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(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, 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, New Jersey 07632 (US).

(72) Inventors: **BARNETT, Stuart, Anthony**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **JONES, Craig, Warren**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **KHOSHDEL, Ezat**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **MERRINGTON, James**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **THOMPSON, Katherine, Mary**; Unilever R&D Port Sunlight Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB).

(74) Agent: **WHALEY, Christopher**; Unilever PLC, Unilever Patent Group, Colworth House, Sharnbrook, Bedford Bedfordshire MK44 1LQ (GB).

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(54) Title: METHOD OF DELIVERING AN ACTIVE AGENT TO SKIN

(57) Abstract: A method of delivering an active agent to skin, preferably axilla, comprising the steps of: a) applying to skin a composition comprising at least 0.1 wt% of core shell microcapsules whereby the microcapsules come into contact with the skin each microcapsule having an inner shell formed of a first synthetic polymer and containing the active agent and the inner shell capable of allowing at least a portion of the active agent to pass from inside the inner shell to outside the inner shell to enable it to come into contact with the skin, the inner shell being coated with a coating of insoluble polyamide with a solubility in water of less than 1g/L at 25°C, the polyamide formed by the reaction of: (iii) at least one low molecular weight dicarboxylic acid having from 3 to 12 carbon atoms, or ester thereof; (ii) at least one poly(alkylene glycol) polyamine having the formula (I) H_2N-(-C(R)H-CH_2-O-)x-C(R)H-CH_2-NH_2 (I) where x ranges from about 2 to 5, R is an alkyl of one to four carbon atoms; (iii) optionally, at least one high molecular weight dicarboxylic acid (dimer) having from 20 to 40 carbon atoms, or ester thereof; and wherein the coating further comprises a crosslinker to improve hardness and further reduce solubility, such that, while the coating is present the release of the active agent onto the skin is retarded; b) Sweating to produce sweat that comes into contact with at least part of the polyamide coating; c) Degrading the polyamide coating by the action of protease enzymes present in the sweat thereby to cause delayed release of the active agent onto the skin, preferably over a period of from 1 hour to 2 days after the microcapsule first comes into contact with sweat.

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METHOD OF DELIVERING AN ACTIVE AGENT TO SKIN

Field of the Invention

The present invention relates to a method of delivering an active agent, preferably perfume, to skin using microcapsules which release the active agent after their exposure to protease.

Background and Prior Art

It has been proposed to design core shell microcapsules to release an active agent as a triggered response of exposure of the shell to enzymes, including those enzymes that naturally occur on skin.

US 2008/0274149 (Evonik) discloses cosmetic skin treatment compositions containing microcapsules that give controlled release of active ingredients on skin by means of enzymatically degradable organic polymers containing ester linkages triggered to release by lipases. We have found that naturally occurring levels of lipases are unreliable as a trigger for skin applications.

WO 2009/126742 (Appian Labs) discloses the release of active ingredients from microcapsules by exposure to metalloproteinase. The microcapsules are coated in crosslinked gelatin which then releases the microcapsules in a controlled manner on exposure to the metalloproteinase that is found at specific sites in an organism to be treated. The technology thus provides targeted release. Crosslinked gelatin is unsuitable as a coating material because it is moisture sensitive and thus very limited in terms of the formulations into which it can be added. Also the most common crosslinkers are chemicals that are undesirable for skin contact (e.g. glutaraldehyde). Furthermore aldehyde cross-linked gelatin coacervate capsules can show a high degree of fragrance leakage during storage and are relatively soft and so can be mechanically prematurely ruptured.

WO 2015/014628 (Unilever) discloses a deodorant spray containing a particle with an insoluble enzymatically degradable shell. Two degradation mechanisms are disclosed, one utilising lipase and one utilising protease. Among the shell materials that can be degraded by proteases nylon or polyamide is taught. We have since determined that nylons are not sufficiently degraded to be of practical utility as triggered release shells. This document also

discloses the possibility to form a secondary coating from any of the shell materials taught. No details are given of the coating material or the particle onto which it is to be coated.

It has been proposed to use polyamides as an encapsulation or microcapsule coating material. Typically this material is mentioned as an alternative but is not the main focus of patent documents.

The following documents disclose polyamide microcapsules which utilise polyoxyamines as a monomer, but not for any kind of biotriggering benefit:

US 2002/0158356 (Institut Francais Petrole) discloses microcapsules made by reaction of acid chlorides (e.g. adipoyl chloride) with polyoxylyeneamine (Jeffamines). According to paras 0053 and 0059 PO is preferred over EO for the latter material. The resulting capsules are over 100 micron diameter.

US 4777089 (Lion) discloses core shell microcapsules, possibly containing perfume in the core, using a water-soluble nylon for the shell AQ Nylon P70 is a copolymer of 1-6 hexadioic acid with α,ω-diethylamine-PEG (CAS 24991-53-5) and caprolactam. The water soluble nylon shell is removed on dilution. Sweat and saliva are mentioned as diluents.

JP 2012/171974 (Sekisui Plastics) discloses microspheres comprising water-soluble polyamide coating layers (AQ-Nylon T70) around (polystyrene) solid resin particles. The delivery of the polyamide from aqueous solution is said to be more environmentally friendly than from another solvent system.

The following documents disclose other polyamide shell or polyamide coated microcapsules, but not for any kind of biotriggering benefit:

US 4835248 (Hoechst, 30/05/1989) discloses sparingly soluble polyamide microcapsules comprising biodegradable polymers of a dicarboxylic acid and a diamine (with carboxy-substitutent). The microspheres can release embedded actives (see examples 12 & 17) as they dissolve. This makes them suited to implanted controlled release systems.

WO 2007/035531 (Du Pont) discloses a method of depositing benefit particles encapsulated with a polyamide on skin where the particle itself can be organic/polymeric nanoparticles. Example 15 used Nylon 6,6.

WO 2013/182855 (Imerys Minerals) discloses encapsulates containing cosmetic ingredients comprising a core, an inner shell with an outer hydrophobic surface and an outer shell of a second cross-linked polymer matrix. The outer shell can be crosslinked polyamide formed using polyfunctional acids or amines, but no examples are given. The two layer shell is intended to reduce leakage of perfume. These particles are designed for rupture release.

US 20150259629 A1 (Unilever) describes the use of Nylon type polyamides as shells for core-shell microcapsules.

US 2015/0252312 (IFF) discloses core-shell poly(urea) or poly(urethane) core fragrance shell capsules stabilized by a "multi-functional amine, amino acid, polymeric mixture or mixture thereof". Suitable poly(amine) cross-linkers include poly(ether-amines) including Jeffamines. The exemplified use is in a fabric conditioner.

US 4409201 (Hoechst) describes "Pressure-resistant microcapsules with a poly(amide) shell and a poly(urethane)-poly(urea) inner mass and process for their manufacture". The exemplified use is for encapsulation of insecticides.

WO 2011/056904 (P&G) discloses an encapsulate comprising a core, an aminoplast shell and an exterior coating of anionic and cationic polymers where both polymers can be polyamides.

US 7196049 (IFF) discloses polymeric encapsulated fragrances suitable for use in personal care and cleaning products. The fragrance is encapsulated by a first polymer material (preferably and aminoplast such as melamine-formaldehyde or urea-formaldehyde or gelatin) which is then coated with a mixture of cationic polymers, preferably polyamides produced as reaction product of polyamines and (halomethyl) oxirane. Exemplified uses are in hair cleansing and laundry products.

US 8329223 (Devan-Micropolis SA) discloses double-walled microcapsules with an outer thermoplastic wall (optionally a polyamide) and an inner wall (preferably an aminoplast). The

microcapsules are applied to fibers so as to produce a slow release of fragrance, antimicrobial, insecticide etc., or for thermoregulation by containing Phase Change Materials (PCMs).

US 5180637 (Sakura Color Products Corp) discloses double-walled microcapsules having a "hydrophobic core, a primary wall composed of an aminoplast, and a secondary wall formed from a polyion complex of a cationic polyamide-epihalohydrin resin having a urea bond in the structural unit with a polystyrenesulfonic acid or salt and a process for making these capsules". The capsules optionally contain a fragrance.

Summary of the Invention

According to the present invention there is provided a method of delivering an active agent to skin, preferably axilla, comprising the steps of:

a) applying to skin a composition comprising at least 0.1 wt% of core shell microcapsules whereby the microcapsules come into contact with the skin each microcapsule having an inner shell formed of a first synthetic polymer and containing the active agent and the inner shell capable of allowing at least a portion of the active agent to pass from inside the inner shell to outside the inner shell to enable it to come into contact with the skin, the inner shell being coated with a coating of insoluble polyamide with a solubility in water of less than 1g/L at 25°C, the polyamide formed by the reaction of:

(i) at least one low molecular weight dicarboxylic acid having from 3 to 12 carbon atoms, or ester thereof;

(ii) at least one poly(alkylene glycol) polyamine having the formula (I)

$$H_2N\text{-}(\text{-}C(R)H\text{-}CH_2\text{-}O\text{-})x\text{-}C(R)H\text{-}CH_2\text{-}NH_2 \qquad (I)$$

where x ranges from about 2 to 5, R is an alkyl of one to four carbon atoms;

(iii) optionally, at least one high molecular weight dicarboxylic acid (dimer) having from 20 to 40 carbon atoms, or ester thereof;

and wherein the coating further comprises a crosslinker to improve hardness and further reduce solubility, such that, while the coating is present the release of the active agent onto the skin is retarded;

b) sweating to produce sweat that comes into contact with at least part of the polyamide coating;

c) degrading the polyamide coating by the action of protease enzymes present in the sweat thereby to cause delayed release of the active agent onto the skin, preferably over a period of from 1 hour to 2 days after the microcapsule first comes into contact with sweat.

Most preferably to obtain insolubility R is C1 alkyl.

Preferred crosslinkers, particularly when the core leaky particle is polyurea are poly isocyanates, most preferably diisocyanates. When used the crosslinker preferably comprises from 1 to 30 wt% of the polyamide coating. Advantageously the crosslinker is immiscible with water.

Preferably the active agent is selected from the group comprising perfumes or fragrances, anti-oxidants, anti-fungals, antimicrobials, anti-inflammatories, sunscreens and mixtures thereof.

The active agent is most preferably perfume.

The small dicarboxylic acid (i) is preferably an aliphatic acid. Preferably it has a chain of from 3 to 6 carbon atoms. A highly preferred small carboxylic acid has been found to be adipic acid.

