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(54) **Titre : MICROCAPSULES A NOYAU STABILISE, PROCEDE DE LEUR PREPARATION ET UTILISATIONS DE CELLES-CI**
(54) **Title: CORE STABILIZED MICROCAPSULES, METHOD OF THEIR PREPARATION AND USES THEREOF**

(57) **Abrégé/Abstract:**
The present invention provides core-stabilized microcapsules, wherein said core comprises at least one active agent encapsulated within a metal oxide shell, processes for their preparations, comparisons comprising them and uses thereof.

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(54) Title: CORE STABILIZED MICROCAPSULES, METHOD OF THEIR PREPARATION AND USES THEREOF

(57) Abstract: The present invention provides core-stabilized microcapsules, wherein said core comprises at least one active agent encapsulated within a metal oxide shell, processes for their preparations, comparisons comprising them and uses thereof.

CORE STABILIZED MICROCAPSULES, METHOD OF THEIR PREPARATION AND USES THEREOF

FIELD OF THE INVENTION

This invention relates to microcapsules having stabilized core, method of their preparation and uses thereof.

BACKGROUND OF THE INVENTION

The following publications are considered pertinent for describing the state of the art in the field of the invention:

- US 5500223
- US 6303149
- US 6238650
- US 6468509
- US 6436375
- US 6337089
- US 5891476
- DE 102004017221
- WO 2008134908
- US 6,270,836
- WO 2008/133482
- WO 2005097056
- S.A.F. Bon *et al.*, Pickering Stabilization as a Tool in the Fabrication of Complex Nanopatterned Silica Microcapsules, *Langmir*, **23**: 9527-9530, 2007.
- C.A. Prestidge *et al.* Nanoparticle encapsulation of emulsion droplets, International Journal of Pharmaceutics **324**:92-100, 2006.
- International Journal of Pharmaceutics, vol.126 (2000) 219-222.
- J. Volkhard et al. *J. Microencapsulation*, 18(2), 149-152, 2001.

There are many known micro-encapsulation methods which employ silica particles as an encapsulating material, the function of which is to allow a delayed but continuous release of the material encapsulated.

US 5500223 describes an encapsulation process, which employs an aqueous dispersion of silica having a particle size not substantially greater than 100 nm. According to the art, an emulsion is formed by high shear mixing of the silica dispersion with the material to be encapsulated and the emulsion is gelled. The process described therein allows hydrophobic materials to be encapsulated in structures which have a high loading of the material and a good degree of imperviousness in the presence of other materials such as surfactants and mineral oils. The use of such process, allows hydrophobic materials such as flavors, fragrances and cosmetic ingredients to be encapsulated for delayed release in a wide variety of products.

US 6303149 describes a process for preparing sol-gel microcapsules loaded with up to 95% (w/w) functional molecules or substances and to the products obtained by such process. The process is conducted in two steps: (a) creating an oil-in-water emulsion by emulsification of a water insoluble solution comprising the sol-gel precursors and the molecules to be loaded, in an aqueous solution under appropriate shear forces; (b) mixing and stirring said emulsion with an aqueous solution at a suitably selected pH to obtain loaded sol-gel microcapsules in suspension. Incorporation of the final product, either in the form of a suspension or a powder, in cosmetic formulations affords a transparent cream when applying to skin and has a smooth and pleasant contact.

Isolating functional molecules or substances in inert matrices has many useful benefits and applications where chemical contact between the functional molecules and the immediate environment should be minimized.

US 6238650 describes a safe and stable sunscreen composition comprising of at least one sunscreen active ingredient in the form of an inert sol-gel microcapsules encapsulating ultraviolet absorbing compounds in any acceptable cosmetic vehicle. The composition described therein, comprises several ultraviolet absorbers that may be encapsulated in the same sol-gel microcapsule or in different capsules. The encapsulation of the ultraviolet absorbers reduces or even prevents the contact between the sunscreen compounds and the human tissue, thus reducing various adverse effects

that are associated with the use of sunscreens, such as photoallergy and phototoxicity, and makes the composition safer for use. The system described therein, facilitates an easy incorporation of the composite sol-gel encapsulated sunscreen in all types of cosmetic vehicles including oil free compositions, with no necessary steps of heating or high shear forces. The sunscreen compositions described therein can comprise any acceptable UVA and/or UVB absorbing compounds at any desired ratio to obtain a desired accumulative ultraviolet screening spectrum.

US 6436375 describes a method for obtaining improved photostability of a sunscreen composition that contains at least two sunscreen active ingredients, which are photo-unstable when formulated together, by microencapsulating at least one of said active ingredients in an encapsulating material suitable for holding the encapsulated active ingredient material, thus reducing or preventing its leaching out of the capsules; and adding other acceptable components and additives needed for the preparation of said composition. The sunscreen active ingredients can be selected from UVA and UVB absorbers, preferably a combination thereof. Preferably, the active ingredients are encapsulated in separate sol-gel microcapsules.

SUMMARY OF THE INVENTION

The present invention provides a process for preparing microcapsules having a core encapsulated within a metal oxide shell, said process comprising:

(a) preparing an oil-in-water emulsion by emulsification of an oily phase comprising at least one active agent and at least one phase changing material in an aqueous phase, wherein at least one of said oily phase and aqueous phase comprise a sol-gel precursor;

(b) subjecting said emulsion to microcapsule forming conditions; thereby obtaining said microcapsules.

In one embodiment of the present invention at least one metal oxide nanoparticle is added to said aqueous phase prior, during or after emulsification of step (a).

The invention further provides microcapsules obtainable by the process of the invention.

