapsulates (in the following passages, the particles may also be referred to as “microcapsule(s)”, “encap(s)”, or “capsule(s)”).

Where the particle is an encapsulate, it is preferably of a core-shell structure, such as a simple particle or complex coacervate; or a matrix particle, most preferably a
10 matrix particle. Encapsulation can provide pore vacancies or interstitial openings depending on the encapsulation techniques employed. The capsules may have a hollow nature. Alternatively, the capsules may be solid porous structures, or a solid infrastructure, for example a “sponge” type encap.

- 15 Core-shell type encapsulates preferably have a volume average particle size in the range from 10 to 100 microns, more preferably from 20 to 75 microns and most preferably from 30 to 60 microns.

Where the encapsulate has a matrix structure, for example where it is lipid
20 derived, it preferably has a volume average particle size of from 0.1 to 100 microns, more preferably from 1 to 50 microns and most preferably from 5 to 30 microns.

The capsule distribution can be narrow, broad or multimodal. Multimodal
25 distributions may be composed of different types of capsule chemistries. The particle comprises a benefit agent, which is hydrophobic, and an enzymatically degradable material.

- 6 -

The particle is broken down by action of protease enzymes on the enzymatically degradable material. This leads to release of the hydrophobic benefit agent. Release typically occurs after partial hydrolysis of the particle.

- 5 The particle is suitable for use in compositions for the treatment of hair and skin, including compositions for use on, for example skin having dandruff or dry skin conditions.

- 10 For example, the particle can be applied from personal care products such as deodorants, anti-perspirant products (aqueous and/or anhydrous), body washes, creams and lotions etc. The composition may be for direct application, for example deodorants, anti-perspirant products, lotions and creams and rinse off compositions, for example body wash.

15 The Enzymatically Degradable Material

The particle comprises at least one insoluble enzymatically degradable material, which is degraded by a protease enzyme.

- 20 The enzymatically degradable material is biodegradable.

The enzymatically degradable material may be natural or synthetic, preferably natural.

- 25 Preferred natural protease degradable materials are selected from natural animal derived proteins and natural plant derived proteins. Non-limiting examples include collagen, gelatin, casein, albumin, gluten, zein, soy protein, keratin and silk.

- 30 A class of encapsulate useful for the present invention are complex coacervates formed from gelatine and an anionic polyelectrolyte, typically selected from

- 7 -

sodium carboxymethylcellulose, alginate, pectin, acacia, carrageenan or dextran sulphate. The complex coacervate particle may be cross-linked, for example by reaction with an aldehyde or dialdehyde to improve mechanical robustness.

- 5 Preferred synthetic materials include aliphatic poly(amides) such as Nylons and aromatic polyamides (poly[aramides]), more preferable aliphatic poly(amides). The materials may be homopolymers, where the amino and carbonyl acid reacting groups are on the same monomer, or copolymers produced from reaction of di- or tri-carbonyl compounds and di- or tri-amines. The carbonyl compounds may be
- 10 carboxylic acid or more preferably acid chlorides.

In one aspect of said encapsulate, said polyamide polymer may comprise at least one water miscible monomer and one water immiscible organic monomer.

- 15 In one aspect of said encapsulate, said water miscible monomer may comprise a material selected from the group consisting of a diamine, a triamine and mixtures thereof.

- In one aspect, said diamines and triamines may be selected from the group
- 20 consisting of diethylene triamine, hexamethylene diamine, ethylene diamine and mixtures thereof.

- In one aspect of said encapsulate, said water immiscible organic monomer may be selected from the group consisting of diacyl chlorides, triacyl chlorides and
- 25 mixtures thereof.

In one aspect, said diacyl chlorides may be selected from the group consisting of sebacoyl dichloride, adipoyl dichloride, and mixtures thereof and said triacyl chlorides may be selected from the group consisting of teraphthaloyl chloride,

- 8 -

trimesoyl chloride, acetyl chloride, benzoyl chloride, 1, 3, 5-benzentricarbonyl chloride, and mixtures thereof.

In one aspect of said encapsulate, said polyamide polymer may comprise two or
5 more water miscible monomers.

Further examples of suitable synthetic polyamides include materials such as nylon 6 (polycaprolactam), nylon 12 (polylauro lactam), nylon 6:6 (poly[hexamethylene adipamide]), nylon 6:10 (**poly**[hexamethylene sebacamide]),
10 or a homo-poly(amino acid) such as poly(lysine) or poly(tyrosine) or hetero-poly(amino acids).

Suitable cosmetic grade porous matrix polyamide particles are supplied by Kobo Products Ltd. under the trade name Microspheres™ and by Evonik Degussa
15 under the trade name Tegolon®.

The enzymatically degradable moiety may be incorporated either in the polymer backbone or in the form of a cross-linking or spacer group. Suitable biodegradable polymers with protease sensitive amide cross-linkers are described
20 in US patent 2011/0274682.

A further class of synthetic encapsulating material may combine both amide and ester linkages in a poly(ester-amide). Certain suitable materials are disclosed in US6221397. Other suitable poly(amide) and poly(ester-amide) materials are
25 manufactured by Arizona Chemical under the trade name Sylvaclear™.

Method of preparation – core shell complex coacervate capsules

Where the particle is a complex coacervate a preferred method of preparation is
30 as described in US Pat. No. 6,045,835. In such a process, an aqueous solution of

- 9 -

a cationic polymer, for example gelatin or a closely related cationic polymer, is formed at an elevated temperature that is high enough to dissolve the gelatine, commonly at least 40°C and in many instances it is unnecessary to exceed 70°C. A range of 40 to 60°C is preferred. The solution is typically dilute, often falling in the range from 1 to 10% w/w and particularly from 2 to 5%. Either before or after dissolution of the gelatin, an oil-in-water emulsion is formed by the introduction of a hydrophobic benefit agent, for example a perfume oil, optionally together with a diluent oil if desired. A polyanion of like negatively charged polymer is introduced and the composition diluted until a pH is attained of below the isoelectronic point of the system, such as below pH 5, and in particular from pH 3.5 to pH 4.5, whereupon a complex coacervate forms around the dispersed hydrophobic benefit agent droplets. The polyanion commonly comprises gum arabic or a charged carboxymethyl cellulose derivative, such as an alkali metal salt, preferably the sodium salt.

The resultant shell is subsequently cross-linked with a short chain aliphatic dialdehyde, for example a C4 to C6 dialdehyde, including in particular glutaraldehyde. The cross-linking step is commonly conducted at a temperature of below ambient such as from 5 to 15°C, and in particular in the region of 10°C. Representative weights and proportions of the reactants and of suitable operating conditions are shown in Examples, 1, 2 or 3 of the aforementioned US Pat. No. 6,045,835. The skilled person by suitable selection of the parameters within the general process outlined therein is well capable of producing capsules having a volume average particle size in the range from 30 to 100 microns, particularly up to 75 microns and especially 40 to 60 microns.

A second encapsulation method, suitable for forming encapsulated hydrophobic benefit agents, such as perfumes, in which the shell comprises a cross-linked coacervated gelatine comprises variations of the above process, as contemplated in WO2006/056096. In such variations, microcapsules comprising a blank

- 10 -

hydrogel shell are first formed in a dry state and brought into contact with an aqueous or aqueous/alcoholic mixture of a fragrance compound, which may be diluted with a diluent oil. The fragrance (or other hydrophobic benefit agent) compound is transported through the hydrogel shell by aqueous diffusion and is retained inside. The resultant fragrance-containing microcapsules are then dried to a powder, which for practical purposes is anhydrous. A preferred ratio of fragrance oil to diluents oil is in the range of from 1:2 to 1:1, more preferably 3:4 to 1:1, for fragrance to diluents oils.

10 Additionally, microcapsules made via the simple or complex coacervation of gelatin are also preferred for use with the coating. Microcapsules having shell walls comprised of polyesters or combinations of these materials are also possible.

15 A representative process used for gelatin encapsulation is disclosed in U.S. Patent No. 2,800,457 though it is recognized that many variations with regard to materials and process steps are possible. Both of these processes are discussed in the context of fragrance encapsulation for use in consumer products in U.S. Patent Nos. 4,145,184 and 5,112,688 respectively.