The dimer dicarboxylic acid is not essential. However, its presence is desirable. It is used at a lower molar level than the small dicarboxylic acid. A preferred dimer acid has 36 carbon atoms.

A preferred inner shell is made from polyurea.

Optionally, the microcapsule has a non-ionic polysaccharide deposition aid fixed covalently to the outside of the coating.

A preferred composition comprising the microcapsules for use in the method of the invention is a deodorant composition comprising at least 0.01 wt% of the microcapsules.

The poly(amide) coated capsules also show enhanced stability to premature payload (active) leakage when applied to the axilla such that the payload is substantially retained through several sweat samples but is released when the efficacy of the AP product starts to fall, potentially several hours after composition application. Preferably the enzymes present in the sweat cause delayed release of the active agent onto the skin over a period of from 1 hour to 2 days after the microcapsule first comes into contact with the sweat containing active protease enzymes.

Detailed Description of the Invention

Definitions

In this specification, the microcapsules may also be referred to as “particle(s)”, “encap(s)”, or “capsule(s)”).

“Active agent” means any material that can be incorporated into the core of a leaky shell core shell particle and which is able to leak from the particle in the absence of any barrier coating applied to the particle. Typically the active agent is selected to have a specific effect on the substrate onto which it intended for it to leak. For example it may be a perfume designed to provide a fresh smell when released onto an axilla. Other suitable examples of active agents are given herein.

“Leaky” means that the inner shell is so formed that it allows some of the active agent to pass from the inside of the shell to the outside e.g. by diffusion.

“Coating” means a complete enough covering of the inner shell by means of a layer of polymer so that all the pores are thereby substantially blocked and diffusion of the active agent is thereby significantly reduced while the coating is present and intact.

"Insoluble" when applied to a polyamide polymer means that the polymer remains intact (does not dissolve) when immersed in warm (37°C) water or buffer solution as described below. An insoluble polyamide has a water solubility of less than 1 g/litre at 25°C.

Core shell microcapsule

The microcapsule is of a core-shell structure. In one embodiment the capsule has one or more shells in which are "leaky". Within these one or more shells are contained the active agent. The active agent is preferably a liquid. Most preferably it is perfume. The leaky one or more shells may be made of any suitable material that is inert to the active agent. In the case of the leaky one or more shells embodiment the capsule is coated with an insoluble protease degradable polyesteramide coating as defined herein.

In another embodiment the insoluble polyesteramide material itself forms an outer coating on an active agent shell and leakage results from its degradation on exposure to protease. Such a microcapsule can, for example, be formed by interfacial polymerisation and it is preferred in that case to encapsulate a hydrophobic material such as perfume to form the discontinuous phase for the emulsion polymerisation. The skilled person will readily be able to devise a suitable process to make such a particle. Such a particle can also be formed by making the polyesteramide coating in the continuous phase from where it will naturally film form to provide a coating around any discrete particles dispersed in that phase. The particles around which the coating forms could for example be dispersed perfume compositions.

The capsule size distribution can be narrow, broad or multimodal. Multimodal distributions may be composed of different types of capsule chemistries.

The particle comprises an active agent, which may be hydrophobic, and a protease degradable insoluble polyesteramide material.

The particle is broken down by action of protease enzymes on the insoluble polyesteramide degradable material. The particles are not water soluble and so have greater versatility than the moisture activated and ruptured particles used previously e.g. in deodorant compositions. Unlike rupture release, the particles exhibit both delayed and controlled (gradual) release of the active agent.

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.

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.

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 %.

Desirably at least 90 wt%, preferably at least 95 wt% and especially at least 99 wt% of the microcapsules have a diameter in the range of from 0.1 µm up to 200 µm, and usually have an average particle diameter of at least 1 µm and especially below 150 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 100 µm.

Polyesteramide outer coating

The outer coating may be formed directly on the active agent or, more preferably it can be formed on a preformed leaky inner shell in order to reduce leakage of active agent from the leaky core shell particle. The coating is made of a second synthetic polymer material. The outer coating shell comprises at least 80% by weight of the outer coating shell of an insoluble crosslinked polyamide which after exposure to subtilisin from *Bacillus licheniformis* for 24 hours at 37°C is degraded to cause it to become more porous to the active agent.

Surprisingly we found that suitable insoluble biodegradable polyamides could be identified using some of the comparative examples in US 5324812. This document discloses and claims water soluble polyamides made from certain small diacids, dimer acids and polyether amines. We have found that by modification of one or more of these components and addition

of a difunctional crosslinking agent to reduce solubility in water to the required low level to render the coating insoluble, it is possible to make an insoluble polyamide that is surprisingly biodegradable when exposed to protease. There are documented instances of protease digestion of polyamides in the prior art, but they all rely on extended exposure of protease producing microorganisms to the polyamide which then aids digestion by a process of adaptation. In the case of our insoluble polyamides the susceptibility to protease attack is immediate.

The insoluble polyamide is degraded by protease enzyme. We have developed a simple screening test to identify suitable polyamide materials.

Rather unexpectedly we have found that a suitable reliable predictor of the degradation of the microcapsule coating by skin proteases is the behaviour of the polyamide materials in contact with a subtilisin enzyme commercially available as Alcalase™. The polyamide will show signs of degradation when exposed to 50 ng/ ml of Alcalase™ (subtilisin from *Bacillus licheniformis)* for 24 hours at 37°C. This test was designed to represent conditions found in a human armpit (axilla). Alcalase™ is a commercially available serine protease enzyme that has been used as an esterase. It was chosen because of its similarity to some proteases known to be naturally present in sweat and its temperature activity profile.

The insoluble polyamides suitable for use in the invention have as an essential precursor poly(alkylene glycol) polyamines. To the best of our knowledge such poly(alkylene glycol) polyamines have hitherto been used only for manufacture of soluble polyamides. It was surprising that by modifying such soluble polyamides to make them insoluble a highly protease responsive insoluble polyamide material could be obtained and that it also proved to be highly suited to use in manufacture of microcapsules, in particular avoiding the common problem of agglomeration of the microcapsules during their manufacture.

Suitable poly(alkylene glycol) polyamines are sold by Huntsman as Jeffamine™ D. The molecular weight of the diamine is preferably in the range 190 to 10000, more preferably 200 to 6000 and most preferably 200 to 600. Selection of the polypropylene glycol based materials has been found to confer insolubility in preference to the normally used polyethylene glycol materials in soluble polyamides.

To form polyamides from the poly(alkylene glycol) polyamines they are reacted with polyfunctional acid chlorides, acids or anhydrides. Acids are preferred.

Highly desirable are small difunctional materials, dicarboxylic acids with from 3 to 10, more preferably 3 to 6 carbon atoms being preferred, most advantageously with an alkylene chain of at least 3 carbon atoms. Adipic acid is most preferred. Whilst aliphatic materials are preferred over the aromatic materials tested we have reason to believe that some aromatic acids could nevertheless usefully provide protease degradable polyamides, even in crosslinked form. Use of the small diacid provides two amide linkages in close proximity in the polyamide coating and without wishing to be bound by theory it is believed that this assists with the susceptibility to protease attack when combined with the poly(alkylene glycol) polyamines.

We have also found that the susceptibility of the coating to protease attack may be enhanced by the presence of an optional dimer acid as taught to be useful for inclusion in water soluble polyamide in US 5324812 and as previously known to be useful as a hot melt flow modifier for polyamides from US 4062819. Preferred dimer acids are obtained by the dimerization of C18 acids such as oleic acid, linoleic acid and mixtures thereof. Such dimer acids have as their principal component C36 dicarboxylic acid and typically have an acid value in the range 180-215. Dimer acids may be hardened by hydrogenisation. Hydrogenated Dimer acids with greater than 90% purity are highly preferred.

Benefits from inclusion of the “dimer acid” are an enhanced compatibility of the encapsulating of the coating with hydrophobic shell polymers. Ensuring the polyamide is non-crystalline and hence more flexible and thus (i) more likely to survive processing and to provide good skin feel properties and (ii) more likely to be susceptible to enzymatic hydrolysis (protease attack) than crystalline regions of the polyamide.

It is preferable if each of the poly(alkylene glycol) polyamine and both the short chain polyacid, acid chloride or anhydride and the dimer acid are aliphatic.

A disadvantage of use of acid chlorides for the present application is that the resulting acid from the condensation reaction must somehow be neutralised either by use of excess amine or by addition of a separate base material to carry out the neutralisation. This then requires either a purification step or the acceptance that the neutralised material remains as an impurity in the aqueous

dispersion of microcapsules. This is believed to be disadvantageous or unacceptable for most skin contact applications.

The coating is crosslinked with a cross linker. We have found that a particularly preferred form of crosslinking is to introduce a polyisocyanate material into the coating. This will then form some polyurea linkages which do not appear to detract from the protease action. Disocyanates are preferred crosslinkers. Advantageously the chosen cross linker is immiscible with the aqueous phase if interfacial or emulsion polymerisation is used. Preferred polyisocyanate materials for use in the invention include: 4,4′-methylenebis(cyclohexyl isocyanate) and polymethylene-polyphenylisocyanate. Preferably 4,4′-methylenebis(cyclohexyl isocyanate). The level of cross linker used preferably lies in the range 0.5 to 40 wt% based on the polyamide coating. More preferred is a level of from 5 to 15 wt%. At these levels of inclusion the crosslinker converts an otherwise soluble polyamide into an insoluble one.

Inner shell

Consisting essentially of a first, preferably synthetic, polymer material.
The inner shell is leaky and thus allows at least 30% by weight of the active agent to escape in the absence of any shear or rupture of the inner shell within 48 hours of exposure of the outer shell coating to protease. The skilled worker will know how to make such a leaky particle for any particular active agent. One particularly suitable material for making such a leaky core shell particle is polyurea. A suitable leaky polyurea core shell particle is described in EP0158449.

Polyureas are formed from diisocyanates or polyisocyanates with diamines or polyamines. Normally to make a microcapsule the cyanate part is present in a dispersed (oily) phase and the amine part is present in the continuous (aqueous) phase. The shell forms via interfacial polymerisation at the phase interface. This reaction and the manufacture of polyurea shell microcapsules is widely known and understood to the skilled person and the invention can be applied to any type of leaky polyurea microcapsule.