In another one of its aspects the invention provides microcapsules comprising a core encapsulated by a metal oxide shell, wherein said core has a viscosity of between about 300cP to about 1,000,000cP (when measured under various conditions, for example as will given herein below) and comprises at least one active agent and at least one phase changing material; wherein the thickness of said metal oxide shell is in the range 0.1-10 micron; and wherein said shell is obtained from a hydrolyzed and polymerized sol gel precursor. In one embodiment said core comprises at least one active agent and at least one phase changing material. In other embodiments said shell of said microcapsules of the invention is obtained from (a) metal oxide nanoparticles, and (b) a hydrolyzed and polymerized sol gel precursor.

The invention further encompasses a composition comprising microcapsules of the invention.

In a further aspect the invention provides a method for treating a surface condition in a subject in need thereof, comprising topically administering to said subject a composition of the invention.

The invention further provides a composition comprising microcapsules of the invention, for the treatment of a disease, disorder or condition selected from acne, infection, inflammation, puritis, psoriasis, seborrhea, contact dermatitis, rosacea, and a combination thereof.

In another aspect the invention provides a use of microcapsules of the invention, for the preparation of a topically administered composition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the finding of a process for obtaining a microcapsule having a metal-oxide shell wherein the incorporation of phase changing material into the core of said microcapsule provides unexpected stability to the encapsulated active agents in the core of said microcapsule.

In some embodiments the present invention a process for obtaining a thick and dense coating on a stable water insoluble core, using in some embodiments metal oxide nanoparticles in combination with a sol-gel precursor, wherein the addition of phase changing material incorporated into said core provides further stability parameters to the encapsulated active agents and to the pharmaceutical composition comprising them.

Thus, in one aspect of the present invention, there is provided a process for preparing microcapsules having a core encapsulated within a metal oxide shell, said process comprising:

(a) preparing an oil-in-water emulsion by emulsification of an oily phase comprising at least one active agent and at least one phase changing material, in an aqueous phase, wherein at least one of said oily phase and aqueous phase comprise a sol-gel precursor;

(b) subjecting said emulsion to microcapsule forming conditions; thereby obtaining said microcapsules.

In the present invention the term ***"core"*** refers to the inside part of the microcapsules comprising at least one active agent and at least one phase changing material that are both surrounded by a metal oxide shell of a microcapsule. It should be noted that additional compounds may be present in said core including for example carriers, excipients, pharmaceutically acceptable polymers or salts etc, all in accordance with the intended use of produced microcapsules, which will be apparent to a skilled artisan preparing said microcapsules. The core of said microcapsule of the invention may comprise said at least one active agent and at least one phase forming material.

In some embodiments the viscosity of said core at room temperature may be about 300cP, 350cP, 400cP, 450cP, 500cP, 550cP, 600cP, 650cP, 700cP, 750cP, 800cP, 900cP, 1000cP, 2000cP, 3000cP, 4000cP, 5000cP, 6000cP, 7000cP, 8000cP, 9000cP, 10,000cP, 20,000cP, 30,000cP, 40,000 cP, 50,000cP, 60,000 cP, 70,000cP, 80,000cP, 90,000cP, 100,000cP, 200,000cP, 300,000cP, 400,000cP, 500,000cP, 600,000cP, 700,000cP, 800,000cP, 900,000cP or 1,000,000cP (when measured under various

conditions). In some embodiments the viscosity of said core at room temperature is between about 300 to 600cP. In other embodiments the viscosity of said core at room temperature is between about 400 to 500cP. In further embodiments the viscosity of said core at room temperature is between about 300 to 10,000cP. In other embodiments the viscosity of said core at room temperature is between about 5,000 to 1,000,000cP. In some further embodiments the viscosity of said core at room temperature is between about 20,000 to 1,000,000cP.

In other embodiments of the invention said core may be solid at room temperature. In other embodiments, said core may be in a semi-solid phase at room temperature.

The oily phase utilized by a process of the invention comprises at least one active agent and at least one phase changing material. Said at least one active agent may be in a form of a water insoluble liquid or dispersion in water-insoluble liquid comprising said at least one active agent.

The oily phase may be constituted by a liquid water-insoluble active agent; which may comprise a first, liquid water-insoluble active agent dissolved and/or dispersed in a second, water insoluble liquid being another active agent or serving as a carrier. In another embodiment said oily phase may comprise a solid active agent dissolved and/or dispersed in a water-insoluble liquid, being another active ingredient or serving as a carrier.

The term ***"water insoluble liquid"*** or ***"dispersion in water-insoluble liquid"*** refers to a solubility of the liquid (including the ingredients included therein, dissolved and/or dispersed) in water of about less than 1 %w/w, preferably 0.5 %w/w and most preferably 0.15 % w/w at room temperature (20-25°C).

Accordingly, the constituents included in the *core* whether solid or liquid ingredients have a solubility of about less than 1 %w/w, preferably 0.5 %w/w and most preferably 0.15 %w/w at room temperature (20-25°C). The water insoluble liquid may be for example squalane oil, polydimethylsiloxane, mineral oil, castor oil, aromatic 200, and mixtures thereof.

In the present invention, the term ***"sol-gel precursor"*** refers to any metal or semi-metal organo-metallic monomer, or a prepolymer (which means several monomers polymerized together) thereof, which allows to obtain a glass or ceramic material by in-situ polymerization (an inorganic sol-gel polymerization process). Preferably the sol-gel

precursor is a metal or semi-metal organo-metallic monomer (e.g. a metal or semi-metal alkoxide monomer.

In the present invention, the term ***"active agent"*** refers to any molecule or substance that can be used in medicine or cosmetics and which grants the final product (cosmetics, drug, etc.), at least one desired property. In some embodiments one active agent is encapsulated within said microcapsule obtained by the process of the invention. In other embodiments at least two different active agents are encapsulated within said microcapsule obtained by the process of the invention. In other embodiments said at least two different active agents are each encapsulated within a separate microcapsule, obtained either independently or simultaneously by the process of the invention.