20

Method of preparation – synthetic protease sensitive core-shell or matrix particles

Core-shell nylon capsules containing perfume may be prepared using the following method:-

25

Step 1:- The following liquids were prepared:-

Liquid A: 2.4 ml perfume and 0.27 g terephthaloyl chloride were mixed until the terephthaloyl chloride dissolved to obtain an oily liquid.

- 11 -

Water solution B: 30 ml deionised water containing 1 wt% polyvinyl alcohol (5-88) was prepared and the pH adjusted to desired value using 1M NaOH.

Water solution C: 3.9 ml Diethylenetriamine was dissolved in 6 ml deionised water.

5

Step 2:- Liquid A was then added to solution B under homogenization at 6000 rpm and the mixture emulsified for 5 min. Solution C was then added dropwise into the emulsion and homogenization was continued for 10 min. The resulting suspension of polyamide capsules, was allowed to age for 24 h to obtain a capsule slurry.

10

Method of preparation – poly(ester) matrix particles

Suitable lipase sensitive poly(ester) particles may be prepared by a variety of processes such as those described by F Tewes, F Boury and J-P Benoit in

15

“Microencapsulation: Methods and Industrial Applications”, 2nd edition, ed. S Benita, CRC Press, 2006, Taylor & Francis Group, Boca Raton, pp. 1-54, including the so-called solvent diffusion, emulsification/solvent evaporation route, coacervation and spray drying.

20

Methodologies for preparing sub-micron particles have been reviewed K Landfester, A Musyanovych and V Mailänder, Journal of Polymer Science, Part A: Polymer Chemistry, Volume 48(3), 2009, pp. 493-515. Preferred methods include a combined emulsion/solvent evaporation with miniemulsion technique reported to be especially useful for encapsulation of actives in pre-formed biodegradable polymers, as reported in F V Leimann, M H Biz, A Musyanovych, C Sayer, K Landfester and P H H de Araújo, Journal of Applied Polymer Science, Volume 128, Issue 5, 2013, pp. 3093-3098.

25

In a further exemplification of the invention, one or more additional coatings of a protease sensitive material may be applied to a pre-formed particle or capsule.

30

- 12 -

For example, a polyester coating could be applied to the outside of a gelatine based complex coacervate.

For liquid compositions, the capsules may be used in the form of a slurry, which preferably comprises about 40% solids. The amount of such a 40% capsule slurry to be used in a composition is up to 10 %, preferably from 0.1 to 5 %, more preferably from 1 to 2 % by weight of the total composition. Amount of capsules, based on dry weight, by weight of the total composition is preferably from 0.04 to 4 wt %, more preferably from 0.1 to 3 wt % and most preferably from 0.2 to 2 wt %.

The Benefit Agent

The benefit agent is present in encapsulated form. It may also be present in non-encapsulated (free) form. The following materials are suitable for both forms.

The benefit agent is a hydrophobic material, selected from a fragrance, an skin care agent, an anti-oxidant, a vitamin, an anti-fungal agent, an anti-inflammatory active, , a skin conditioning agent, a sunscreen and mixtures thereof.

Suitable benefit agents include perfume raw materials, silicone oils, waxes, hydrocarbons, higher fatty acids, essential oils, lipids, skin coolants, vitamins, sunscreens, antioxidants, glycerine, malodour reducing agents, odour controlling materials, softening agents, insect and moth repelling agents, colourants, chelants, bodyfying agents, wrinkle control agents, sanitization agents, skin care agents, glycerine, natural actives, preservatives, , chemosensates, (for example menthol), sunless-tanning agents (for example dihydroxyacetone), emollients (for example sunflower oil and pertrolatum) and mixtures thereof.

Skin

For skin compositions the preferred benefit agents include one or more of fragrances, skin lightening agents, skin conditioning agents, for example 12-hydroxy stearic acid, antimicrobials, oils and insect repellents.

Suncreens and skin lightening

Preferred sunscreens and/or skin lightening agents are vitamin B3 compounds. Suitable vitamin B3 compounds are selected from niacin, niacinamide, nicotinyl alcohol, or derivatives or salts thereof. Other vitamins which act as skin lightening agents can be advantageously included in the skin lightening composition to provide for additional skin lightening effects. These include vitamin B6, vitamin C, vitamin A or their precursors. Mixtures of the vitamins can also be employed in the composition for use in the method of the invention. An especially preferred additional vitamin is vitamin B6. Other non-limiting examples of skin lightening agents useful herein include adapalene, aloe extract, ammonium lactate, arbutin, azelaic acid, butyl hydroxy anisole, butyl hydroxy toluene, citrate esters, deoxyarbutin, 1,3 diphenyl propane derivatives, 2, 5 di-hydroxyl benzoic acid and its derivatives, 2-(4-acetoxyphenyl)-1,3-dithane, 2-(4-hydroxyphenyl)-1,3 diethane, ellagic acid, glucopyranosyl-1-ascorbate, gluconic acid, glycolic acid, green tea extract, 4-Hydroxy-5-methyl-3[2H]-furanone, hydroquinone, 4-hydroxyanisole and its derivatives, 4-hydroxy benzoic acid derivatives, hydroxycaproic acid, inositol ascorbate, kojic acid, lactic acid, lemon extract, linoleic acid, magnesium ascorbyl phosphate, 5-octanoyl salicylic acid, 2,4 resorcinol derivatives, 3,5 resorcinol derivatives, salicylic acid, 3,4,5 trihydroxybenzyl derivatives, and mixtures thereof. Preferred sunscreens useful in the present invention are 2-ethylhexyl-p-methoxycinnamate, butyl methoxy dibenzoylmethane, 2-hydroxy-4-methoxybenzophenone, octyl dimethyl-p-aminobenzoic acid and mixtures thereof. Particularly preferred sunscreen is

- 14 -

chosen from 2-ethyl hexyl-p-methoxycinnamate, 4,- t-butyl-4'- methoxydibenzoyl-methane or mixtures thereof. Other conventional sunscreen agents that are suitable for use in skin lightening compositions for use in the method of the invention include 2-hydroxy-4-methoxybenzophenone, octyldimethyl- p-aminobenzoic acid, digalloyltriolate, 2,2-dihydroxy-4- methoxybenzophenone, ethyl-4-(bis(hydroxypropyl)) aminobenzoate, 2- ethylhexyl-2- cyano-3,3-diphenylacrylate, 2-ethylhexylsalicylate, glyceryl- p-aminobenzoate, 3,3,5-trimethylcyclohexyl-salicylate, methylanthranilate, p-dimethyl-aminobenzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethyl- amino-benzoate, 2-phenylbenzimidazole-5- sulfonic acid, 2-(p- dimethylaminophenyl)-5-sulfonic benzoxazoic acid and mixtures of these compounds.

Examples of particularly sunscreen payloads are UV-B filters such as 2-ethylhexyl-4-methoxycinnamate (sold commercially under the trade name Parsol MCX by DSM), and UV-A filters such as benzophenone or 4-tert-butyl-4'-methoxydibenzoylmethane (Avobenzon, sold commercially under the trade name Parsol 1789 by DSM).

Antioxidants, anti-ageing actives and anti-inflammatory actives

Suitable actives include Retinol (Vitamin A), ascorbyl palmitate (Vitamin C palmitate), Cholecalciferol (Vitamin D3), tocopheryl (Vitamin E) acetate, Vitamin E palmitate, linoleic acid (Vitamin F), carotenoids such as beta-carotene and curcumin, phenols and polyphenols (e.g. resveratrol).

Preferred anti-oxidants include vitamin E, retinol, antioxidants based on hydroxytoluene such as Irganox™ or commercially available antioxidants such as the Trollox™ series.

Perfumes

Perfume and fragrance materials (which include pro-fragrances) are a particularly preferred benefit agent.