When a diisocyanate is used it may be linear aliphatic, cycloaliphatic or aromatic.
Suitable, aromatic polyisocyanates comprise, but are not limited to, 2,4-and 2,6-toluene diisocyanate, naphthalene diisocyanate, diphenyl methane diisocyanate and triphenyl methane-p,p'p"- trityl triisocyanate, polymethylene polyphenylene isocyanate, 2,4,4'-diphenylether

triisocyanate, 3,3'-dimethyl-4,4'- diphenyl diisocyanate, 3,3'-dimethoxy-4,4'diphenyl diisocyanate, and 4,4'4"-triphenylmethane triisocyanate.

Suitable aliphatic polyisocyanates comprise, but are not limited to dicyclohexylmethane 4,4 '-diisocyanate, hexamethylene-1,6-diisocyanate, isophorone diisocyanate, trimethyl-hexamethylene diisocyanate, trimer of hexamethylenel,1,6-diisocyanate, trimer of isophorone diisocyanate, 1 ,4-cyclohexane diisocyanate, urea of hexamethylene diisocyanate, trimethylene diisocyanate, propylene-1 ,2-diisocyanate and butylenes-1,2-diisocyanate and mixtures thereof.

Suitable diamines can comprise amines such as ethylene diamine (EDA), phenylene diamine, toluene diamine, hexamethylene diamine, diethylenetriamine, tetraethylene pentaamine, pentamethylene hexamine, 1,6-hexane diamine, Methylene tetramine, 2,4-diamino-6-methyl- 1,3,5 triazine 1,2-diaminocyclohexane, 4,4'-diamino-diphenylmethane, 1,5-diaminonaphthalene, 2,4,4'-triaminodiphenylether, bis(hexa-methylenetriamine), 1,4,5,8-tetraaminoanthraquinone, isophorone diamine, diamino propane and diaminobutane, and mixtures thereof. Polymeric amines may also be used, for example Jeffamines (polyether amine) and poly(ethyleneimine).

Water soluble diamine or amine salt or polyamines or polyamines salts are preferred as the amine is usually present in the aqueous phase. Combinations of polyisocyanates and diamines are preferred because the plural functionality enables networked structures and having the plural functional material in the disperse phase reduces the chance of bonds forming between adjacent particles and clumping resulting.

Other suitable materials are disclosed, for example, in US2012/0148644 and US2014/0017287. Isocyanate-based capsule wall technologies are also disclosed in WO 2004/054362; EP 0 148149; EP 0 017 409; U.S. 4,417,916, U.S. 4,124,526, US 6,566,306, US 6,730,635, WO 90/08468, WO 92/13450, US 4,681, 806, US 4,285,720, US 6,340,653 and EP 2673078.

A suitable polyurea inner shell material is that formed by reaction of polymeric methylene diphenyl diisocyanate and hexamethylene diamine.

The Active agent

Preferably the active agent is a liquid. Alternatively it may be a solid, in which case it is preferably dispersed in a liquid. The active agent may be either hydrophobic or hydrophilic. The active ingredient payload (active agent) carried in the core of the microcapsule is preferably a hydrophobic active selected from the group consisting of: perfumes, flavouring agents, antimicrobial actives, anti-dandruff agents, UV protection agents, insect repellents, moisturisers, anti-oxidants, emollients and skin conditioners, and mixtures thereof. More preferably it is a hydrophobic material 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. Even more preferably it is a fragrance or antimicrobial active. Most preferably it is a fragrance (perfume).

A microcapsule may comprise either a single active agent or alternatively it may comprise more than one active agent. The active agent(s) may take up all of the available core volume or the active agent(s) may be dispersed or dissolved in a carrier material inside the core. In that case it is the combination of the liquid carrier material and the active agent that will diffuse through the pores in the shells.

Suitable active 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, bodifying 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 petrolatum) and mixtures thereof.

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

Preferred sunscreens and/or skin lightening active 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- hydroxylphenyl)-1,3 diethane, ellagic acid, gluc- pyranosyl-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, hydroxycaprylic 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 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, digalloyltrioleate, 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 (Avobenzone, sold commercially under the trade name Parsol 1789 by DSM).

Suitable antioxidants, anti-ageing actives and anti-inflammatory active agents 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.

Perfume and fragrance active agents

Perfume and fragrance materials (which include pro-fragrances) are particularly preferred active agents.

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

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

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 to -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 microcapsule.

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 to 250°C.

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:

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, 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, 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 Benzyl Acetate, Methyl Eugenol, Methyl Heptenone, Methyl Heptine Carbonate, Methyl Heptyl Ketone, Methyl Hexyl Ketone, Methyl Phenyl Carbinyl 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, Phenyl Acetate, Propyl 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 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.

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 250°C at 1 bar pressure include the following materials:- anethol, methyl heptine carbonate, ethyl aceto acetate, para cymene, nerol, decyl aldehyde, para cresol, methyl phenyl carbinyl 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, fructone, herbavert, iso cyclo citral, methyl isobutenyl tetrahydro pyran, iso propyl quinoline, 2,6-nonadien-1 -ol, 2-methoxy-3- (2-methylpropyl)-pyrazine, methyl octine carbonate, tridecene-2-nitrile, 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 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, phenyl acetaldehyde dimethyl acetal, phenyl propyl alcohol, phenyl 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, methyl anthranilate, vanillin, amyl

salicylate, coumarin, ambrox, bacdanol, benzyl salicylate, butyl anthranilate, cetalox, ebanol, cis-3-hexenyl salicylate, lilial, 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 -one, oxocyclohexadecen-2-one / habanolide, florhydral, intreleven aldehyde eugenol, amyl cinnamic aldehyde, hexyl cinnamic aldehyde, hexyl salicylate, methyl dihydro jasmonate, sandalore, veloutone, undecavertol, exaltolide/cyclopentadecanolide, zingerone, methyl cedrylone, sandela, dimethyl benzyl carbinyl butyrate, dimethyl benzyl carbinyl isobutyrate, triethyl citrate, 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 from:- Bergamot, cedar atlas, cedar wood, clove, geranium, guaiac wood, jasmine, lavender, lemongrass, lily of the valley, lime, neroli, musk, orange blossom, patchouli, peach blossom, petitgrain or petotgrain, pimento, rose, rosemary, and thyme.

Another group of perfumes that may be used as active agents are the so-called ‘aromatherapy’ materials. These include many components also used in perfumery, including components of essential oils such as Clary Sage, Eucalyptus, Geranium, Lavender, Mace Extract, Neroli, Nutmeg, Spearmint, Sweet Violet Leaf and Valerian.

The active 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), 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 (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 (Foeniculum vulgare), Garlic Oil (Allium sativum), Geranium oil (also known as 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 (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.

The active agent is optionally used with 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 which active agents. The carrier oils are hydrophobic materials that are miscible with hydrophobic active agent materials suitable for use in the present invention. Suitable oils are those having reasonable affinity for the active 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.

Microcapsule modification

It can be useful to modify the polyester amide coating by covalently bonding to it a material to improve deposition of the microcapsules onto a desired substrate. The substrate may be fabric, skin or even hair and the deposition. Preferred deposition aids are polymers. Particularly preferred deposition aids are polysaccharides and most preferred are nonionic polysaccharide deposition polymers.

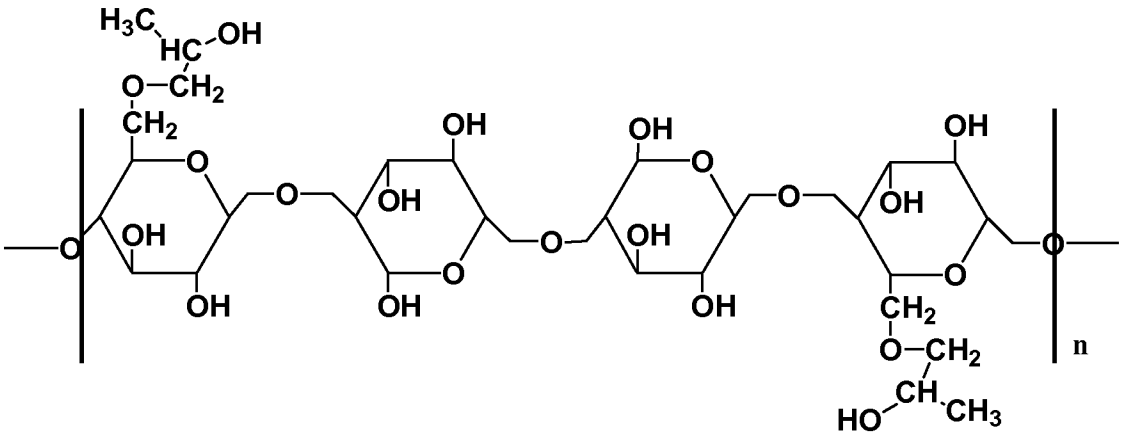
Preferred nonionic polysaccharide deposition polymers may be selected from the group consisting of: tamarind gum (preferably consisting of xyloglucan polymers), guar gum, locust bean gum (preferably consisting of galactomannan polymers), and other industrial gums and polymers, which include, but are not limited to, Tara, Fenugreek, Aloe, Chia, Flaxseed, Psyllium seed, quince seed, xanthan, gellan, welan, rhamsan, dextran, curdlan, pullulan, scleroglucan, schizophyllan, chitin, hydroxyalkyl cellulose, arabinan (preferably from sugar beets), de- branched arabinan (preferably from sugar beets), arabinoxylan (preferably from rye and wheat flour), galactan (preferably from lupin and potatoes), pectic galactan (preferably from potatoes), galactomannan (preferably from carob, and including both low and high viscosities), glucomannan, lichenan (preferably from icelandic moss), mannan (preferably from ivory nuts), pachyman, rhamnogalacturonan, acacia

gum, agar, alginates, carrageenan, chitosan, clavan, hyaluronic acid, heparin, inulin, cellodextrins, cellulose, cellulose derivatives and mixtures thereof.

Non-hydrolysable nonionic polysaccharides are most preferred. The polysaccharide preferably has a ß-1,4-linked backbone. However, dextran which does not have such a backbone is also preferred.

Preferably the polysaccharide is a cellulose, a cellulose derivative, or another ß-1,4-linked polysaccharide having an affinity for cellulose, preferably mannan, glucan, glucomannan, xyloglucan, galactomannan and mixtures thereof. More preferably, the polysaccharide is selected from the group consisting of xyloglucan and galactomannan. Most preferably, the deposition polymer is locust bean gum, xyloglucan, guar gum or mixtures thereof.