As used herein the term ***"metal oxide nanoparticles"*** refers to substantially pure metal oxide nanoparticles consisting essentially of or comprised wholly of metal oxide. In some embodiments metal oxide nanoparticles do not include organic material, in particular not polystyrene.

The term "***phase changing material***" (PCM) is meant to encompass any substance capable of changing its state of matter (phase), or at least its viscosity, in accordance with the temperature it is exposed to. PCMs typically have a high heat of fusion which enables them to melt and solidify at certain temperatures, and are capable of storing and releasing large amounts of energy. Heat is absorbed or released when the PCM material changes from solid to liquid and vice versa. When PCMs reach the temperature at which they change phase or viscosity (for example their melting temperature), they absorb large amounts of heat at an almost constant temperature. The PCM continues to absorb heat without a significant raise in temperature until all the material is transformed to the liquid phase. When the ambient temperature around a liquid material falls, the PCM solidifies, releasing its stored latent heat. In accordance with an embodiment of the present invention a phase changing material utilized by a process of the invention is an organic material, which is non-reactive with any compound utilized by a process of the invention and is characterized by the fact that at room temperature said PCM has a viscosity of between about 300cP to 1,000,000cP (when measured under various conditions). In some embodiments the viscosity of said PCM at room temperature may be 300cP, 350cP, 400cP, 450cP, 500cP, 550cP, 600cP, 650cP, 700cP, 750cP, 800cP, 900cP, 1000cP, 2000cP, 3000cP, 4000cP, 5000cP, 6000cP, 7000cP, 8000cP, 9000cP, 10,000cP, 20,000cP, 30,000cP, 40,000 cP, 50,000cP,

60,000 cP, 70,000cP, 80,000cP, 90,000cP, 100,000cP, 200,000cP, 300,000cP, 400,000cP, 500,000cP, 600,000cP, 700,000cP, 800,000cP, 900,000cP or 1,000,000cP (when measured under various conditions).

In one embodiment, said at least one phase changing material is selected from natural or synthetic paraffins (e.g. having a molecular formula of C_nH_{2n+2}, wherein n=10-100), C_{10}-C_{100} alkane, C_{10}-C_{100} alkene (having at least one double bond), C_{10}-C_{100} alkyne (having at least one triple bond), aliphatic alcohols (e.g. having a molecular formula of $CH_3(CH_2)_nOH$ n=10-100) and fatty acids (e.g. having a molecular formula of $CH_3(CH_2)_{2n}COOH$ n=10-100), or any combination thereof.

In some embodiments said at least one phase changing material is at least one natural or synthetic paraffin. In some embodiments said at least one phase changing material is a C_{10}-C_{100} aliphatic alcohol (in other embodiments C_{10}, C_{20}, C_{30}, C_{40}, C_{50}, C_{60}, C_{70}, C_{80}, C_{90} to C_{100} aliphatic alcohol). In further embodiments said at least one phase changing material is a C_{10}-C_{100} aliphatic fatty acid (in other embodiments C_{10}, C_{20}, C_{30}, C_{40}, C_{50}, C_{60}, C_{70}, C_{80}, C_{90} to C_{100} aliphatic fatty acid).

In one embodiment said PCMs are liqudified (or at least become substantially or partially liquidified, pleable or semi-solid, and capable of being handled by a process of the invention) at a temperature range of between about 35°C to about 60°C, more preferably in a temperature range of between about 35°C to about 45°C.

Examples of phase changing materials capable of being used by the processes of the invention include, but are not limited to: Carnauba wax (m.p. 82-86°C), Beeswax pure (m.p. 61-65°C), Beeswax white pure, (m.p. 61-65°C), Beeswax bleached technical (m.p. 61-65°C), Montan wax bleached (m.p. 80-86°C), Montan wax bleached, partially saponified (m.p. 99-105°C), Montanic acid (m.p. 81-87°C), Hydrocarbon wax synthetic (m.p. 106-114°C), Microcrystalline wax (m.p. 89-95°C), Microcrystalline wax (m.p. 76-82°C), Hardwax partially saponified (m.p. 104-109°C), Beeswax yellow (m.p. 61-66°C), Polishing Wax (m.p. 78-84°C), Castor wax (m.p. 83-89°C), Microwax (m.p. 89-95°C), Microwax (m.p. 80-86°C), Microwax (m.p. 76-82°C), Ozokerite (m.p. 72-79°C), Microcrystalline wax, plastic (m.p. 76-82°C), Microcrystalline wax, soft (m.p. 74-80°C), Wax blend (m.p. 62-68°C), Polyolefin wax (m.p. 65-75°C), Lanolin, Shellac, Bayberry wax (m.p. 45°C), Candelilla wax (m.p. 67–79°C), Ouricury wax, Rice bran

wax (m.p. 77 - 86°C), Soy candle (wax), Paraffin (m.p. 47 - 64°C), Chinese wax, and any combinations thereof.

In one embodiment of a process of the invention, said at least one phase changing material is in a liquid state. Thus, prior to the addition of said at least one PCM, its temperature is raised until it is substantially homogenously liquidified. In a further embodiment of the present invention, a process of the invention is carried out under a temperature wherein said at least one phase changing material is in a liquid state, throughout the entire emulsification and encapsulation process disclosed herein above and below. It is noted that said at least one PCM utilized by a process of the present invention, is selected such that its heat of fusion allows for processes of the invention to be carried out substantially without compromising the active agents used, the emulsion formed and the metal oxide shell produced for the microcapsules of the invention.

In one embodiment of the present invention at least one metal oxide nanoparticle is added to said aqueous phase prior, during or after emulsification of step (a).