5

The pro-fragrance can, for example, be a food lipid. Food lipids typically contain structural units with pronounced hydrophobicity. The majority of lipids are derived from fatty acids. In these 'acyl' lipids the fatty acids are predominantly present as esters and include mono-, di-, triacyl glycerols, phospholipids, glycolipids, diol
10 lipids, waxes, sterol esters and tocopherols. In their natural state, plant lipids comprise antioxidants to prevent their oxidation. While these may be at least in part removed during the isolation of oils from plants some antioxidants may remain. These antioxidants can be pro-fragrances. In particular, the carotenoids and related compounds including vitamin A, retinol, retinal, retinoic acid and
15 provitamin A are capable of being converted into fragrant species including the ionones, damascones and damscenones. Preferred pro-fragrance food lipids include olive oil, palm oil, canola oil, squalene, sunflower seed oil, wheat germ oil, almond oil, coconut oil, grape seed oil, rapeseed oil, castor oil, corn oil, cottonseed oil, safflower oil, groundnut oil, poppy seed oil, palm kernel oil, rice
20 bran oil, sesame oil, soybean oil, pumpkin seed oil, jojoba oil and mustard seed oil. Perfume components which are odiferous materials are described in further detail below.

The perfume is typically present in an amount of from 10-85% by total weight of
25 the particle, preferably from 15 to 75% by total weight of the particle. The perfume suitably has a molecular weight of from 50 to 500Dalton. Pro-fragrances can be of higher molecular weight, being typically 1-10 kD.

Useful components of the perfume include materials of both natural and synthetic
30 origin. They include single compounds and mixtures. Specific examples of such

- 16 -

components may be found in the current literature, e.g., in Fenaroli's Handbook of Flavour Ingredients, 1975, CRC Press; Synthetic Food Adjuncts, 1947 by M. B. Jacobs, edited by Van Nostrand; or Perfume and Flavour Chemicals by S. Arctander 1969, Montclair, N.J. (USA). These substances are well known to the person skilled in the art of perfuming, flavouring, and/or aromatizing consumer products, i.e., of imparting an odour and/or a flavour or taste to a consumer product traditionally perfumed or flavoured, or of modifying the odour and/or taste of said consumer product.

- 10 By perfume in this context is not only meant a fully formulated product fragrance, but also selected components of that fragrance, particularly those which are prone to loss, such as the so-called 'top notes'.

Top notes are defined by Poucher (Journal of the Society of Cosmetic Chemists 6(2):80 [1955]). Examples of well known top-notes include citrus oils, linalool, linalyl acetate, lavender, dihydromyrcenol, rose oxide and cis-3-hexanol. Top notes typically comprise 15-25%wt of a perfume composition and in those embodiments of the invention which contain an increased level of top-notes it is envisaged at that least 20%wt would be present within the particle.

20

Typical perfume components which it is advantageous to employ in the embodiments of the present invention include those with a relatively low boiling point, preferably those with a boiling point of less than 300, preferably 100-250 Celsius.

25

It is also advantageous to encapsulate perfume components which have a low LogP (i.e. those which will be partitioned into water), preferably with a LogP of less than 3.0. These materials, of relatively low boiling point and relatively low LogP have been called the "delayed blooming" perfume ingredients and include the following materials:

30

- 17 -

Allyl Caproate, Amyl Acetate, Amyl Propionate, Anisic Aldehyde, Anisole,
 Benzaldehyde, Benzyl Acetate, Benzyl Acetone, Benzyl Alcohol, Benzyl Formate,
 Benzyl Iso Valerate, Benzyl Propionate, Beta Gamma Hexenol, Camphor Gum,
 Laevo-Carvone, d-Carvone, Cinnamic Alcohol, Cinamyl Formate, Cis-Jasmone,
 5 cis-3-Hexenyl Acetate, Cuminic Alcohol, Cyclal C, Dimethyl Benzyl Carbinol,
 Dimethyl Benzyl Carbinol Acetate, Ethyl Acetate, Ethyl Aceto Acetate, Ethyl Amyl
 Ketone, Ethyl Benzoate, Ethyl Butyrate, Ethyl Hexyl Ketone, Ethyl Phenyl Acetate,
 Eucalyptol, Eugenol, Fenchyl Acetate, Flor Acetate (tricyclo Decenyl Acetate),
 Frutene (tricyclo Decenyl Propionate), Geraniol, Hexenol, Hexenyl Acetate,
 10 Hexyl Acetate, Hexyl Formate, Hydratropic Alcohol, Hydroxycitronellal, Indone,
 Isoamyl Alcohol, Iso Menthone, Isopulegyl Acetate, Isoquinolone, Ligustral,
 Linalool, Linalool Oxide, Linalyl Formate, Menthone, Menthyl Acetphenone,
 Methyl Amyl Ketone, Methyl Anthranilate, Methyl Benzoate, Methyl Benyl
 Acetate, Methyl Eugenol, Methyl Heptenone, Methyl Heptine Carbonate, Methyl
 15 Heptyl Ketone, Methyl Hexyl Ketone, Methyl Phenyl Carbiny Acetate, Methyl
 Salicylate, Methyl-N-Methyl Anthranilate, Nerol, Octalactone, Octyl Alcohol, p-
 Cresol, p-Cresol Methyl Ether, p-Methoxy Acetophenone, p-Methyl
 Acetophenone, Phenoxy Ethanol, Phenyl Acetaldehyde, Phenyl Ethyl Acetate,
 Phenyl Ethyl Alcohol, Phenyl Ethyl Dimethyl Carbinol, Prenyl Acetate, Propyl
 20 Bornate, Pulegone, Rose Oxide, Safrole, 4-Terpinenol, Alpha-Terpinenol, and /or
 Viridine.

It is commonplace for a plurality of perfume components to be present in a
 formulation. In the encapsulates of the present invention it is envisaged that there
 25 will be four or more, preferably five or more, more preferably six or more or even
 seven or more different perfume components from the list given of delayed
 blooming perfumes given above present in the particles.

The invention compositions herein contain both encapsulated fragrance and non-
 30 encapsulated fragrance. The combined weight of encapsulated and non-

- 18 -

encapsulated fragrance is often at least 0.5% of the total composition weight and in many suitable compositions is up to 8% by weight thereof, and in many desirable embodiments is from 1 to 5% by weight of the composition. The weight of non-encapsulated fragrance is commonly at least 0.1 % by weight of the total composition weight, often at least 0.2% and particularly at least 0.4%. In many desirable embodiments, the compositions contain up to 2% non-encapsulated fragrance based on the total composition weight (propellant-free). The weight ratio of the encapsulated fragrance to non-encapsulated fragrance is at the discretion of the formulator, but in practice is often at least 1 :10, in many compositions at least 1 :5 and in some preferred compositions at least 1 :3. Said weight ratio is commonly up to 10:1, often up to 5:1 and in at least some desirable compositions is up to 3:1.

Subject to the aforementioned constraints, the respective fragrances can comprise any perfume component or preferably a mixture of components. Each fragrance commonly comprises at least 6 components, particularly at least 12 components and often at least 20 components.

The perfume component oils herein commonly have a ClogP value of at least 0.1 and often at least 0.5.

Representative fragrance oils having a boiling point of below 250⁰C at 1 bar pressure include the following materials:- anethol, methyl heptine carbonate, ethyl aceto acetate, para cymene, nerol, decyl aldehyde, para cresol, methyl phenyl carbonyl acetate, ionone alpha, ionone beta, undecylenic aldehyde, undecyl aldehyde, 2,6-nonadienal, nonyl aldehyde, octyl aldehyde, phenyl acetaldehyde, anisic aldehyde, benzyl acetone, ethyl-2-methyl butyrate, damascenone, damascone alpha, damascone beta, flor acetate, frutene, fructose, herbavert, isocyclo citral, methyl isobutenyl tetrahydro pyran, iso propyl quinoline, 2,6-nonadien-1 -ol, 2-methoxy-3- (2-methylpropyl)-pyrazine, methyl octine carbonate, thdecene-

- 19 -

2-nitthle, allyl amyl glycolate, cyclogalbanate, cyclal C, melonal, gamma nonalactone, cis 1,3-oxathiane-2-methyl-4-propyl, benzaldehyde, benzyl acetate, camphor, carvone, borneol, bornyl acetate, decyl alcohol, eucalyptol, linalool, hexyl acetate, iso-amyl acetate, thymol, carvacrol, limonene, menthol, iso-amyl
 5 alcohol, phenyl ethyl alcohol, alpha pinene, alpha terpineol, citronellol, alpha thujone, benzyl alcohol, beta gamma hexenol, dimethyl benzyl carbinol, phenyl ethyl dimethyl carbinol, adoxal, allyl cyclohexane propionate, beta pinene, citral, citronellyl acetate, citronellal nitrile, dihydro myrcenol, geraniol, geranyl acetate, geranyl nitrile, hydroquinone dimethyl ether, hydroxycitronellal, linalyl acetate,
 10 phenyl acetaldehyde dimethyl acetal, phenyl propyl alcohol, prenyl acetate, triplal, tetrahydrolinalool, verdox, and cis-3-hexenyl acetate.