Alternatively the nonionic polysaccharide may be Hydroxypropyl Cellulose with a molecular weight in excess of 40 kDa. Hydroxypropyl Cellulose (HPC) has the repeat structure shown in generalised terms below:



Especially good results may be obtained when the HPC is one with a viscosity in 2 wt% aqueous solution of 1000 to 4000 mPa.s. Viscosity measurements are done using a Brookfield viscometer, Spindle #3, @30 rpm. Lower viscosity materials are measured using Spindle #2, @60 rpm. HPC is an ether of cellulose in which some of the hydroxyl groups in the repeating glucose units have been hydroxy-propylated forming $-OCH_2CH(OH)CH_3$ groups using propylene oxide. The average number of substituted hydroxyl groups per glucose unit is referred to as the degree of substitution (DS). Complete substitution would provide a DS of 3. However, as the hydroxy-propyl group itself contains a hydroxyl group, this can also be etherified during preparation of HPC. When

this occurs, the number of moles of hydroxy-propyl groups per glucose ring, moles of substitution (MS), can be higher than 3.
The majority (typically around 75% for a DS of 3) of the mass of HPC is found in the substituent groups rather than the backbone.

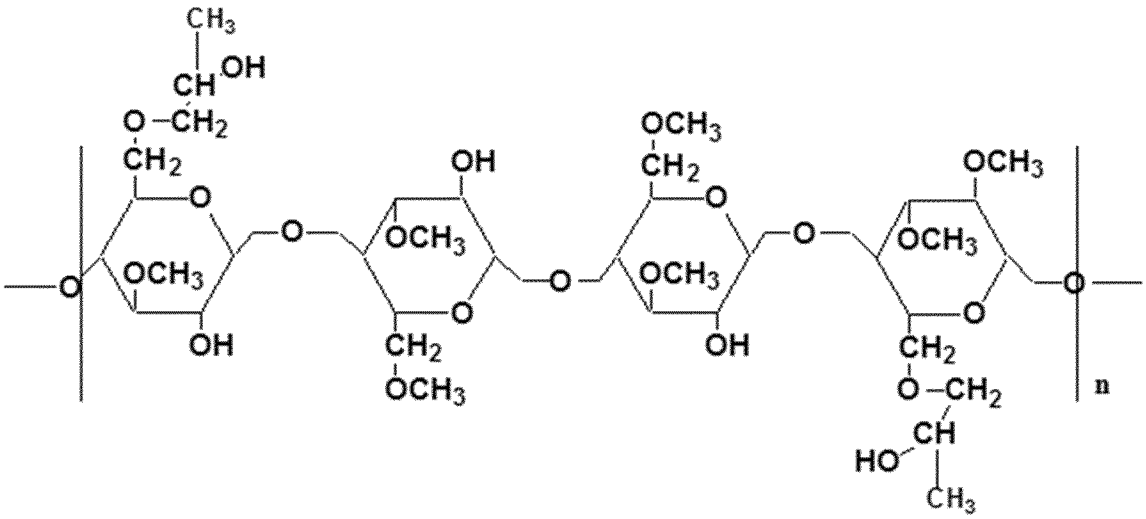
A particularly preferred HPC has Mw 910 kDa and MS 3.5.

Also, nonionic polysaccharides selected from the group consisting of: hydroxy-propyl methyl cellulose, hydroxy-ethyl methyl cellulose, hydroxy-propyl guar, hydroxy-ethyl ethyl cellulose and methyl cellulose may be used.

The ring spacing of these ß-1,4-linked polymers is such that each alternate ring of the polymer is well placed to allow a pseudo hydrogen-bond interaction with the pi-electron clouds of the phthalate rings in polyester. Moreover, these polymers have a balance of hydrophobicity and hydrophillicity which means that they are able to interact with a fabric without being so hydrophobic as to be insoluble. Other nonionic, modified polysaccharides, for example hydroxyl-ethyl cellulose, do not have the correct properties and show poor performance as deposition polymers, especially on polyester.
In those ethers of cellulosics in which some of the hydroxyl groups in the repeating glucose units have been hydroxy-alkylated the average number of substituted hydroxyl groups per glucose unit is referred to as the degree of substitution (DS). Complete substitution would provide a DS of 3. However, if the substituent group itself contains a hydroxyl group, this can also be etherified. When this occurs, the number of moles of substituent groups per glucose ring, moles of substitution (MS), can be higher than 3.

Some of the –OH groups (where present) in the hydroxyl-alkyl pendant group may be replaced with alkyl ethers. Typically these are C_1-C_{20} alkyl ethers, and may, in specific cases be C_{16}-C_{22} ethers. The most preferred alkyl chain is stearyl.

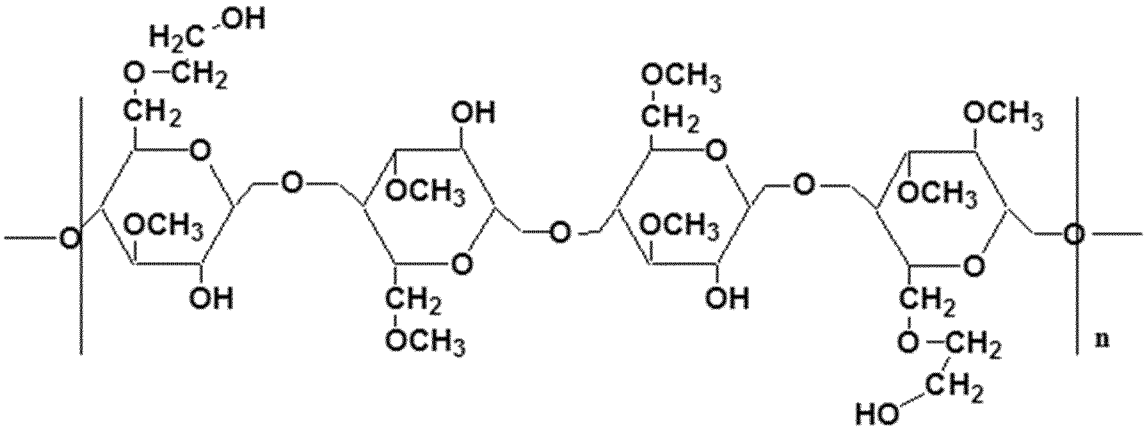
Hydroxy-propyl methyl cellulose (HPMC), has the repeat structure shown in generalised terms below:



Since the hydroxypropoxy substituents can be attached to each other on side chains, the degree of substitution for HPMC can be higher than 3.

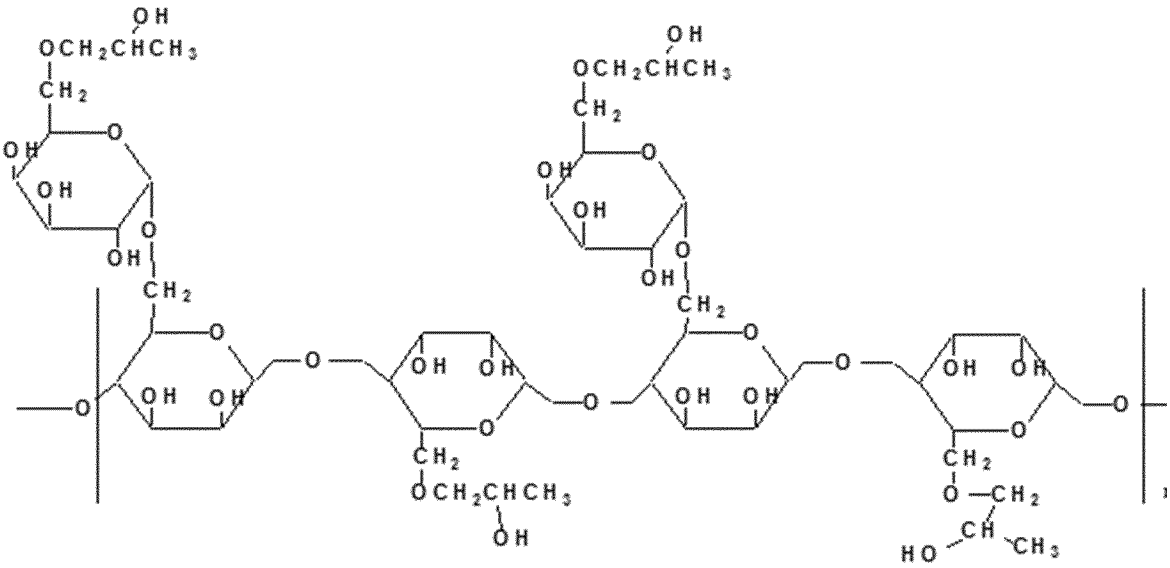
In useful derivatives of HPMC "Sangelose" some of the –OH groups in the hydroxyl-propyl pendant group are replaced with alkyl ethers. Typically these are C_1-C_{20} alkyl ethers, and may, in specific cases be C_{16}-C_{22} ethers. The most preferred alkyl chain is stearyl.

Hydroxy-ethyl methyl cellulose (HEMC), has the repeat structure shown in generalised terms below:



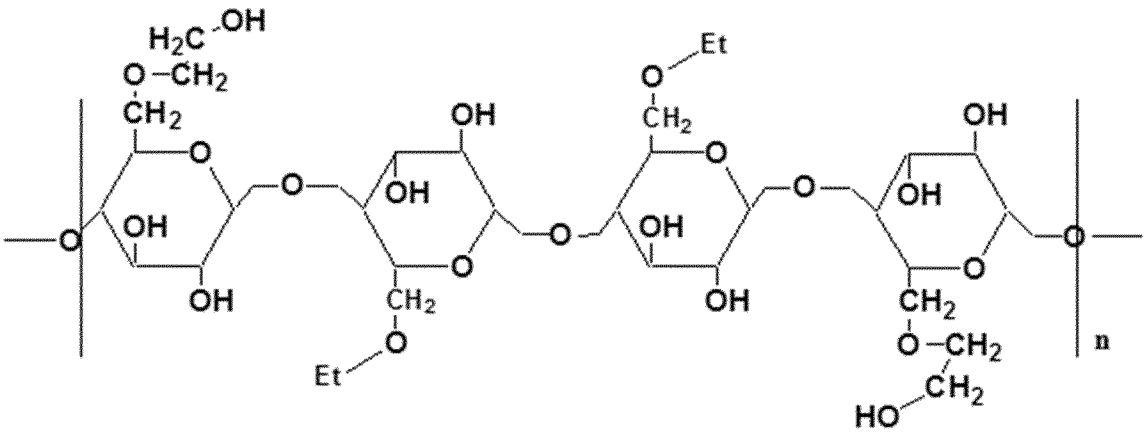
Since the ethoxy substituents can be attached to each other on side chains, the degree of substitution can be higher than 3.