In a further embodiment of a process of the invention, the process further comprises a step of cooling obtained microcapsules to room temperature. It is noted that upon cooling of said obtained microcapsules, the viscosity of said core, comprising said at least one active agent and at least one PCM, changes to have values of between about 300cP to 1,000,000cP (when measured under various conditions). It should be understood that such PCMs used by a process of the invention are accumulated in the core of obtained microcapsules and are not incorporated in any part of the metal-oxide shell formed by encapsulation process of the invention.

It is further noted that such microcapsules obtained by a process of the invention, demonstrate a higher stability, as measured in the amount of leakage measured upon long term storage of said microcapsules.

In some embodiments of the invention, microcapsules obtained by a process of the invention are stable for a period of at least 2 weeks at room temperature. In some embodiments of the invention, microcapsules obtained by a process of the invention are stable for a period of at least 2 months at room temperature. In some embodiments of the invention, microcapsules obtained by a process of the invention are stable for a period of between about 2 weeks to 2 years at room temperature. In other embodiments microcapsules obtained by a process of the invention are stable for a period of between

about 2 months to about 2 years at room temperature. In this context it should be noted that a stability of a microcapsule of the invention, obtained by a process of the invention is measured by the ability of said microcapsule to substantially maintain said at least one active agent within said microcapsule, with a maximal leakage of between about 0 to 5% of said active agent, for a set period of time under conditions of temperature and RH specified.

In a further embodiment of a process of the invention, said microcapsules encapsulating said at least one active agent and at least one phase changing material have a viscosity of between about 300cP to about 1,000,000cP.

According to an embodiment of the present invention said core comprises a pharmaceutical agent, cosmetic agent, or agrochemical agent.

Additionally according to an embodiment of the present invention said core comprises a dermatological agent.

Further according to an embodiment of the present invention said dermatological agent is selected from anti-fungal agents, anti-bacterial agents, anti-inflammatory agents, anti-puritic agents, anti-psoriatic agents, anti-acne agents, anti-rosacea agents, and any combinations thereof.

In some embodiments, an anti-acne agent is selected from benzoyl peroxide, retinoid, and mixtures thereof. The retinoid may be for example tretinoin (all trans retinoic acid, ATRA), tazarotene, iso-tretinoin, adapalene or mixtures thereof.

According to an embodiment of the present invention said metal oxide nanoparticles are selected from Silica, Titania, Zirconia, ZnO, and any mixtures thereof.

According to another embodiment of the present invention said metal oxide nanoparticles have a particle size diameter (d50) in the range of 1-100 nm. In other embodiments particle size diameter (d50) is in the range of 1-50 nm, more preferably 5-30 nm.

By the term "***particle size diameter (d50) in the range of 1-100 nanometer***" is meant to encompass particles of which at least 50% by volume have diameters in the range of 1-100 nanometer.

Unless otherwise indicated, the nanoparticle size will be given using the D_{90} value, i.e. the size of at least 90% of said particles (measured by volume). Thus, for example, when referring to nanoparticles having a diameter of at least about 10 nm, it

should be understood to mean that the D_{90} value of said nanoparticles is 10 nanometer. D_{90} values may be measured by laser diffraction.

According to another embodiment, a process of the present invention further comprising adding at least one metal oxide salt to said aqueous phase either prior, during or after emulsification in step (a). In another embodiment said metal oxide salt is selected from sodium silicate, potassium silicate, sodium titanate, potassium titanate, sodium zirconate, potassium zirconate, and mixtures thereof. In another embodiment the weight ratio between metal oxide nanoparticles and metal oxide salt is in the range 99:1 to 1:2 , preferably 50:1 to 2:1, more preferably 50:1 to 10:1.

According to an embodiment the process of the present invention further comprising adding a binding or cross-linking additive selected from a polymeric agent, a di- or tri-valent metal salt, a polyelectrolyte, and mixtures thereof, to said aqueous phase either prior, during or after emulsification of step (a). It is noted that when using these type of binding or cross-linking additive the prepared microcapsules will have a more cross-linked and stronger metal oxide shell.

In one embodiment, said polymeric agent is selected from sodium alginate, polyvinyl alcohol, carboxymethyl cellulose, polyvinyl pyrrolidone, and mixtures thereof.

In another embodiment, said di- or tri-valent metal salt is selected from aluminum sulfate, sodium aluminate, sodium borate, calcium chloride, and mixtures thereof.

Without being bound to theory the binding or cross-linking additives may provide such strengthening and cross-linking properties of microcapsules shell as follows:

Aluminum sulfate - the positively charged aluminum cations may be attracted to the negatively charged metal oxide nanoparticles and as such may work as cross-linkers between the metal oxide nanoparticles which are adsorbed on the oil droplet-water interface

Sodium aluminate - sodium aluminate may react with the silanol groups on the metal oxide nanoparticles surface, and as such may work as cross-linkers between the metal oxide nanoparticles which are adsorbed on the oil droplet-water interface.

PVA (polyvinyl alcohol) may adsorb onto the metal oxide shell via hydrogen bonds and also can be cross-linked by sodium borate.

Sodium borate - sodium borate may cross-link the PVA with the metal oxide shell of the microcapsules.

Sodium alginate - sodium alginate may adsorb onto the metal oxide shell (produced from adsorption of metal oxide nanoparticles) and may be cross-linked by addition of calcium chloride.

PDAC 7 (polyquaternium 7) - PDAC 7 may be used for coating of the metal oxide shell. PDAC 7 which is positively charged may adsorb onto the negatively charged metal oxide shell and as such decrease the "gaps" between the metal oxide nanopartices and thus strengthen the shell.

CMC (carboxymethyl cellulose) - CMC may be used for additional coating of the metal oxide shell. It can be used after coatings with PDAC 7.