Representative fragrance oils having a boiling point at 1 bar pressure of at least 250°C include:- ethyl methyl phenyl glycidate, ethyl vanillin, heliotropin, indol,
 15 methyl anthranilate, vanillin, amyl salicylate, coumarin, ambrox, bacdanol, benzyl salicylate, butyl anthranilate, cetalo, ebanol, cis-3-hexenyl salicylate, lillal, gamma undecalactone, gamma dodecalactone, gamma decalactone, calone, cymal, dihydro iso jasmonate, iso eugenol, lyral, methyl beta naphthyl ketone, beta naphthol methyl ether, para hydroxyl phenyl butanone, 8-cyclohexadecen-1 -
 20 one, oxocyclohexadecen-2-one / habanolide, florhydral, intrelven aldehyde eugenol, amyl cinnamic aldehyde, hexyl cinnamic aldehyde, hexyl salicylate, methyl dihydro jasmonate, sandalore, veloutone, undecavertol, exaltolide/cyclopentadecanolide, zingerone, methyl cedrylone, sandela, dimethyl benzyl carbonyl butyrate, dimethyl benzyl carbonyl isobutyrate, triethyl citrate,
 25 cashmeran, phenoxy ethyl isobutyrate, iso eugenol acetate, helional, iso E super, ionone gamma methyl, pentalide, galaxolide, phenoxy ethyl propionate. The fragrances employed herein, either into the capsules or not encapsulated can comprise a pre-formed blend, either extracted from natural products, or possibly created synthetically. Representatives of such pre-formed blends include oils
 30 from:- Bergamot, cedar atlas, cedar wood, clove, geranium, guaiac wood,

- 20 -

jasmine, lavender, lemongrass, lily of the valley, lime, neroli, musk, orange blossom, patchouli, peach blossom, petitgrain or petotgrain, pimento, rose, rosemary, and thyme.

5 Aromatherapy

Another group of perfumes with which the present invention can be applied are the so-called 'aromatherapy' materials. These include many components also used in perfumery, including components of essential oils such as Clary Sage,
10 Eucalyptus, Geranium, Lavender, Mace Extract, Neroli, Nutmeg, Spearmint, Sweet Violet Leaf and Valerian.

Insect repellents

15 The benefit agent may also be an insect repellent material (where insect should be read broadly to include other pests which are arthropods but not strictly hexapods – for example ticks). Many of these materials overlap with the class of perfume components and some are odourless to humans or have a non-perfume odour. Commonly used repellents include: DEET (N,N-diethyl-m-toluamide),
20 essential oil of the lemon eucalyptus (*Corymbia citriodora*) and its active compound p-menthane-3,8-diol (PMD), Icaridin, also known as Picaridin, D-Limonene, Bayrepel, and KBR 3023, Nepetalactone, also known as "catnip oil", Citronella oil, Permethrin, Neem oil and Bog Myrtle. Known insect repellents derived from natural sources include: *Achillea alpina*, alpha-terpinene, Basil oil
25 (*Ocimum basilicum*), *Callicarpa americana* (Beautyberry), Camphor, Carvacrol, Castor oil (*Ricinus communis*), Catnip oil (*Nepeta* species), Cedar oil (*Cedrus atlantica*), Celery extract (*Apium graveolens*), Cinnamon (*Cinnamomum Zeylanicum*, leaf oil), Citronella oil (*Cymbopogon fleusus*), Clove oil (*Eugenic caryophyllata*), Eucalyptus oil (70%+ eucalyptol, also known as cineol), Fennel oil
30 (*Foeniculum vulgare*), Garlic Oil (*Allium sativum*), Geranium oil (also known as

- 21 -

Pelargonium graveolens), Lavender oil (*Lavandula officinalis*), Lemon eucalyptus (*Corymbia citriodora*) essential oil and its active ingredient p-menthane-3,8-diol (PMD), Lemongrass oil (*Cymbopogon flexuosus*), Marigolds (*Tagetes* species), Marjoram (*Tetranychus urticae* and *Eutetranychus orientalis*), Neem oil
5 (*Azadirachta indica*), Oleic acid, Peppermint (*Mentha x piperita*), Pennyroyal (*Mentha pulegium*), Pyrethrum (from *Chrysanthemum* species, particularly *C. cinerariifolium* and *C. coccineum*), Rosemary oil (*Rosmarinus officinalis*), Spanish Flag Lantana camara (*Helopeltis theivora*), *Solanum villosum* berry juice, Tea tree oil (*Melaleuca alternifolia*) and Thyme (*Thymus* species) and mixtures thereof.

10

The particle optionally comprises a carrier oil (also referred to herein as a diluent). It will be clear to a skilled person which oils are suitable for use with a certain benefit composition. The carrier oils are hydrophobic materials that are miscible in the benefit agent materials used in the present invention.

15

Suitable oils are those having reasonable affinity for the benefit agent. Suitable materials include, but are not limited to triglyceride oil, mono and diglycerides, mineral oil, silicone oil, diethyl phthalate, polyalpha olefins, castor oil and isopropyl myristate. Preferably, the oil is a triglyceride oil, most preferably a capric/caprylic triglyceride oil.

20

The Surface

The composition of the invention is for the treatment of an axillary surface. The surface produces protease enzymes.

25

Proteases

Protease enzyme classes, suitable for use in the present invention, may be found in the MEROPS database (<http://merops.sanger.ac.uk/>) from the Wellcome Trust
30 at the Sanger Institute.

- 22 -

Natural skin proteases, particularly serine proteases, specifically kallikreins are referenced in the following documents:-

5 C Caubet, N Jonca, M Brattsand, M Guerrin, D Bernard, R Schmidt, T Egelrud, M Simon and Guy Serre, *Journal of Investigative Dermatology*, Volume 122, pp.1235-1244, 2004.

P Ovaere, S Lippens, P Vandenabeele and W Declercq, *Trends in Biochemical Sciences*, Volume 34, No.9, 453-463, 2009.

10

Suitable proteases include those classified by the European Classification number EC 3.4.21.- (Serine Proteases), with preferred skin specific proteases classified as EC 3.4.21.8: kallikreins.

15 **The Active Ingredient**

The active ingredient is for the treatment of skin or hair. The active ingredient is selected from surfactants, polymers, moisturisers, humectants and emollients, antifungals, antiperspirant actives, deodorant actives, skin health actives, and
20 mixtures thereof..

The composition may further comprise various additional ingredients known to a person skilled in the art. Such additional ingredients include but are not limited to: perfumes, chemosensates, pigments or dyes, optical brighteners, preservatives,
25 sunscreens, emulsifiers, gelling agents, thickening agents, humectants (e.g. glycerine, sorbitol).

Surfactants

The active ingredient may be a surfactant, selected from anionic surfactant, non-ionic surfactant, cationic surfactant, zwitterionic surfactant, amphoteric surfactant and mixtures thereof.

Where the surface is hair or scalp, the composition may comprise an alkyl sulphate and/or ethoxylated alkyl sulfate anionic surfactant, preferably at a level of from 2 to 16 wt.%, preferably from 3 to 14 wt.%, more preferably from 4 to 10 wt.%.