Hydroxy-propyl guar (HPG), has the repeat structure shown in generalised terms below:



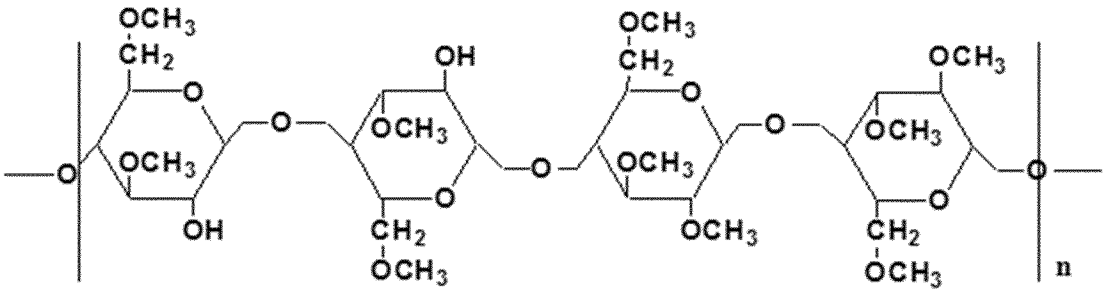
Since the hydroxypropoxy substituents can be attached to each other on side chains, the degree of substitution in HPG can be higher than 3.

Hydroxy-ethyl ethyl cellulose (HEEC), has the repeat structure shown in generalised terms below:



HEEC is less preferred than other nonionic polysaccharide delivery aids disclosed herein.

Methyl cellulose (ME), has the repeat structure shown in generalised terms below:



The theoretical maximum degree of substitution (DS) is 3.0. However, more typical values are 1.3 to 2.6.

Especially good results may be obtained when the deposition polymer is one which has a viscosity in 2 wt% aqueous solution of over 1000 mPa.s. Viscosity measurements are made using a Brookfield viscometer, Spindle #3, @30 rpm. Lower viscosity materials are measured using Spindle #2, @60 rpm.

Preferably the nonionic polysaccharide deposition polymer has a molecular weight above 50 kDa and more preferably above 140 kDa, most preferably above 500 kDa. As the molecular weight is increased the performance of the deposition polymer generally increases.

DS is typically in the range from 1.0 to 3, more preferably above 1.5 to 3, most preferably, where possible from 2.0 to 3.0.

A typical MS for the deposition polymer is 1.5 to 6.5. Preferably the MS is in the range from 2.8 to 4.0, more preferably above 3.0, most preferably from 3.2 to 3.8.

The deposition aid, when used, can be fixed either to the inner shell before the coating is applied or subsequently to the coating. The latter is preferred.

Compositions comprising the microcapsules

The microcapsules are designed to be used at low levels of from 0.1 to 10 wt% in a wide range of microcapsule containing compositions including both personal care and home care products. Suitable personal care compositions include deodorants, antiperspirants, hair treatment products, skin treatment product and skin treatment products. The formulation of those products is not affected by the presence of the microcapsule except that it may be beneficial to thicken them or

otherwise structure them to maintain an even dispersal of the microcapsules and it is desirable that they do not comprise active proteases that also attack the polyamide coating used.

Among the active ingredients that may be employed in such compositions there may be mentioned surfactants, polymers, moisturisers, humectants and emollients, antifungals, antiperspirant actives, deodorant actives, skin health actives, and mixtures thereof.

The compositions 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, sunscreens, emulsifiers, gelling agents, thickening agents, humectants (e.g. glycerine, sorbitol).

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, e.g. electrolytes, hygiene agents, e.g. anti-bacterials and antifungals, thickeners, skin active agents, colourants, whiteners, gel-control agents, freeze-thaw stabilisers, bactericides, preservatives (for example 1,2-benzisothiazolin-3-one), hydrotropes, perfumes and mixtures thereof.

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

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 phase commonly constitutes from 10 wt% and particularly from 30 wt% of the total composition, often up to 97 wt%. The balance of the composition comprises the oil phase, including any suspended material and the emulsifier or emulsifiers.

When added to a deodorant composition, the composition typically contains a deodorant active and preferably contains an antiperspirant active.

Herein, deodorant actives include antiperspirant actives and also deodorant actives that do not also give an antiperspirant benefit.

When employed, deodorant actives that are not also antiperspirant actives have a level of incorporation that is preferably from 0.01% to 3% and more preferably from 0.03% to 0.5% by weight of the composition. Preferred deodorant actives are those that are more efficacious than simple alcohols such as ethanol. Examples include quaternary ammonium compounds, like cetyltrimethylammonium salts; chlorhexidine and salts thereof; and diglycerol monocaprate, diglycerol monolaurate, glycerol monolaurate, and similar materials, as described in "Deodorant Ingredients", S.A.Makin and M.R.Lowry, in "Antiperspirants and Deodorants", Ed. K. Laden (1999, Marcel Dekker, New York). More preferred are polyhexamethylene biguanide salts (also known as polyaminopropyl biguanide salts), an example being Cosmocil CQ available from Arch Chemicals; 2',4,4'-trichloro,2-hydroxy-diphenyl ether (triclosan); and 3,7,11-trimethyldodeca-2,6,10-trienol (farnesol).

Antiperspirant actives are preferably incorporated in an amount of from 0.5 to 50 wt%, particularly from 5 to 30 wt% and especially from 10 to 26 wt% of the composition. It is often considered that the main benefit from incorporating of up to 5 wt% 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.

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.

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. A preferred amino acid is 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.

Compositions according to the invention may be emulsions. In such compositions, any antiperspirant active present is commonly dissolved in the aqueous phase, commonly at a weight concentration in that phase of between 10 and 55%. 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 30 mm, 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 compounds along with a minority (less than 50% w/w and often less than 20% w/w) of other compounds.

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 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-hydroxysteahc acid.

A gellant is often employed in a stick or soft solid composition at a concentration of from 1.5 to 30 wt%, 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.

Optional ingredients include wash-off agents, often present in an amount of up to 10 wt% 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 C_5 to C_{22} alkyl moiety and a hydrophilic moiety which can comprise a polyoxyalkylene group (POE or POP) and/or a polyol.

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 wt%; a moisturiser, such as glycerol or polyethylene glycol (mol wt 200 to 600), for example in an amount of up to about 5 wt%; skin active agents such as allantoin or lipids, for example in an amount of up to 5 wt%; colours; skin cooling agents other than the already mentioned alcohols, such a menthol and menthol derivatives, often in an amount of up to 2 wt%, all of these percentages being by weight of the composition. A further optional ingredient 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 wt%.

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

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 containing 4 to 6 EO units or a mixture of 2 to 4 with 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.

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 emulsifiers comprises steareth-2 and a selection from steareth-15 to steareth-30. The invention compositions desirably are substantially or totally free from water- soluble short chain monohydric alcohols (commonly recognised as up to C_6) and especially ethanol. Substantially in this context indicates a proportion of less than 5% and preferably less than 1 wt% of the respective full or base composition.

Suitable compositions may be aerosol compositions. Such compositions 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 wt% 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 of antiperspirant active in the base composition is often from 5 to 60 wt% and especially 10 to 45 wt%.

During the manufacture of compositions using the microcapsules of the invention, it is especially desirable for the microcapsules to be incorporated into the composition with mixing at a rate and power input that does not damage the microcapsules.

The invention will now be further described, by way of example only, and with reference to the following examples.

Comparative Example A - Protease enzyme degradability of Nylon particles

Building on the teaching in WO 2015/014628 the following commercial materials were sourced from Kobo and used as supplied:

(a) Nylon-6 Microsphere TR-1 (13 micron diameter porous particles)
(b) Nylon-6 Microsphere TR-2 (20 micron diameter porous particles);
(c) Nylon 12: Kobo Microsphere SP10 (10 micron diameter porous particles).

A buffer solution containing 50 mM MES, 2-(N-morpholino)ethanesulfonic acid, was prepared and adjusted to pH 6.0 by dropwise addition of 0.1 M hydrochloric acid.
Slurries of the materials at 5 or 50 mg nylon polymer in 1 ml total volume solution were prepared in each of the following solutions:
i). 0.01 mg/ml Alcalase L serine protease in pH 6 MES buffer;
ii). 0.1 mg/ml Alcalase L serine protease in pH 6 MES buffer;
iii). 1.0 mg/ml Alcalase L serine protease in pH 6 MES buffer;
iv). pH 6.0 MES buffer (as an enzyme-free control).

In a first experiment, the samples were incubated at 37°C with shaking at 200 rpm for 15 hours before being allowed to cool followed by visual assessment and sampling of the supernatant liquor for analysis by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FTIR) for detection of breakdown products.

Following the incubation, all the samples looked identical to sample (iv), which contained no enzyme.

TLC conditions were based on those reported for analysis of nylon hydrolysis products in the open literature (E G Tsatsaroni and A H Kehayoglou, Die Angewandte Makromolekulare Chemie, 1987, Volume 147, pp. 35-40).

TLC analysis of the experimental samples showed no evidence for the formation of nylon degradation products resulting from protease driven hydrolysis.

In a second experiment, mixtures (ii) and (iv) were replicated using fresh materials and substituting water for the buffer. The samples were treated in an identical manner to those in the first experiment, except that the duration of the incubation was extended and additional aliquots of protease enzyme were added at specific time points in order to mimic the continual release of enzyme in the axilla and avoid the issues of enzyme auto-degradation. Following the initial 16 hour incubation, an additional 0.1 ml volume dosage of concentrated enzyme in water was added to sample (ii) in order to increase the enzyme concentration to 0.2 mg/ml and the sample was incubated with shaking for a further 8 hours. An additional third dose of enzyme (0.1 ml) was then

added to sample (ii) increasing the total enzyme concentration to 0.3 mg/ml and the sample was incubated for a further 16 hours. Sample (iv) was treated in a similar manner but adding aliquots of water in place of the enzyme. The total incubation time for these samples was therefore 40 hours.

The samples were allowed to cool and subject to visual assessment, sampling of the supernatant liquor for analysis by TLC, FTIR and the solid residues retained for assessment by optical microscopy.

As in the first experiment, the visual assessments and TLC failed to show any evidence for nylon digestion. No obvious bands were detected by FTIR. Finally, optical microscopy of the solids showed no obvious modification of the surfaces of the particles relative to that of the untreated samples.
It was concluded that these nylon polyamide materials showed no protease degradation and were unsuitable for protease triggered controlled release from microcapsules.