In one embodiment, said polyelectrolyte is selected from Polyquaternium-7 (Dimethyldiallylammonium chloride acrylamide copolymer), Polyquaternium-1 [Poly[(dimethyliminio)-2-butene-1,4-diyl chloride],α-[4-[tris(2-hydroxyethyl)ammonio]-2-butenyl]-ω-[tris(2-hy droxyethyl)ammonio]-, dichloride], Polyquaternium-10 [Cellulose 2-hydroxyethyl 2-(2-hydroxy-3-(trimethylammonio)propoxy)ethyl-2-hydroxy-3-(trimethylammonio)propyl ether, chloride], Chitosan, Polylysine, and mixtures thereof.

According to one embodiment at least one of said oily and aqueous phases comprise at least one surfactant. In one embodiment said surfactant is selected from a cationic surfactant, an anionic surfactant, a non-ionic surfactant and mixtures thereof. In one embodiment the at least one surfactant is a cationic surfactant. In a further embodiment said at least one cationic surfactant is cetyltrimethyl ammonium chloride (CTAC).

In another embodiment said oily phase may comprise a hydrophobic surfactant, hydrophobic polymeric surfactant, or mixtures thereof. In one embodiment the hydrophobic surfactant or hydrophobic polymeric surfactant is a non-ionic surfactant. The hydrophilic surfactant may be for example an anionic, a cationic, a non-ionic surfactant, or mixtures thereof.

In some embodiments the concentration of the cationic surfactant in the aqueous phase may be from 0.1 to 5% (w/w), in other embodiments from 1 to 5% (w/w). It is appreciated that the concentration of the surfactant will also depend on the percentage

of the oily phase and aqueous phase. In some embodiments the concentration of the surfactant may be 5 – 10 % (w/w) from the weight of the oily phase.

According to another embodiment of the present invention said oily phase comprises a sol-gel precursor.

According to a further embodiment of the present invention said sol-gel precursors are selected from metal alkoxide monomers, semi-metal alkoxide monomers, metal ester monomers, semi-metal ester monomers and from monomers of the formula $M(R)_n(P)_m$, wherein M is a metallic or semi metallic element, R is a hydrolysable substituent, n is an integer from 2 to 6, P is a non polymerizable substituent and m is and integer from 0 to 6, a partially hydrolyzed and partially condensed polymer of any of the above, and mixtures of any of the above. In one embodiment, said metallic or semi metallic element is selected from Si, Ti, Zr, Al, and Zn.

In another embodiment, said sol-gel precursors are selected from silicon alkoxide monomers, silicon ester monomers, monomers of the formula $Si(R)_n(P)_m$, wherein R is a hydrolysable substituent, n is an integer from 2 to 4, P is a non polymerizable substituent and m is an integer from 0 to 4, a partially hydrolyzed and partially condensed polymer of any of the above, and mixtures of any of the above. In one embodiment, said silicon alkoxide monomer is selected from tetramethoxy silane, tetraethoxy silane, and mixtures thereof. In a further embodiment, said monomers of the formula $Si(R)_n(P)_m$ are selected from methyl trimethoxysilane, dimethyl dimethoxysilane, and mixtures thereof. In yet a further embodiment, said sol-gel precursor is a monomer (e.g. a metal alkoxide monomer, a semi-metal alkoxide monomer) as described hereinbefore.

According to an embodiment of the present invention the pH of said aqueous phase is in the range 2-9. In another embodiment, the pH of said aqueous phase is in the range 2-7, even more preferably the pH is in the range 3-5.

According to an embodiment of the present invention said microcapsule forming conditions comprise isolating the microcapsules through procedures selected from at least one of: separation by centrifuge, filtration, evaporation, re-suspension in aqueous medium, and dialysis.

In another embodiment of the present invention said microcapsules forming conditions comprise altering the pH of the formed emulsion to a range of between about 2 to about 9, preferably the pH is in the range 3-5.

According to another embodiment of the present invention said microcapsule forming conditions comprise stirring of said emulsion. In some embodiments said stirring may be for example by mechanical stirrer at 200-500 rpm.

According to another embodiment of the present invention said microcapsule forming conditions comprise drying the obtained microcapsules in suspension.

According to another embodiment the product obtained by a process of the invention is a suspension of said formed microcapsules.

According to a further embodiment of the present invention the product obtained by a process of the invention is a powder of said microcapsules.

In another aspect of the present invention there is provided microcapsules obtainable by the process of the present invention.

Yet in another aspect of the present invention there is provided microcapsules comprising a core encapsulated by a metal oxide shell, wherein said core has a viscosity of between about 300cP to about 1,000,000cP (when measured under various conditions); wherein the thickness of said metal oxide shell is in the range 0.1-10 micron; and wherein said shell is obtained from (a) metal oxide nanoparticles, and (b) a hydrolyzed and polymerized sol gel precursor.

In some embodiments the viscosity of said core at room temperature may be 350cP, 400cP, 450cP, 500cP, 550cP, 600cP, 650cP, 700cP, 750cP, 800cP, 900cP, 1000cP, 2000cP, 3000cP, 4000cP, 5000cP, 6000cP, 7000cP, 8000cP, 9000cP, 10,000cP, 20,000cP, 30,000cP, 40,000 cP, 50,000cP, 60,000 cP, 70,000cP, 80,000cP, 90,000cP, 100,000cP, 200,000cP, 300,000cP, 400,000cP, 500,000cP, 600,000cP, 700,000cP, 800,000cP, 900,000cP or 1,000,000cP (when measured under various conditions).

It is noted that viscosity value measurement depends on the instrument of measurement, spindle used, speed and temperature of measurement. Unless otherwise mentioned the viscosity measurements given in the present invention were measured using a Brookfield LVDV-II + Pro viscometer equipped with a small sample adaptor, spindle #21 at 6 RPM and temperature of 30°C.