Preferred alkyl sulfates are C₈₋₁₈ alkyl sulfates, more preferably C₁₂₋₁₈ alkyl sulfates, preferably in the form of a salt with a solubilising cation such as sodium, potassium, ammonium or substituted ammonium. Examples are sodium lauryl sulfate (SLS) or sodium dodecyl sulfate (SDS).

Preferred alkyl ether sulfates are those having the formula: RO(CH₂CH₂O)_nSO₃M; wherein R is an alkyl or alkenyl having from 8 to 18 (preferably 12 to 18) carbon atoms; n is a number having an average value of greater than at least 0.5, preferably between 1 and 3; and M is a solubilising cation such as sodium, potassium, ammonium or substituted ammonium. An example is sodium lauryl ether sulfate (SLES).

A preferred ethoxylated alkyl sulfate anionic surfactant is sodium lauryl ether sulfate (SLES) having an average degree of ethoxylation of from 0.5 to 3, preferably 1 to 3.

Compositions may comprise one or more further anionic cleansing surfactants which are cosmetically acceptable and suitable for topical application to the hair.

- 24 -

Examples of further suitable anionic cleansing surfactants are the alkaryl sulphonates, alkyl succinates, alkyl sulphosuccinates, alkyl ether sulphosuccinates, N-alkyl sarcosinates, alkyl phosphates, alkyl ether phosphates, and alkyl ether carboxylic acids and salts thereof, especially their sodium, magnesium, ammonium and mono-, di- and triethanolamine salts. The alkyl and acyl groups generally contain from 8 to 18, preferably from 10 to 16 carbon atoms and may be unsaturated. The alkyl ether sulphosuccinates, alkyl ether phosphates and alkyl ether carboxylic acids and salts thereof may contain from 1 to 20 ethylene oxide or propylene oxide units per molecule.

Typical anionic cleansing surfactants for use in compositions of the invention include sodium oleyl succinate, ammonium lauryl sulphosuccinate, sodium lauryl ether sulphosuccinate, sodium dodecylbenzene sulphonate, triethanolamine dodecylbenzene sulphonate, lauryl ether carboxylic acid and sodium N-lauryl sarcosinate.

Suitable preferred additional anionic cleansing surfactants are sodium lauryl ether sulphosuccinate(n)EO, (where n is from 1 to 3), lauryl ether carboxylic acid (n) EO (where n is from 10 to 20).

Mixtures of any of the foregoing anionic cleansing surfactants may also be suitable.

If added, the total amount of additional anionic cleansing surfactant in shampoo compositions of the invention may generally range from 0.5 to 45 wt.%, preferably from 1.5 to 35 wt.%, more preferably from 5 to 20 wt.%, calculated by total weight anionic cleansing surfactant based on the total weight of the composition.

The composition can include co-surfactants, to help impart aesthetic, physical or cleansing properties to the composition.

- 25 -

An example of a co-surfactant is a nonionic surfactant, which can be included in an amount ranging from 0.5 to 8%, preferably from 2 to 5% by weight based on the total weight of the composition.

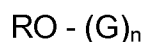
5 For example, representative nonionic surfactants that can be included in compositions of the invention include condensation products of aliphatic ($C_8 - C_{18}$) primary or secondary linear or branched chain alcohols or phenols with alkylene oxides, usually ethylene oxide and generally having from 6 to 30 ethylene oxide groups.

10

Other representative nonionic surfactants include mono- or di-alkyl alkanolamides. Examples include coco mono- or di-ethanolamide and coco mono-isopropanolamide.

15 Further nonionic surfactants which can be included in compositions of the invention are the alkyl polyglycosides (APGs). Typically, the APG is one which comprises an alkyl group connected (optionally via a bridging group) to a block of one or more glycosyl groups. Preferred APGs are defined by the following formula:

20



wherein R is a branched or straight chain alkyl group which may be saturated or unsaturated and G is a saccharide group.

25 R may represent a mean alkyl chain length of from about C_5 to about C_{20} . Preferably R represents a mean alkyl chain length of from about C_8 to about C_{12} . Most preferably the value of R lies between about 9.5 and about 10.5. G may be selected from C_5 or C_6 monosaccharide residues, and is preferably a glucoside. G may be selected from the group comprising glucose, xylose, lactose, fructose,
30 mannose and derivatives thereof. Preferably G is glucose.

- 26 -

The degree of polymerisation, n , may have a value of from about 1 to about 10 or more; preferably, the value of n lies from about 1.1 to about 2; most preferably the value of n lies from about 1.3 to about 1.5.

- 5 Suitable alkyl polyglycosides for use in the invention are commercially available and include for example those materials identified as: Oramix NS10 ex Seppic; Plantaren 1200 and Plantaren 2000 ex Henkel.

- 10 Other sugar-derived nonionic surfactants which can be included in compositions of the invention include the C_{10} - C_{18} N-alkyl (C_1 - C_6) polyhydroxy fatty acid amides, such as the C_{12} - C_{18} N-methyl glucamides, as described for example in WO 92/06154 and US 5,194, 639, and the N-alkoxy polyhydroxy fatty acid amides, such as C_{10} - C_{18} N-(3-methoxypropyl) glucamide.

- 15 A preferred example of a co-surfactant is an amphoteric or zwitterionic surfactant, which can be included in an amount ranging from 0.1 to about 10 wt.%, preferably from 0.5 to 8, more preferably from 1 to 5 wt.%, based on the total weight of the composition.

- 20 Examples of amphoteric or zwitterionic surfactants include alkyl amine oxides, alkyl betaines, alkyl amidopropyl betaines, alkyl sulphobetaines (sultaines), alkyl glycinate, alkyl carboxyglycinates, alkyl amphotacetates, alkyl amphopropionates, alkylamphoglycinates, alkyl amidopropyl hydroxysultaines, acyl taurates and acyl glutamates, wherein the alkyl and acyl groups have from 8 to 19 carbon atoms.

- 25 Typical amphoteric and zwitterionic surfactants for use in shampoos of the invention include lauryl amine oxide, cocodimethyl sulphopropyl betaine, lauryl betaine, cocamidopropyl betaine and sodium cocoamphoacetate.

- 30 A particularly preferred amphoteric or zwitterionic surfactant is cocamidopropyl betaine.

- 27 -

Mixtures of any of the foregoing amphoteric or zwitterionic surfactants may also be suitable. Preferred mixtures are those of cocamidopropyl betaine with further amphoteric or zwitterionic surfactants as described above. A preferred further amphoteric or zwitterionic surfactant is sodium cocoamphoacetate.

5

The total amount of surfactant (including any co-surfactant, and/or any emulsifier) in a composition of the invention is generally from 1 to 50%, preferably from 2 to 40%, more preferably from 10 to 25% by total weight surfactant based on the total weight of the composition.

10

Further Optional Ingredients

The compositions for use in the invention may contain one or more other ingredients. Such ingredients include further preservatives (e.g. bactericides), pH buffering agents, perfume carriers, polyelectrolytes, anti-wrinkle agents, anti-oxidants, sunscreens, anti-corrosion agents, pearlisers and/or opacifiers, natural oils/extracts, processing aids, eg electrolytes, hygiene agents, eg anti-bacterials and antifungals, thickeners, skin benefit agents, colourants, whiteners, gel-control agents, freeze-thaw stabilisers, bactericides, preservatives (for example 1,2-benzisothiazolin-3-one), hydrotropes, perfumes and mixtures thereof.

20

The compositions for use in the invention may also contain pH modifiers such as hydrochloric acid or lactic acid.

25

Although it is particularly suitable to employ anhydrous compositions herein, which is to say compositions that do not contain a discernible aqueous phase, any water present being associated with some other ingredient, in some embodiments of the present invention, the antiperspirant or deodorant compositions can additionally comprise an aqueous phase, and commonly together with an oil phase, the composition is in the form of an emulsion. In such compositions, the aqueous

30

- 28 -

phase commonly constitutes from 10 % and particularly from 30% by weight of the total composition, often up to 97% by weight. The balance of the composition comprises the oil phase, including any suspended material and the emulsifier or emulsifiers. Emulsions according to the present invention particularly suitably
5 comprise shear-sensitive encapsulated fragrance.