Example 1 - Design and synthesis of poly(amide) material library

A poly(amide) material library was prepared by condensation polymerisation using mixtures of three components: an aliphatic or aromatic di-acid, hydrogenated fatty acid dimer ("dimer acid"), and one or more polyetheramine diamine, triamine or mixtures thereof. For each small molecule diacid (Ac1 to Ac8), up to 4 variants were made with different polyetheramine compositions (PEAm1 to PEAm3). All materials contained the same level of "dimer acid" (DAc1). Table 1 lists the monomers used.

Table 1 - Monomers used in poly(amide) resin library synthesis

a). Di-acids

Synthesis code	Chemical name	Description	CAS
Ac1	Adipic (hexanedioic) acid	C6 aliphatic diacid	124-04-9
Ac2	Methyl malonic (2-Methylpropanedioic) acid	Branched C3 aliphatic diacid	516-05-2
Ac3	Succinic (butanedioic) acid	C4 aliphatic diacid	110-15-6
Ac4	Benzyl malonic [**2-(phenylmethyl)-** propanedioic)] acid	Branched aromatic substituted C3 aliphatic diacid	616-75-1
Ac5	Phenyl succinic (2-phenylbutanedioic) acid	Branched aromatic substituted C4 aliphatic diacid	635-5-8
Ac6	Mucic (tetrahydroxyhexanedioic) acid	Hydroxyl substituted C6 aliphatic diacid	526-99-8
Ac7	Terephthalic (benzene-1,4-dicarboxylic) acid	Phenyl bridged diacid	100-21-0
Ac8	Diglycolic (oxodiacetic) acid	Ether bridged diacid	110-99-6
DAc1	Dimer acid (Hydrogenated)[1]	Principally methylene bridged C36 aliphatic dimer [C18-unsaturated fatty acid dimers (dilinoleic acid), hydrogenated]*	68783-41-5

[1] Fine chemical grade material ex. Sigma Aldrich, average molecular weight Mn ca. 570. Commercial analogues are available under the trade names EMPOL (BASF), JARIC (Jarchem), and PRIPOL (Croda).

(b). Poly(etheramine)

Synthesis code	Description	Average molecular weight, Mr	CAS
PEAm1	Poly(propylene glycol) bis(2-aminopropyl ether)	400	9046-10-0
PEAm2		230	
PEAm3	Trimethylolpropane tris[poly(propylene glycol), amine terminated] ether	440	39423-51-3

The syntheses were carried out using the following generic methodology:

The dimer acid, small molecule di-acid, polyetheramine and water were added to a vial and heated to 180°C for 30 minutes until all the water had evaporated. A nitrogen blanket was applied to the reaction and the temperature increased to the range 230 to 240 °C for 3 hours. The polymer was decanted whilst hot into a suitable storage vessel. The products were transparent, pale yellow viscous liquids or gums.

Table 2 lists the reaction mixture used to synthesise a representative polyamide, comprising a mixture of adipic acid, "dimer acid" and polyetheramine PEAm1 (henceforth coded as JAD400, see Table 4).

Table 2 - Reaction mixture for synthesis of a representative poly(amide), JAD400

	Mol. Wt.	Wt (g)	Moles	Total mass (g) for 5 g of Polymer Solids
Adipic Acid	146	0.584	0.004	1.211
"Dimer Acid"	ca.570	0.228	0.0004	0.473
PEAm1	400	1.600	0.004	3.317
Water	N/A	1.090	N/A	2.260
Total		3.502		7.260

The poly(amides) were prepared at a fixed mole ratio of approximately 1:10:10 "Dimer acid":di-acid:polyetheramine and the compositions of the full library of materials are summarised in Table 3.

Table 3 - Molar compositions of poly(amide) library materials

Variant	Polyamide composition (mol %)				
	"Dimer acid"	"Diacid"	Polyetheramine		
	DAc1	Ax[2]	PEAm1	PEAm2	PEAm3
Acx-1	4.8	47.6	47.6	0	0
Acx-2	4.8	47.6	0	47.6	0
Acx-3	4.8	47.6	23.8	23.8	0
Acx-4	4.8	47.6	41.6	0	6.0

[2] Where Ax = 1 to 8, denotes the small molecule diacid used, e.g. A1 = Adipic acid

A total of 31 poly(amides) were prepared comprising the full array of combinations of diacids and polyamines other than the combination of PEAm1/ PEAm2 with "Dimer acid" and benzyl malonic acid. For ease of reference, the materials were coded as shown in Table 4.

Table 4 - Code names for poly(amide) materials

	Polyetheramine			
Di-acid	PEAm1	PEAm2	PEAm1/ PEAm2	PEAm1/ PEAm3
Ac1	JAD-400	JAD-230	JAD-400/230	JAD-400T
Ac2	JMMD-400	JMMD-230	JMMD-400/230	JMMD-400T
Ac3	JSD-400	JSD-230	JSD-400/230	JSD-400T
Ac4	JBD-400	JBD-230	Not prepared	JBD-400T
Ac5	JPD-400	JPD-230	JPD-400/230	JPD-400T
Ac6	JMD-400	JMD-230	JMD-400/230	JMD-400T
Ac7	JTD-400	JTD-230	JTD-400/230	JTD-400T
Ac8	JDD-400	JDD-230	JDD-400/230	JDD-400T

Example 2 - In vitro biodegradability of poly(amide) materials by a protease enzyme

Alcalase 2.4 L™ subtilisin from *Bacillus Licheniformis* (Sigma Aldrich cat. no. P4860; Novozymes) was considered a relevant model for proteases of both bacterial and human origin to carry out testing of poly(amide) materials for susceptibility to enzyme hydrolysis. Incubations were carried out

in freshly prepared pH 6 MES [2-(N-morpholino)ethane-sulfonic acid] buffer at 37 °C using the following protocol:

A fresh buffer solution was prepared by dissolving MES powder in high purity water at 50 mM concentration, and then adjusting the pH to 6 by dropwise addition of 2.0 M sodium hydroxide or 2.0 M hydrochloric acid, using a calibrated pH meter. A stock solution containing 1.0 µg/ml Alcalase™ specific enzyme protein was prepared by serial dilution in ice-cold pH 6 MES buffer. A 20-fold dilution of this sample with a specific enzyme content of 50 ng/ml Alcalase™ was then prepared by further dilution in order to mimic the protease enzyme activity detected in ex vivo human sweat.

0.02 g of each poly(amide) resin was transferred to a polypropylene Eppendorf tube and treated with 1 ml of pH 6 MES buffer or buffered 50 ng/ml Alcalase™ protease or buffered 1.0 µg/ml Alcalase™ protease. These mixtures, containing 2% w/w poly(amide), were incubated for 24 hours at 37°C and 100 rpm agitation.

The samples were allowed to stand and cool to ambient temperature for 30 minutes before being visually assessed to identify differences between protease enzyme treated samples and buffer treated control samples. In a separate experiment, the solubilities of the various poly(amide) resins in the buffer solution were also assessed after just 30 minutes incubation at 37°C and 100 rpm agitation. The results of these combined observations are summarised in Table 5 (a).

Table 5 (a) - Visual assessment of the physical aspect of mixtures of 2.0 µg/ml poly(amide) resins in buffer or buffered protease enzyme solutions, following incubation.

Poly(amide) Resin Code	**Raw material description**	**Solubility in buffer after 30 minutes incubation at 37 °C**	**Visual observations after 24 hours incubation at 37 °C, cooling and standing for 30 minutes**		
			Buffer	Buffered protease (50 ng/ml Alcalase™)	Buffered protease (1 µg/ml Alcalase™)
JAD-400	yellow oil	2	2	9	6
JAD-230	yellow oil	2	2	2	2
JAD-400/230	yellow oil	2	1	1	1

JAD-400T	yellow oil	2	1	1	1
JMMD-400	yellow oil	2	2	2	2
JMMD-230	yellow oil	2	2	2	7
JMMD-400/230	yellow oil	2	4	4	5
JMMD-400T	yellow oil	2	2	2	2
JSD-400	yellow oil	1	1	1	1
JSD-230	yellow oil	2	2	2	2
JSD-400/230	yellow oil	2	2	2	2
JSD-400T	yellow oil	2	2	2	2
JBD-400	yellow oil	2	7	7	7
JBD-230	yellow oil	2	8	8	8
JBD-400T	yellow oil	2	7	7	7
JPD-400	off-white oil	2	2	2	2
JPD-230	yellow oil	2	2	2	2
JPD-400/230	yellow oil	2	2	2	2
JPD-400T	yellow oil	2	2	2	2
JMD-400	brown oil	2	2	2	2
JMD-230	brown oil	2	2	2	2
JMD-400/230	brown oil	2	2	2	2
JMD-400T	black rubbery solid	3	3	3	3
JTD-400	off-white highly viscous oil	2	2	2	2
JTD-230	pale pink highly viscous oil	2	2	2	2
JTD-400/230	pale yellow viscous oil	2	2	2	2
JTD-400T	off-white highly viscous oil	2	2	2	2

JDD-400	off-white viscous oil	2	9	9	9
JDD-230	yellow glassy solid	3	3	3	3
JDD-400/230	yellow viscous oil	2	2	2	2
JDD-400T	yellow viscous oil	2	2	2	2

Key

1= clear liquid

2= clear liquid with residual oil

3= clear liquid with residual solids

4= slightly turbid liquid

5= moderately turbid liquid

6=highly turbid liquid

7= slightly turbid liquid with residual oil

8= slightly turbid liquid with residual solids

9= moderately turbid liquid with residual oil

A useful biotriggered release coating resin for use with aqueous capsule slurries should combine the properties of low aqueous solubility with susceptibility to modification by enzymes. Examination of the samples treated with buffer alone showed that most of poly(amide) resins were substantially insoluble in the aqueous buffer and remained primarily as oils or solids.

Comparisons between the enzyme treated and non-enzyme treated control samples showed that three of the poly(amide) resins, coded JAD-400, JMMD-230 and JMMD-400/230, became more turbid following treatment with protease enzyme. In order to rule out the possibility that these materials were more readily emulsified as a result of interaction with protein in the enzyme solution, rather than modification of the poly(amide) by the protease enzyme, replicate studies were carried out substituting a non-enzyme containing solution of bovine serum albumin (BSA) protein for the enzyme.