In some embodiments, a microcapsule of the invention is capable of being stable (i.e. maintain at least about 0 to 5 % of said encapsulated at least one active agent) for a period of between about 2 weeks to about 2 years at room temperature. In other embodiments, a microcapsule of the invention is capable of being stable for a period of

between about months to about 2 years at room temperature. In other embodiments, a microcapsule of the invention is capable of being stable for a period of at least 2 weeks at room temperature. In further embodiments, a microcapsule of the invention is capable of being stable for a period of at least 2 months at room temperature.

Further according to another embodiment of the invention the metal oxide shell has a width (thickness) of about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 1, 1.5, 2 or 5 micron or above, preferably up to 10 micron. The core, shell, etc. constituents may be as described in the present invention.

The width of the metal oxide layer may be determined for example by a Transmission Electron Microscope or Confocal Microscope such that in a circular cross sectional area of the microcapsules the smallest width is at least e.g. 0.1 micron (the width is determined as the smallest distance from the outer surface of the microcapsules (i.e. metal oxide surface) to the core-metal oxide interface).

In another aspect of the present invention there is provided a composition comprising microcapsules of the present invention.

Further in another aspect of the present invention there is provided a method for treating a surface condition in a subject in need thereof, comprising topically administering to said subject a composition of the present invention, wherein the core material comprises a dermatological agent.

The term ***"treating"*** or ***"treatment"*** as used herein includes any treatment of a condition, disease or disorder associated with a patient's body surface such as the skin or mucosal membrane, and includes inhibiting the disease or disorder (i.e. arresting its development), relieving the disease or disorder (i.e. causing regression of the disease or disorder), or relieving the conditions caused by the disease (i.e. symptoms of the disease). The concentrations of the dermatological agents that can be used for treatment of a specific disease or disorder may be as described in The Merck index an encyclopedia of chemical drugs and biologicals, Rahway, NJ; Merck & Co; 1989.

Although individual needs may vary, determination of optimal ranges for effective amounts of the compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of a pharmaceutical composition, which can be adjusted by one skilled in the art, will vary depending on the age, health, physical condition, weight, type and extent of the disease or disorder of the recipient,

frequency of treatment, the nature of concurrent therapy (if any) and the nature and scope of the desired effect(s).

When referring to pharmaceutical compositions comprising a compound of the subject invention it should be understood to encompass admixtures of microcapsules of the invention, with pharmaceutically acceptable auxiliaries, and optionally other therapeutic agents. The auxiliaries must be "*acceptable*" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intrathecal) administration or administration via an implant. The compositions may be prepared by any method well known in the art of pharmacy. Such methods include the step of bringing in association compounds used in the invention or combinations thereof with any auxiliary agent.

Auxiliary agent(s), also named accessory ingredient(s), include those conventional in the art, such as carriers, fillers, binders, diluents, disintegrants, lubricants, colorants, flavouring agents, anti-oxidants, and wetting agents.

Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets, dragées or capsules, or as a powder or granules, or as a solution or suspension. The composition may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material, including instructions for the use of the composition for a use as hereinbefore described.

For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injections. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of sterile liquid carrier, for example water, prior to use.

For transdermal administration, e.g. gels, patches or sprays can be contemplated. Compositions or formulations suitable for pulmonary administration e.g. by nasal inhalation include fine dusts or mists which may be generated by means of metered

dose pressurized aerosols, nebulisers or insufflators.

The exact dose and regimen of administration of the composition will necessarily be dependent upon the therapeutic or nutritional effect to be achieved and may vary with the particular formula, the route of administration, and the age and condition of the individual subject to whom the composition is to be administered.

According to an embodiment of the present invention said surface is skin or mucosal membrane.

According to another embodiment of the present invention said surface condition is a skin disease or disorder selected from acne, infection, inflammation, puritis, psoriasis, seborrhea, contact dermatitis, rosacea, and a combination thereof.

Additionally, in another aspect of the present invention there is provided a composition comprising microcapsules as described in the present invention, wherein the core comprises a dermatological agent, for treatment of a disease or disorder selected from acne, infection, inflammation, puritis, psoriasis, seborrhea, contact dermatitis, rosacea, and a combination thereof.

Yet, in another aspect there is provided a use of the microcapsules of the present invention, wherein said core comprises a dermatological agent for the preparation of a topically administered composition.

According to an embodiment of the invention said topical administration is for treating a disease or disorder selected from acne, psoriasis, seborrhea, contact dermatitis, infection, rosacea, inflammation, and a combination thereof.

In another aspect of the present invention there is provided a composition for pest control comprising the microcapsules of the invention, wherein said core comprises a pesticide. In one embodiment of the present invention said pesticide is selected from a herbicide, an insecticide, a fungicide, and mixtures thereof. According to yet another embodiment of the present invention said composition is for use in crop protection or non-crop pest control.

DETAILED DESCRIPTION OF EXAMPLARY EMBODIMENTS

The following Examples are representative of techniques employed by the inventors in carrying out aspects of the present invention. It should be appreciated that while these techniques are exemplary of preferred embodiments for the practice of the invention, those of skill in the art, in light of the present disclosure, will recognize that

numerous modifications can be made without departing from the spirit and intended scope of the invention.

Unless otherwise indicated ***"%"*** refers to weight per weight (w/w) %.

"BPO (75%)" refers to 75% w/w BPO (Benzoyl peroxide) with 25% w/w water.

"Ludox TM 50 (50%)" refers to a dispersion of silica nanoparticles (average particle size diameter of about 20-30 nm) in water (50% w/w in water). Ludox TM 50 was obtained from Sigma-Aldrich, Israel.

"Ludox AM-30" refers to colloidal silica stabilized with sodium aluminate and dispersed in water (30 % w/w in water).

Ludox AM-30 was obtained from Sigma-Aldrich, Israel.

"CTAC (29 %)" refers to a solution of cetyl trimethyl ammonium chloride 29% w/w in water.

"PVA (10%)" refers to a solution of polyvinyl alcohol 10 % w/w in water.