The composition preferably contains an antiperspirant active. Antiperspirant actives are preferably incorporated in an amount of from 0.5-50%, particularly from 5 to 30% and especially from 10% to 26% of the weight of the composition.

10 It is often considered that the main benefit from incorporating of up to 5% of an antiperspirant active in a stick composition is manifest in reducing body odour, and that as the proportion of antiperspirant active increases, so the efficacy of that composition at controlling perspiration increases.

15 Antiperspirant actives for use herein are often selected from astringent active salts, including in particular aluminium, zirconium and mixed aluminium/zirconium salts, including both inorganic salts, salts with organic anions and complexes. Preferred astringent salts include aluminium, zirconium and aluminium/zirconium halides and halohydrate salts, such as chlorohydrates.

20

Aluminium halohydrates are usually defined by the general formula $Al_2(OH)_xQ_y \cdot wH_2O$ in which Q represents chlorine, bromine or iodine, x is variable from 2 to 5 and $x + y = 6$ while wH_2O represents a variable amount of hydration. Especially effective aluminium halohydrate salts, known as activated aluminium
25 chlorohydrates, are described in EP-A-6739 (Unilever NV et al).

Zirconium actives can usually be represented by the empirical general formula: $ZrO(OH)_{2n-nz}B_z \cdot wH_2O$ in which z is a variable in the range of from 0.9 to 2.0 so that the value $2n-nz$ is zero or positive, n is the valency of B, and B is selected
30 from the group consisting of chloride, other halide, sulphamate, sulphate and

- 29 -

mixtures thereof. Possible hydration to a variable extent is represented by wH_2O . Preferable is that B represents chloride and the variable z lies in the range from 1.5 to 1.87. In practice, such zirconium salts are usually not employed by themselves, but as a component of a combined aluminium and zirconium-based antiperspirant.

Antiperspirant complexes based on the above-mentioned astringent aluminium and/or zirconium salts can be employed. The complex often employs a compound with a carboxylate group, and advantageously this is an amino acid.

Examples of suitable amino acids include dl-tryptophan, dl- β -phenylalanine, dl-valine, dl-methionine and β -alanine, and preferably glycine. It is highly desirable to employ complexes of a combination of aluminium halohydrates and zirconium chlorohydrates together with amino acids such as glycine, which are disclosed in US-A-3792068 (Luedders et al).

The proportion of solid antiperspirant salt in a suspension (anhydrous) composition normally includes the weight of any water of hydration and any complexing agent that may also be present in the solid active.

For incorporation of compositions according to the present invention, desirably at least 90%, preferably at least 95% and especially at least 99% by weight of the particles have a diameter in the range of from 0.1 μm up to 100 μm , and usually have an average particle diameter of at least 1 μm and especially below 20 μm . In some highly desirable contact compositions the particles by weight have a weight average particle size of at least 2 μm and particularly below 10 μm , such as in the range of from 3 to 8 μm .

Compositions according to the invention may be emulsions. In such compositions, the antiperspirant active is commonly dissolved in the aqueous phase, commonly at a weight concentration in that phase of between 10 and 55%.

- 30 -

In many suitable emulsions, the concentration of antiperspirant active is chosen in relation to the weight of oils (including any non-encapsulated fragrance oils), decreasing progressively from a ratio of about 3:1 to 5:1 when the proportion of oils is below 10% to a ratio in the range of 3:2 to 2:3 when the oils content is at least 50% of the total weight of the composition (excluding any propellant). The invention compositions may include one or more thickeners or gellants (sometimes called structuring or solidifying agents) to increase the viscosity of or solidify the liquid carrier in which the particulate materials are suspended as is appropriate for application from respectively soft solid (anhydrous cream) dispensers or stick dispensers.

Compositions according to the invention may be stick compositions. Such compositions desirably have a hardness as measured in a conventional penetration test (Seta) of less than 30mm, preferably less than 20 mm and particularly desirably less than 15 mm. Many have a penetration of from 7 to 13 or 7.5 to 10 or 12.5 mm. The conventional penetration test employed herein, utilises a lab plant penetrometer equipped with a Seta wax needle (weight 2.5 grams) which has a cone angle at the point of the needle specified to be 9°10' +/- 15'. A sample of the composition with a flat upper surface is used. The needle is lowered onto the surface of the composition and then a penetration hardness measurement is conducted by allowing the needle with its holder to drop under the combined weight of needle and holder of 50 grams for a period of five seconds after which the depth of penetration is noted. Desirably the test is carried out at six points on each sample and the results are averaged. The gellants for forming stick compositions herein are usually selected from one or more of two classes: non-polymeric fibre-forming gellants and waxes, optionally supplemented by incorporation of a particulate silica and/or an oil-soluble polymeric thickener. Waxes, when employed, are often selected from hydrocarbons, linear fatty alcohols, silicone polymers, esters of fatty acids or mixtures containing such

- 31 -

compounds along with a minority (less than 50% w/w and often less than 20% w/w) of other compounds.

5 Non-polymeric fibre-forming gellants, when employed, are typically dissolved in a water-immiscible blend of oils at elevated temperature and on cooling precipitate out to form a network of very thin strands that are typically no more than a few molecules wide. One particularly effective category of such thickeners comprises N-acyl aminoacid amides and in particular linear and branched N-acyl glutamic acid dialkylamides, such as in particular N-lauroyl glutamic acid di n-butylamide
10 and N-ethylhexanoyl glutamic acid di n-butylamide and especially mixtures thereof. Such amido gellants can be employed in anhydrous compositions according to the present invention, if desired, with 12-hydroxystearic acid.

15 A gellant is often employed in a stick or soft solid composition at a concentration of from 1.5 to 30%, depending on the nature of the gellant or gellants, the constitution of the oil blend and the extent of hardness desired. The anhydrous compositions can contain one or more optional ingredients, such as one or more of those selected from those identified below.

20 Optional ingredients include wash-off agents, often present in an amount of up to 10% w/w to assist in the removal of the formulation from skin or clothing. Such wash-off agents are typically nonionic surfactants such as esters or ethers containing a C₈ to C₂₂ alkyl moiety and a hydrophilic moiety which can comprise a polyoxyalkylene group (POE or POP) and/or a polyol.

25

The compositions herein can incorporate one or more cosmetic adjuncts. Such adjuncts can include skin feel improvers, such as talc or finely divided (i.e. high molecular weight) polyethylene, i.e. not a wax, for example Accumist™, in an amount of 1 up to about 10%; a moisturiser, such as glycerol or polyethylene glycol (mol wt 200 to 600), for example in an amount of up to about 5%; skin
30

- 32 -

benefit agents such as allantoin or lipids, for example in an amount of up to 5%; colours; skin cooling agents other than the already mentioned alcohols, such a menthol and menthol derivatives, often in an amount of up to 2%, all of these percentages being by weight of the composition. A further optional ingredient
5 comprises a preservative, such as ethyl or methyl parabens or BHT (butyl hydroxy toluene) such as in an amount of from 0.01 to 0.1 % w/w.

The invention composition and particularly compositions intended to be delivered from a roll-on dispenser or a pump spray, conveniently comprise emulsions. In
10 such emulsions the total oil content is often less than 10% by weight of the total composition, for example comprising between 0.5 and 2% by weight of fragrance oils (non-encapsulated) and from 1 to 6% by weight of other oils, selected for example from the carrier oils described hereinbefore. It is particularly suitable to employ from 1 to 5% by weight of a triglyceride oil, such as sunflower seed oil.

15 Emulsions commonly employ a non-ionic surfactant acting as an emulsifier or mixture of emulsifiers providing an HLB value in the region of 6 to 10. An especially desirable range of emulsifiers comprises a hydrophilic moiety provided by a polyalkylene oxide (polyglycol), particularly polyethylene oxide, such as
20 containing 4 to 6 EO units or a mixture of 2-4 plus 10 to 30 EO units and a hydrophobic moiety provided by an aliphatic hydrocarbon, preferably containing at least 10 carbons and commonly linear. The hydrophobic and hydrophilic moieties can be linked via an ester or ether linkage, possibly via an intermediate polyol such as glycerol.