The BSA solution was prepared in the same buffer at concentrations equivalent to the total protein content (as determined using the Pierce BCA colorimetric assay), 2.5 µg/ml BSA in the case of the 1.0 µg/ml specific enzyme Alcalase™ solution and 0.125 µg/ml BSA in the case of the 50 ng/ml

specific enzyme Alcalase™ solution. Fresh samples of the poly(amide) were incubated with this non-enzyme containing BSA solution at concentrations of 2.0 µg/ml under exactly the same conditions as for the studies with the protease enzyme. Visual observations of samples from these studies are listed in Table 5 (b).

Table 5 (b) - Visual assessment of the physical aspect of mixtures of 2.0 µg/ml poly(amide) resins in buffer or buffered protein solutions, following incubation.

Poly(amide) Resin Code	**Raw material description**	**Solubility in Buffer after 30 minutes incubation at 37 °C**	**Visual observations after 24 hours incubation at 37 °C**		
			Buffer	Buffered protein (0.125 µg/ml BSA	Buffered protein (2.5 µg/ml BSA)
JAD-400	yellow oil	slightly soluble (residual oil present)	2	2	2
JMMD-230	yellow oil	slightly soluble (residual oil present)	2	2	9
JMMD-400/230	yellow oil	slightly soluble (residual oil present)	2	2	2

These results show that the turbidity observed following enzyme treatment of the JMMD-230 sample could be due to an interaction with protein rather than resulting from the specific action of the enzyme. However, the JAD-400 and JMMD-400/230 samples showed no evidence of turbidity when treated with the non-enzymatic protein solution demonstrating that the change in the dispersion properties was due to the protease activity of the Alcalase™ enzyme.

Assessment of the JAD-400 enzyme treated sample by optical microscopy indicated that the increased turbidity reflected the presence of small droplets of oil, which were not observed in the enzyme-free buffered samples. Thus, the JAD-400 poly(amide) resins sample showed evidence of

increased turbidity and ease of dispersion in aqueous solution because of contact with the protease enzyme.

The JAD-400 and JMMD-400/230 materials were next treated with *ex vivo* human sweat using an identical protocol to that outlined above. Two additional materials that had not shown obvious signs of sensitivity to the Alcalase™ enzyme, JPD-230 and JPD-400/230 were tested in the same manner. *Ex vivo* sweat was collected from female panellists, pooled and filter sterilized to remove bacterial and human cells. Analysis using a BODIPY-FL casein fluorescence assay showed the sample to have a protease activity of 46.0 +/- 2.8 ng/ml equivalent Alcalase™. The results of these studies are shown in Table 5(c).

Table 5 (c) – Visual assessment of the physical aspect of mixtures of 2.0 µg/ml poly(amide) resins in buffer or ex vivo human sweat, following incubation.

Poly(amide) Resin Code	**Raw material description**	**Solubility in Buffer after 30 minutes incubation at 37 °C**	**Visual observations after 24 hours incubation at 37 °C**	
			Buffer	**Sweat**
JAD-400	yellow oil	2	2	6
JMMD-400/230	yellow oil	2	4	5
JPD-230	off-white oil	2	2	2
JPD-400/230	yellow oil	2	2	2

Both the JAD-400 and JMMD-400/230 materials showed similar behaviours when treated with *ex vivo* sweat to those observed when these materials were treated with the model protease, while the JPD-230 and JPD-400/230 materials were likewise unaffected.

As the JMMD-400/230 sample was more soluble in aqueous solution and did not show such a pronounced modification in properties when treated with the protease enzyme or sweat, it was

deemed a less suitable coating material than JAD-400. The JAD-400 material was therefore tested in capsule coating studies.

Example 3 - Coating of poly(urea) fragrance capsules with an outer layer of insoluble poly(amide)

Micron sized poly(urea) core-shell fragrance capsules may be prepared by an interfacial emulsion polycondensation process based on the one described in US 2012/0148644. For this example leaky polyurea capsules were sourced from IFF as a 40% solids slurry comprising 29% of encapsulated fragrance enclosed in a shell prepared by polymerization of poly (p-methylenediphenyldiisocyanate) and hexamethylene diamine.

Coated polyurea encaps were prepared by physically absorbing a layer of the poly(amide) coded as JAD-400 (from examples 1 and 2) onto the surface of the poly(urea) particle and then optionally crosslinking the poly(amide). Three different crosslinkers were examined: a small molecule aliphatic anhydride, a small molecule aliphatic isocyanate and an oligomeric aromatic isocyanate. The materials used are listed in Table 6.

Table 6 - Components used in preparation of poly(amide) coated poly(urea) capsules

Synthesis code	Chemical name	Description	CAS
DTPA	diethylenetriaminepentaacetic acid dianhydride	Aliphatic dianhydride	23911-26-4
MCHI	4,4′-methylenebis(cyclohexyl isocyanate)	Aliphatic diisocyanate	5124-30-1
PMPII	polymethylene-polyphenylisocyanate	Aromatic/isocyanate-functional copolymer	9016-87-9
JAD400[1]	n/a	Dimer acid/adipic acid/polyetheramine PEAm[1] condensation copolymer	N/A
PU Tornado AA[2]	n/a	Polyurea encap with commercial fragrance payload ('Tornado') ex. IFF	N/A

[1] Polyamide Mn = 5884

[2] Solids = 40 wt%, fragrance content = 29 wt%

For each crosslinker, three inclusion levels, equating to 1%, 10% and 30% cross-linker based on the weight of capsule solids were prepared by the following methodology:
Polyamide (2.44 g) was dissolved in ethanol (19 g). Separately, PU Tornado AA slurry (21 g) was diluted with water (21 g) and transferred to a stoppered round bottom flask, equipped with a magnetic stirrer. The ethanolic polyamide solution was added to the PU Tornado slurry, dropwise over 10 minutes. Stirring was continued at ambient temperature for a further 50 minutes. Nine 6 g aliquots of this JAD-400 coated PU tornado AA coated capsule slurry were transferred to vials. Each vial was dosed with one of the three crosslinkers, at one of three different levels: 8, 80 or 240 mg (equivalent to 1, 10 or 30 wt% of the core particles). Following addition of the crosslinker, the vials were sealed, shaken and then left on a roller-mixer for 45 minutes. The vials were then transferred to a water bath and heated 50 °C for 30 minutes. The samples were given code names as in Table 7:

Table 7 - Code names for cross-linked poly(amide) coated poly(urea) capsules

Crosslinker	Crosslinker Inclusion Level		
	1 wt%	10 wt%	30 wt%
diethylenetriaminepentaacetic acid dianhydride	DTPA1	DTPA2	DTPA3
4,4′-methylenebis(cyclohexyl isocyanate)	MCHI1	MCHI2	MCHI3
polymethylene-polyphenylisocyanate	PMPPI1	PMPPI2	PMPPI3

Example 4 - Triggered release of encapsulated fragrance in response to protease enzyme or human sweat

The leakage of encapsulated fragrance was assessed by headspace GCMS from , JAD-400 poly(amide) coated polyurea (PU) Tornado AA capsules and MCHI2 cross-linked coated poly(urea) Tornado AA capsules in the presence of buffer, Alcalase 2.4L™ liquid subtilisin protease or ex vivo sweat.

Buffer and buffered Alcalase™ solutions were prepared as described in Example 2. Ex vivo sweat was collected from female panellists, pooled and filter sterilized to remove bacterial and human cells. Analysis using a BODIPY-FL casein fluorescence assay showed the sample to have a protease activity of 52.0 +/- 1.3 ng/ml equivalent Alcalase™. Perfume standard solutions containing 0 to 0.6% Tornado AA fragrance were prepared by solubilizing the fragrance oil in 2.0% Synperonic A20.

Experimental samples were prepared as follows: JAD-400 poly(amide)coated and MCHI2 cross-linked JAD-400 poly(amide) coated PU Tornado AA capsule slurries containing 10% fragrance were diluted to 0.5% fragrance content in either pH 6 MES buffer, buffered Alcalase™ model protease enzyme or ex vivo sweat as shown in Table 8. The mixtures were sealed in vials and placed in an incubator shaker for 24 hours at 200 rpm agitation and 37 °C.

Table 8 - Compositions of fragrance capsule mixtures with buffer, buffered protease and sweat.

#	Composition
4A	0.5% MCHI2 cross-linked JAD 400 coated PU Tornado AA fragrance capsule in 95% pH 6 MES buffer
4B	0.5% MCHI2 cross-linked JAD 400 coated PU Tornado AA fragrance capsule in 1.0 µg/mL Alcalase™ model protease/95% pH 6 MES buffer
4C	0.5% MCHI2 cross-linked JAD 400 coated PU Tornado AA fragrance capsule in 95% ex vivo sweat
4D	0.5% JAD 400 coated PU Tornado AA fragrance capsule in 95% pH 6 MES buffer
4E	0.5% JAD 400 coated PU Tornado AA fragrance capsule in 1.0 µg/mL Alcalase™ model protease/95% pH 6 MES buffer
4F	0.5% JAD 400 coated PU Tornado AA fragrance capsule in in 95% ex vivo sweat

Following incubation the samples were allowed to cool to ambient temperature for 10 minutes before removing 25 µl sample aliquots and pipetting onto 5.5 cm x 5.0 cm pieces of Whatman 541 hardened Ashless filter paper placed around the inner wall of a GC headspace vials. The pipette tips were rinsed with an additional 25 µl water, which was also dispensed onto the filter paper.

The samples were allowed to equilibrate for at least 2 hours before solid phase microextraction (SPME) sampling of the headspace air in the vials, desorption and analysis via GC-MS, measuring selected major components from the perfume. Three replicate samples were analysed for each combination of capsule system and treatment. The results of these studies, expressed as GC peak areas for individual fragrance components, are listed in Table 9.