"sodium silicate (25 %)" refers to a solution of sodium silicate 25%w/w in water.

"GMIS" refers to glyceryl monoisostearate. GMIS was obtained from Scher Chemicals, USA.

"aluminum sulfate solution (50 %)" or ***"aluminum sulfate (50 %)"*** refers to a solution of aluminum sulfate decaoctahydrate 50% w/w in water.

"PDAC 7 (5 %)" refers to a solution of polyquaternium 7 (Diallyldimethylammonium chloride/acrylamide copolymer), 5 % w/w in water.

"CMC (10 %)" refers to a solution of sodium salt of carboxymethyl cellulose 10 % w/w in water.

"sodium aluminate (50 %)" refers to solution of sodium aluminate 50 % w/w in water.

"sodium borate (5 %)" refers to solution of sodium borate 5 % w/w in water.

"sodium alginate (5 %)" refers to solution of sodium alginate 5 % w/w in water.

"Beeswax" refers to Beeswax pure (m.p. 61-65°C), Beeswax white pure, (m.p. 61-65°C), Beeswax bleached technical (m.p. 61-65°C).

"PVP K30 (40%)" refers to solution of PVP K30 (Polyvinylpyrrolidone K-30) 40 % w/w in water.

Example 1: Encapsulation process ATRA (E-ATRA)

Core-Shell step

1. Aqueous phase (phase A): 2.53 g CTAC (30.7%) and 386.27 g WFI were stirred with a magnetic stirrer to homogeneity.
2. Beeswax ingredient: 30.0 g Beeswax, heated to 70 °C until Beeswax was liquid.
3. Oil phase: 90.0 g TEOS, and 97.01 g Squalane were stirred with a magnetic stirrer to dissolution. 30.0 g ATRA were added to solution and stirred, using same magnetic stirrer, for additional 10 min and milled in Dynomill at 5000 rpm for 10 min. Milled oil phase was heated to 55 °C under magnetic stirring, using a water bath.
4. Aqueous phase was heated to 55 °C under magnetic stirring, using a water bath.
5. In a 1L beaker, 91.37 g milled oil phase and 5.83 g Beeswax, were mixed for 5 minutes at 55 °C under magnetic stirring, using a water bath (phase B).
6. Phase C: 14.0 g Sodium silicate solution (25%) and 30.0 g HCl 5N.
7. Phase B mixed under high shear mixing at 4000 rpm (Polytron 6100).
8. Phase A was added to Phase B, and mixed with high shear at 4000 rpm for 1 min. after which high shear speed was reduced to 3000 rpm.
9. Phase C was added until pH 7.0±0.2 was reached.
10. HCl 5N was added to emulsion until pH 3.0±0.2 was reached.
11. Emulsion was mixed with high shear for additional 2 min at 3000 rpm.
12. Emulsion was stir for 17hr. at 50 °C at 80 rpm and then cool to 25 °C until core-shell suspension was achieved.

Coating step (optional)

13. 150.0 g of core-shell suspension was placed under high-shear at 2500 rpm.
14. 5% NaOH 5N were added until pH 5.0 + 0.2.
15. 1.2 g PDAC-7 (3%) was added and mixture was stirred for 1 min.
16. 1.2 g Sodium silicate (25%) was added and pH adjusted to 5.0 + 0.2 with HCl 5N solution, and mixture was stirred for 1 min. (1st cycle).
17. Coating cycle (steps 15-16) was repeated at least 10 times.

The viscosity of the core of the obtained microcapsules was measured to be between 475 to 565cP (as measured using a Brookfield LVDV-II + Pro viscometer equipped with a small sample adaptor, spindle #21 at 6 RPM and temperature of 30°C).

Example 2 - Encapsulation of BPO (Benzoyl peroxide) (BPO dispersed in DC-246)

a) Preparing the oil phase: A mixture of 67.68 g BPO (75%), 132.04 g DC-246 (cyclohexasiloxane, Dow Cornig, USA) and 10.06 g Span 65 as dispersant agent and 45.6 g of TEOS (tetraethoxy silane) were milled first by high shear at 4000 rpm for 2 minutes and then by microfluidizer for 15 minutes.

b) Preparing the water phase: An aqueous phase including 6.06 g of Myrj 45 (polyoxyethylene (8) stearate), 2.68 g CTAC (29 %), 64.54 g PVA (10 %) and 328.13 g of water was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 6000 rpm for 2 minutes. Then, 49.93 g of Ludox TM 50 (50 %) and 5 ml of sodium silicate (25 %) were added, and then the pH was adjusted to 3. The mixture was transferred to reactor and stirred for 20 h.

Example 3 - Encapsulation of BPO (BPO dispersed in DC-350)

a) Preparing the oil phase: A mixture of 67.49 g BPO (75%), 130.92 g DC-350 (polydimethylsiloxane, obtained from Dow corning, USA) and 10.16 g cetyl alcohol as dispersant agent and 45.42 g of TEOS were milled first by high shear at 4000 rpm for 2 minutes and then by microfluidizer for 15 minutes.

b) Preparing the water phase: A water phase including 5.69 g of Myrj 45 (polyoxyethylene (8) stearate), 2.25 g CTAC (29 %), 65.05 g PVA (10 %) and 327.24 g of water, was prepared.

The two phases were preheated at 50 °C and then the oil phase (a) was added to the water phase (b) under shearing at 5000 rpm for 2 minutes. Then, 50.09 g of Ludox TM 50 (50 %) were added and the solution became viscous. Then, 5 ml of sodium silicate (25 %) was diluted up to 100.09 g with water and the resulted solution was added to the viscous mixture under shearing of 5000 rpm for 1 minute. The pH was adjusted to 3 and then the mixture was transferred to reactor and stirred for 20 h.