25 Preferably the hydrophobic aliphatic substituent contains at least 12 carbons, and is derivable from lauryl, palmityl, cetyl, stearyl, olearyl and behenyl alcohol, and especially cetyl, stearyl or a mixture of cetyl and stearyl alcohols or from the corresponding carboxylic acids. Particularly conveniently, the combination of
30 emulsifiers comprises steareth-2 and a selection from steareth-15 to steareth-30.

- 33 -

The invention compositions desirably are substantially or totally free from water-soluble short chain monohydric alcohols (commonly recognised as up to C₆) and especially ethanol. Substantially in this context indicates a proportion of less than 5% and preferably less than 1 % by weight of the respective full or base composition.

Compositions according to the invention may be aerosol compositions. Such compositions herein comprise a base composition, namely a full composition except for a propellant mixed with a propellant. The base composition commonly comprises the antiperspirant and/or deodorant active, the liquid carrier and often a suspending aid. Many suitable aerosol compositions are anhydrous. Such compositions typically have a proportion of carrier oils that is commonly from 50 to 95% by weight of the base composition, and the mixture commonly includes one or more volatile oils such as a volatile silicone oil and one or more non-volatile oils, often in a weight ratio of from 10:1 to 1 :2 and particularly from 5:1 to 1 :1. The concentration antiperspirant active in the base composition is often from 5% to 60% and especially 10% to 45% by weight.

During the manufacture of compositions according to the invention, it is especially desirable for the fragrance capsules to be incorporated into the composition with mixing at a rate and power input that does not damage the capsules. One convenient process sequence for preparing a stick or soft composition according to the present invention comprises first forming a solution of the structurant combination in the water-immiscible liquid or one of the water- immiscible liquids. This is normally carried out by agitating the mixture at a temperature sufficiently high that all the structurants dissolve (the dissolution temperature) such as a temperature in a range from 70 to 140⁰C. Any oil-soluble cosmetic adjunct can be introduced into oil phase, either before or after the introduction of the gellants. However, the fragrance oil, be it encapsulated or free, is commonly the last ingredient to be incorporated into the composition, after the antiperspirant active

- 34 -

on account of its sensitivity often to elevated temperature. Commonly the resultant structurant solution is allowed to cool to a temperature that is intermediate between that at which the gellants dissolved and the temperature at which it would set, often reaching a temperature in the region of 60 to 90°C.

5

In some routes, the carrier oils can be mixed together prior to introduction of the gellants and the antiperspirant or deodorant active. In other preparative routes, it is desirable to dissolve all or a fraction of the gellants and especially for amido gellants in a first fraction of the composition, such as a branched aliphatic alcohol, e.g. isostearyl alcohol or octyldodecanol, optionally in conjunction with an alcohol having some water-miscibility and boiling point above the dissolution temperature of the amido gellant in the alcoholic fluid. This enables the remainder of the carrier fluids to avoid being heated to the temperature at which the structurants dissolve or melt. Such a process commonly involves mixing the fractions intensively in for example a "Sonolator"™. In the invention compositions, the fragrance capsules are most desirably introduced after any intensive mixing step. The proportion of the carrier fluids for dissolving the structurants is often from 25 to 50% by weight of the carrier fluids. In other preparative routes the particulate material is introduced into preferably a second fraction of the carrier oils, for example silicone and/or ester and/or hydrocarbon oils and thereafter, and thereafter the first fraction containing dissolved structurant and second fraction containing suspended particulate material are mixed at a temperature above that at which the composition gels, and often from 5°C to 30°C above the regular setting temperature of the composition, dispensing containers are filled and cooled or allowed to cool to ambient temperature.

10

15

20

25

Examples**Example 1:- Preparation of lipid based microcapsules**

5 Lipid based microcapsules for use in these examples were prepared as follows:-

1. Suppocire DM (7.1 g; supplied by Gatte-Fosse) and Cithrol DPHS (1.0 g; supplied by Croda) were added to a small bottle. The mixture was then melted at 75°C.
- 10 2. Gelucire 44/14 (1.5 g; supplied by Gatte-Fosse), Stearic acid (0.2 g), vitamin E acetate (3.15 g; supplied by DSM) and water (7.4 g) were placed in a beaker and warmed to 75°C with thorough mixing. The temperature was maintained using a water bath.
3. The resulting mixtures of steps 1 and 2 were then combined with thorough
15 mixing.
4. 100 ml of water at a temperature of 75°C was subsequently added and mixed for 2 minutes at 75°C using an Ultra Turrax T25 disperser set at 13,500 l/min.
5. The water bath was then removed and the stirring speed reduced to 6,000
20 l/min. The temperature was allowed to drop to 50 °C. The mixture was then stirred using an overhead stirrer until the temperature had dropped to 30 °C.

The volume size distribution of the capsules was 40µm and the fragrance
25 content of the capsules was 40%.

The lipid based microcapsules were then used in the tests described below.

- 36 -

Example 2:- *in vitro* degradation of gelatin based microcapsules

The composition and method for preparing the glutaraldehyde cross-linked gelatine based microcapsules is described above whereby oil filled blank
5 glutaraldehyde cross-linked gelatin shells are prepared and a fragrance oil is added and allowed to diffuse through the shell.

Alcalase™ L, (Sigma Aldrich cat. no. P4860; Novozymes) was considered a relevant model for proteases of both bacterial and human origin to carry out
10 testing of microcapsules for susceptibility to enzyme hydrolysis. Enzyme incubation was carried out in freshly prepared pH 6 (25 mM) MES [2-(N-morpholino)ethane-sulfonic acid] buffer at 37°C.

A suspension of 10 mg encap solids was prepared in 25 mM of MES buffer with
15 pH adjusted at 6. Stock solutions of specific enzyme protein, Alcalase L were prepared, in such concentrations, 0, 0.1, 0.5, 1 and 2µg/ml. 10µl of the enzyme stock solution was added to the capsules solutions at t=0hour, t=2hours and t=4hours. The solutions were kept at 37°C and agitated at 1000rpm on an Eppendorf incubator-shaker until t=6hours. Mixing was then stopped and aliquots
20 taken for the various analysis.

The release of protein into solution due to protease digestion of the gelatin capsules was determined using the Bio-Rad DC protein assay kit (Bio-Rad Laboratories; Hercules, California, US). Following enzyme hydrolysis, encap
25 suspensions were first syringe-filtered through a 0.2µm PTFE membrane filter. Protein concentration was determined spectrophotometrically at 750nm. Reference samples of bovine serum albumin protein were used to produce a linear standard curve to estimate protein concentration.

Table 1:- protein release from microcapsules of the invention.

Alcalase (ug/ml)	Protein release (ug/ml)
0.0	75
0.1	103
0.2	100
0.5	227
1.0	248
2.0	282

It will be seen that protein residues were released from the microcapsules during incubation.

5

Example 3: *in vivo* degradation of gelatine based microcapsules

An olfactive assessment of fragrance intensity was then carried out using a panel of 35, male, trained assessors was carried out in order to evaluate whether protease labile microcapsules can provide improved fragrance longevity when exposed to a natural enzyme skin condition compared with a low enzyme condition. The methodology was as follows:-

10

An aqueous dispersion of microcapsules (1.5% w/w) was prepared in a viscous suspending liquid (1% Klucel M hydroxypropylcellulose, ex. Aqualon).

15

A 15 x 5 cm area of living human skin was first washed with a mild soap based detergent. A similar control area, on the opposing side of the same subject, was additionally washed with alcohol to sterilise the skin of bacteria.

20

The aqueous solution of microcapsules was then applied to the washed or sterilised skin at a dosage of 30 mg, applied by pipette and gently spread over the skin. Application to the washed only skin was in accordance with the process of

- 38 -

the invention (designated 1); application to the washed and sterilised skin was a control (designate A).

A fragrance assessment was then carried out using a panel of trained assessors at 3 h and 6 h post treatment. Fragrance intensity was scored on a scale of 0 – 5, where 0 = no fragrance and 5 equates to intense fragrance.