Table 9 - Relative fragrance leakage from poly(amide) coated and cross-linked poly(amide) coated poly(urea) fragrance capsules (mean peak area +/- 95% confidence limit)

			Fragrance component					
			Limonene		Eucalyptol		Camphor	
#	Encap	Treatment	Mean	95% CI	Mean	95% CI	Mean	95% CI
4A	MCHI2	Buffer	7.36E+05	1.35E+05	3.27E+05	5.36E+04	6.66E+05	8.71E+04
4B	MCHI2	Alcalase™	1.30E+06	2.06E+05	4.02E+05	5.71E+04	8.84E+05	5.63E+04
4C	MCHI2	Sweat	1.09E+06	1.07E+05	2.71E+05	1.14E+04	5.28E+05	3.68E+04
4D	JAD-400	Buffer	1.82E+06	6.28E+04	4.36E+05	5.50E+03	8.28E+05	3.51E+04
4E	JAD-400	Alcalase™	2.38E+06	3.84E+04	5.22E+05	2.27E+04	9.47E+05	7.22E+04
4F	JAD-400	Sweat	1.93E+06	3.08E+05	3.82E+05	4.14E+04	6.66E+05	6.29E+04

			Fragrance component					
			3,7-dimethyl-1-octene		Linalyl acetate		Ortho-butyl cyclohexyl acetate	
#	Encap	Treatment	Mean	95% CI	Mean	95% CI	Mean	95% CI
4A	MCHI2	Buffer	2.31E+05	3.16E+04	4.74E+04	9.86E+03	5.94E+05	8.74E+04
4B	MCHI2	Alcalase™	4.62E+05	8.03E+03	1.42E+05	6.38E+03	1.06E+06	5.51E+04
4C	MCHI2	Sweat	2.35E+05	2.83E+04	4.86E+04	8.10E+03	5.49E+05	6.21E+04
4D	JAD-400	Buffer	3.23E+05	3.20E+04	8.22E+04	1.20E+04	9.36E+05	8.97E+04
4E	JAD-400	Alcalase™	3.70E+05	4.54E+04	9.82E+04	1.83E+04	1.08E+06	1.35E+05
4F	JAD-400	Sweat	2.49E+05	3.32E+04	6.51E+04	9.36E+03	7.04E+05	8.82E+04

Comparing the results between samples 4A and 4B, it is clear that leakage of almost all fragrance components from the MCHI cross-linked JAD-400 coated capsules is increased by incubation in the protease solution (4B) relative to the buffer treated control samples (4A). Similarly, comparing the results between samples 4(D) and (4E), it is clear that leakage of many fragrance components from the JAD-400 coated capsules is increased by incubation in the protease solution (4E) relative to the buffer treated control samples (4D). The exposure to alkalase and sweat shows that the coating is degraded and the perfume release is increased compared to the buffer control. The increase is larger for the crosslinked coating.

Further, comparing the results between samples 4A and 4C, a statistically significant increase in the leakage of limonene is observed following incubation of the MCHI cross-linked JAD-400 coated capsules in sweat relative to the buffer treated control.

Example 5 - In vivo testing of the inventive capsules for deodorancy

Oil-in-water anti-perspirant roll-on compositions containing poly(etheramide) coated leaky poly(urea) capsules suiteable for use in the method of the invention (Example 5A – see Table 10) or a capsule free control composition (Comparative Example 5B) were prepared in the same manner. The quantity of water was adjusted in each case to allow for addition or otherwise of the capsule slurry.

The aqueous phase of the roll-on deodorant compositions was prepared by weighing the water, aluminium chlorohydrate and Steareth-20 into a large beaker and mixing with a Heidolph overhead stirrer set at 150 rpm while heating to 50°C. The oil phase was prepared by weighing the sunflower seed oil and Steareth-2 into a glass jar and heating in an oven to 70°C. This mixture was allowed to cool to approximately 55°C before pouring the oil phase into the aqueous phase. The contents of the beaker were then allowed to cool to approximately 40°C with continuous mixing using the overhead stirrer and a free fragrance oil used in a commercial antiperspirant roll on composition was added, before stirring for a further 2 minutes. The contents of the beaker were then mixed for a further 2 minutes using a high shear Silverson homogenizer (using a medium sized head at 6,500 rpm).

The inventive MCHI2 coated fragrance capsule slurry for 5A was prepared as described in Example 3. The slurry contained 17.5% of the coated capsule solids (of which 9.7% was a fragrance designed to match the free oil perfume), 29.9% ethanol and 52.6% water. This slurry was dosed at 2.3% on the total roll-on formulation weight.

Polyetheramide coated fragrance capsules for use according to the invention (5A) were incorporated at a level equating to 0.22% encapsulated fragrance oil by adding the capsule slurry to the base while mixing using the Heidolph overhead stirrer at ca. 300 rpm. The mixture was mixed for a further 20 minutes under the same conditions to ensure that the capsules were uniformly distributed throughout the composition.

Approximately 20 g quantities of these formulations were transferred into standard deodorant roll-on applicator packaging.

Table 10 - Compositions of antiperspirant roll-on compositions

	% inclusion (w/w)	
Ingredient	5A	5B*
Sunflower oil	2.00	2.00
Steareth-2	2.60	2.60
Steareth-20	0.60	0.60
Aluminium chlorohydrate	15.00	15.00
Free Fragrance oil	1.00	1.00
MCHI2 coated capsule	2.30	0.00
Encapsulated fragrance content	*0.22*	*0.00*
Ethanol	*0.69*	*0.00*
Water	to 100	to 100

* Comparative example

The deodorancy performances of compositions (5A) and (5B) were tested in a head to head test design, with different products used in the left and right axilla of each panellist, according to the following protocol.

Deodorancy protocol

The panel employed comprised 44 individuals who had been instructed to use control ethanolic deodorant products during the two weeks prior to the test. At the start of the test, panellists were washed with unfragranced soap and different products (0.30g +/- 30 mg dose) applied to each axilla. Product application was randomised to take into account any left/right bias. Panellists were instructed not to consume spicy food or alcohol, and not to wash under their own axillae, during the duration of the test. At least five expert assessors determined the intensity of axillary odour at set times (selected from 3.5 hours and 7 hours) after application, scoring the intensity on a scale of 0-5, where 0 is no malodour. A minimum of 41 panellists were assessed at each time point and the entire assessment was repeated a total of four times. The malodour scores were subject to statistical analysis (mixed model analysis of variance). Table 11 shows the results of the comparison between compositions 5A and 5B.

Table 11 - Mean malodour scores arising from treatment of axillary skin treated with inventive coated poly(urea) fragrance capsule containing composition (5A) and a capsule free composition (5B).

Product Code	Mean malodour Score	Mean difference	Statistical Significant Difference	Significance	p-value
3.5 hours after application					
5A	1.27	0.14	0.08	99.9%	<0.0001
5B	1.41				
7 hours after application					
5A	1.67	0.14	0.10	99.9%	<0.0001
5B	1.81				

A comparison of the data shown in Table 11 shows that the microcapsule used in accordance with the method of the invention containing formulation (5A) scored statistically significantly lower on malodour intensity than the capsule free control composition (5B) at 3.5 and 7 hours after application.

CLAIMS

1. A method of delivering an active agent to skin, preferably axilla, comprising the steps of:

a) applying to skin a composition comprising at least 0.1 wt% of core shell microcapsules whereby the microcapsules come into contact with the skin each microcapsule having an inner shell formed of a first synthetic polymer and containing the active agent and the inner shell capable of allowing at least a portion of the active agent to pass from inside the inner shell to outside the inner shell to enable it to come into contact with the skin, the inner shell being coated with a coating of insoluble polyamide with a solubility in water of less than 1g/L at 25°C, the polyamide formed by the reaction of:

(ii) at least one low molecular weight dicarboxylic acid having from 3 to 12 carbon atoms, or ester thereof;

(ii) at least one poly(alkylene glycol) polyamine having the formula (I)

H_2N-(-C(R)H-CH_2-O-)x-C(R)H-CH_2-NH_2 (I)

where x ranges from about 2 to 5, R is an alkyl of one to four carbon atoms;

(iii) optionally, at least one high molecular weight dicarboxylic acid (dimer) having from 20 to 40 carbon atoms, or ester thereof;

and wherein the coating further comprises a crosslinker to improve hardness and further reduce solubility , such that, while the coating is present the release of the active agent onto the skin is retarded;

b) sweating to produce sweat that comes into contact with at least part of the polyamide coating;

c) degrading the polyamide coating by the action of protease enzymes present in the sweat thereby to cause delayed release of the active agent onto the skin after the microcapsule first comes into contact with sweat.

2. A method according to claim 1 wherein R is C1 alkyl.

3. A method according to any preceding claim wherein the crosslinker is a difunctional crosslinker.

4. A method according to any preceding claim wherein the crosslinker is immiscible with water.

5. A method according to any preceding claim wherein the crosslinker is a diisocyanate.

6. A method according to any preceding claim in which the crosslinker comprises from 1 to 30 wt% of the polyamide coating.

7. A method according to any preceding claim wherein the active agent is perfume.

8. A method according to any preceding claim wherein the dicarboxylic acid (i) is an aliphatic acid.

9. A method according to any preceding claim wherein the dicarboxylic acid (i) has a chain of from 3 to 6 carbon atoms.

10. A method according to claim 9 wherein the dicarboxylic acid (i) is adipic acid.

11. A method according to any preceding claim wherein the dicarboxylic acid of dimer (iii) is present and has 36 carbon atoms.

12. A method according to any preceding claim wherein the inner leaky shell is formed from polyurea.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/081812

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K8/26 A61K8/11 A61Q15/00 A61K8/84 A61K8/88
A61K9/48 C11D3/50
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)
A61K A61Q C11D

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, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/017287 A1 (LEI YABIN [US] ET AL) 16 January 2014 (2014-01-16) paragraphs [0006], [0008], [0117], [0050] - [0076], [0090]; examples	1-12
X	WO 2013/182855 A2 (IMERYS MINERALS LTD [GB]) 12 December 2013 (2013-12-12) page 3, lines 25-36 page 12, lines 4-6,9 page 13, lines 19-23 page 17, lines 1-5 page 15, lines 1-16	1-12
A	US 5 271 934 A (GOLDBERG MARVIN E [US] ET AL) 21 December 1993 (1993-12-21) cited in the application the whole document	1-12

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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

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2017	27/03/2017

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, Fax: (+31-70) 340-3016	Mitchell, Gemma

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INTERNATIONAL SEARCH REPORT

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PCT/EP2016/081812

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 451 953 A2 (TEXACO CHEMICAL [US]) 16 October 1991 (1991-10-16) cited in the application the whole document	1-12
A	US 5 324 812 A (SPERANZA GEORGE P [US] ET AL) 28 June 1994 (1994-06-28) cited in the application the whole document	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/081812

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014017287 A1	16-01-2014	NONE	
WO 2013182855 A2	12-12-2013	EP 2858745 A2	15-04-2015
		US 2015190774 A1	09-07-2015
		WO 2013182855 A2	12-12-2013
US 5271934 A	21-12-1993	NONE	
EP 0451953 A2	16-10-1991	CA 2038668 A1	11-10-1991
		DE 69117087 D1	28-03-1996
		DE 69117087 T2	05-06-1996
		EP 0451953 A2	16-10-1991
		JP H04227633 A	17-08-1992
		US 5053484 A	01-10-1991
US 5324812 A	28-06-1994	NONE	