A statistical program was used to perform an Analysis of Variance on the fragrance scores (implemented with the SAS General Linear Models procedure), using a model incorporating fixed effects of subject, day, side, assessor and treatment. The minimum difference required for significance at the 5% and 1% level was estimated from the model error and compared to the actual difference between the least square means calculated for each treatment. The treatment difference was deemed to be significant when the least square means differed by more than the minimum significant difference.

Table 2: Fragrance intensity arising from washed and sterilised skin treated with enzyme sensitive gelatin encaps containing perfume.

Test area	Mean fragrance score	Mean difference	Statistical significant difference	Significance	p-value
3 hours after application					
A	1.64	0.09	0.087	*	0.0491
1	1.73				
6 hours after application					
A	1.19	0.10	0.08	**	0.0078
1	1.29				

Significance levels: ** - 99% * - 95%

- 39 -

The ethanol wash sterilised the skin, and either removed or deactivated skin enzymes. After 3 hours Example 1, in accordance with the invention, has significantly higher perfume intensity.

CLAIMS

1. A composition, which is not an ethanolic based deodorant spray composition, for treating axilla skin, wherein the skin has a naturally occurring enzyme population comprising protease and/or lipase, wherein the composition comprises:-
- 5
- a) a particle, having a particle size of from 1 to 100 microns, comprising
- 10
- i) an insoluble enzymatically degradable material, preferably natural, wherein the enzymatically degradable material is degraded by a protease enzyme; and
- ii) a hydrophobic benefit agent selected from a fragrance, a skin care agent, an anti-oxidant, a vitamin, an anti-fungal agent, an anti-inflammatory active, a skin conditioning agent, a
- 15
- sunscreen and mixtures thereof; and
- b) an active ingredient selected from surfactants, polymers, moisturisers, humectants and emollients, antimicrobials, antiperspirant actives, deodorant actives, skin health actives, and mixtures thereof.
- 20
2. A composition as claimed in claim 1, which is a deodorant or antiperspirant composition.
3. A composition as claimed in claim 1 or claim 2, wherein the particle is a core shell encapsulate and the shell comprises the enzymatically degradable material.
- 25
4. A composition as claimed in any preceding claim, wherein the enzymatically degradable material is selected from natural animal derived proteins and natural plant derived proteins.
- 30

- 41 -

5. A composition as claimed in claim 4, wherein the enzymatically degradable material is selected from collagen, gelatin, casein, albumin, gluten, zein, soy protein, keratin, lipid based materials and fats.
- 5 6. A composition as claimed in any preceding claim, wherein the enzymatically degradable material is a synthetic material.
7. A composition as claimed in claim 6, wherein the enzymatically degradable material is selected from polyester, polyamide and nylon.
- 10 8. A composition as claimed in any preceding claim, wherein the active ingredient is an antiperspirant active.
- 15 9. A method of treating axilla skin wherein the skin has a naturally occurring enzyme population comprising protease, said method comprising applying to the skin a composition, which is not an ethanolic based deodorant spray composition, wherein the composition comprises:-
- 20 a) a particle, having a particle size of from 0.1 to 100 microns, comprising
- i) an insoluble enzymatically degradable material, preferably natural, wherein the enzymatically degradable material is degraded by protease enzyme; and
- 25 ii) a hydrophobic benefit agent selected from a fragrance, an skin care agent, an anti-oxidant, a vitamin, an anti-fungal agent, an anti-inflammatory active, a skin conditioning agent, a sunscreen and mixtures thereof; and
- 30 b) an active ingredient selected from surfactants, polymers, moisturisers, humectants and emollients, antimicrobials, antiperspirant actives, deodoarant actives, skin health actives, and mixtures thereof

- 42 -

such that release of the hydrophobic benefit agent is delayed.

10. A method as claimed in claim 9, wherein the composition is defined by any of claims 2 to 8.

5

11. A process for treating an axilla surface; said surface producing protease enzymes; wherein the process comprises the step of treating the surface with a composition as defined by any one of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/065379

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61Q15/00 A61K8/11
ADD.

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)
A61Q 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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 271 934 A (GOLDBERG MARVIN E [US] ET AL) 21 December 1993 (1993-12-21) the whole document	1-6,9-11
X	US 2008/274149 A1 (SEILER MATTHIAS [DE] ET AL) 6 November 2008 (2008-11-06) cited in the application paragraph [0026] - paragraph [0030] paragraph [0075]; claims; examples ----- -/-	1,3,6,7



Further documents are listed in the continuation of Box C.



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 application or patent 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

26 September 2014

Date of mailing of the international search report

07/10/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Donovan-Beermann, T

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/065379

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. KROMIDAS ET AL: "Release of antimicrobial actives from microcapsules by the action of axillary bacteria", INTERNATIONAL JOURNAL OF COSMETIC SCIENCE, vol. 28, no. 2, 1 April 2006 (2006-04-01), pages 103-108, XP055093809, ISSN: 0142-5463, DOI: 10.1111/j.1467-2494.2006.00283.x cited in the application the whole document	1-4,8-11
A	US 6 232 487 B1 (ANDERSON DENISE [CH] ET AL) 15 May 2001 (2001-05-15) column 2, line 32 - line 41; claims; examples	1
X	WO 2009/126742 A2 (APPIAN LABS LLC [US]; WINDSOR J BRIAN [US]; NITIN NITIN [US]) 15 October 2009 (2009-10-15) cited in the application claims; examples	1,3-5
X	WO 2004/104021 A2 (DOW CORNING [US]; GENECOR INT INC [US]; KUMAR MANOJ [US]; MAZEAUD ISAB) 2 December 2004 (2004-12-02) page 11, line 20 - line 23 page 11, line 29 - line 30 page 19, line 6 - line 31; claims; examples	1-5,8
X	WO 99/17871 A1 (GIVAUDAN ROURE INT [CH]; SOPER JON C [US]) 15 April 1999 (1999-04-15) claims	1-6,8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/065379

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5271934	A	21-12-1993	NONE
US 2008274149	A1	06-11-2008	CA 2626562 A1 03-05-2007 DE 102005051342 A1 26-04-2007 EP 1940356 A1 09-07-2008 JP 2009512721 A 26-03-2009 US 2008274149 A1 06-11-2008 WO 2007048464 A1 03-05-2007
US 6232487	B1	15-05-2001	AU 722609 B2 10-08-2000 AU 7309998 A 07-01-1999 BR 9802199 A 20-07-1999 CA 2241397 A1 23-12-1998 DE 69808557 D1 14-11-2002 DE 69808557 T2 10-07-2003 DE 69835624 T2 09-08-2007 EP 0887338 A1 30-12-1998 EP 1223160 A2 17-07-2002 ES 2183313 T3 16-03-2003 ES 2269545 T3 01-04-2007 JP 3124255 B2 15-01-2001 JP H11116537 A 27-04-1999 SG 93818 A1 21-01-2003 US 6232487 B1 15-05-2001
WO 2009126742	A2	15-10-2009	US 2009269405 A1 29-10-2009 WO 2009126742 A2 15-10-2009
WO 2004104021	A2	02-12-2004	CA 2524710 A1 02-12-2004 EP 1624864 A2 15-02-2006 JP 4850709 B2 11-01-2012 JP 2007503467 A 22-02-2007 US 2004228913 A1 18-11-2004 WO 2004104021 A2 02-12-2004
WO 9917871	A1	15-04-1999	AT 217804 T 15-06-2002 AU 744495 B2 28-02-2002 AU 9181798 A 27-04-1999 BR 9812887 A 08-08-2000 CA 2304556 A1 15-04-1999 CN 1285768 A 28-02-2001 DE 69805537 D1 27-06-2002 DE 69805537 T2 05-12-2002 EP 1027147 A1 16-08-2000 ES 2175771 T3 16-11-2002 JP 3616009 B2 02-02-2005 JP 2004513187 A 30-04-2004 PL 339768 A1 02-01-2001 TR 200000959 T2 23-10-2000 US 6045835 A 04-04-2000 WO 9917871 A1 15-04-1999