Example 4 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 68.64 g BPO (75%), 129.58 g squalane (obtained fron from Lake Oil, Spain) and 5.08 g GMIS as dispersant agent and 89.85 g of TEOS were milled first by high shear at 10000 rpm for 2 minutes and then by microfluidizer for 15 minutes.

b) Preparing the water phase: A water phase including 1.18 g CTAC (29 %), 65.10 g PVA (10 %) and 329.93 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 5000 rpm for 30 seconds. Then, 49.64 g of Ludox TM 50 (50 %) was added and shearing continued further 30 seconds. Then, 20.72 g of aluminum sulfate solution (50 %) were added and the obtained pH was 3. The mixture was transferred to reactor preheated at 40 °C and the mixture was stirred at 118 rpm for 4 hours. Then, the temperature was decreased to room temperature and stirring continued for 20 h.

Example 5 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 80.63 g BPO (75%), 108.15 g squalane (obtained fron from Lake Oil, Spain) and 5.71 g GMIS as dispersant agent and 27.97 g of TEOS were milled first by high shear at 10000 rpm for 1 minute and then by microfluidizer for 15 minutes.

b) Preparing the water phase: A water phase including 1.02 g CTAC (29 %), 60.27 g PVA (10 %) and 290.09 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 5000 rpm for 30 seconds. Then, 30.58 g of Ludox TM 50 (50 %) was added and shearing continued further 30 seconds. Then, 20.09 g of aluminum sulfate solution (50 %) were added under shearing for 30 seconds and the obtained pH was 3.2. The mixture was transferred to reactor preheated at 40 °C and the mixture was stirred at 100 rpm for 4 hours. Then, the temperature was decreased to room temperature and stirring continued for 20 h.

Example 6 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 53.19 g BPO (75%), 75.21 g squalane and 5.12 g GMIS as dispersant agent and 80.68 g of TEOS were milled first by high shear at 10000 rpm for 1 minute and then by microfluidizer for 15 minutes.

b) Preparing the water phase: A water phase including 4.16 g CTAC (29 %), 6.5 g PVA (10 %) and 280.45 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 5000 rpm for 30 seconds. Then, 90.11 g of Ludox TM 50 (50 %) was added and shearing continued further 30 seconds. Then, 9.96 g of aluminum sulfate dissolved in 15.19 g water were added and the resulted mixture was milled at 6100 rpm for 1 minute. The mixture was then transferred to reactor preheated at 38.8°C and it was stirred at 118 rpm for 4 hours. Then, the temperature was decreased to room temperature and stirring continued for 20 h.

Example 7 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 106.35 g BPO (75%), 88.09 g squalane and 4.91 g GMIS as dispersant agent and 41.05 g of TEOS were milled first by high shear at 10000 rpm for 1 minute. A thick mixture was obtained and it could not be milled by microfluidizer.

b) Preparing the water phase: A water phase including 1.31 g CTAC (29 %), 6.3 g PVA (10 %) and 283.1 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 5000 rpm for 30 seconds. Then, 60.66 g of Ludox TM 50 (50 %) was added and shearing continued further 30 seconds. Then, 50.18 g of aluminum sulfate (50 %) were added and the resulted mixture was milled at 6000 rpm for 1 minute. The mixture was then transferred to reactor preheated at 41.8 °C and it was stirred at 100 rpm for 4 hours. Then, the temperature was cooled down to room temperature and stirring continued for 20 h.

Example 8 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 106.24 g BPO (75%), 61.12 g squalane and 5.65 g cetyl alcohol as dispersant agent and 60.49 g of TEOS were milled first by high shear at 10000 rpm for 1.5 minutes. A thick mixture was obtained and it could not be milled by microfluidizer.

b) Preparing the water phase: A water phase including 1.09 g CTAC (29 %), 61.52 g PVA (10 %) and 269.45 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 5000 rpm for 30 seconds. Then, 59.87 g of Ludox TM 50 (50 %) was added and shearing continued further 1 minute. Then, 21.87 g of aluminum sulfate (50 %) were added and the resulted mixture was milled at 6000 rpm for 1 minute. The mixture was then transferred to reactor preheated at 40 °C and stirred for 4 hours. Then, the temperature was cooled down to room temperature and stirring continued for 20 h.

Example 9 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 105.28 g BPO (75%), 130.13 g squalane and 5.48 g Span 20 and 32.51 g of TEOS were milled first by high shear at 10000 rpm for 1 minute. A thick mixture was obtained and it could not be milled by microfluidizer.

b) Preparing the water phase: An aqueous phase including 4.31 g CTAC (29 %), 6.5 g PVA (10 %) and 279.8 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 4000 rpm and then 90.41 g of Ludox TM 50 (50 %) was added and shearing continued 1 minute. Then, 20.88 g of aluminum sulfate (50 %) were added and the resulted mixture was milled at 5000 rpm for 1 minute. The mixture was then transferred to reactor preheated at 39.2 °C and stirred at 103 rpm for 4 hours. Then, the temperature was cooled down to room temperature and stirring continued for 60 h.

Example 10 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 80.25 g BPO (75%), 107.04 g squalane and 5.01 g cetyl alcohol and 30.40 g of TEOS were milled first by high shear at 10000 rpm for 1 minute. A thick mixture was obtained and it could not be milled by microfluidizer.

b) Preparing the water phase: A water phase including 4.33 g CTAC (29 %), 6.16 g PVA (10 %) and 279.59 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 4000 rpm and then 59.43 g of Ludox TM 50 (50 %) was added, and then the resulted mixture was homogenized at 8000 rpm for 1 minute since the mixture was very thick. Then, 49.45 g of aluminum sulfate (50 %) were added and the resulted mixture was milled at 8000 rpm for 30 seconds. The mixture was then transferred to reactor preheated at 41.2 °C

and stirred at 103 rpm for 4 hours. Then, the temperature was cooled down to room temperature and stirring continued for 20 h.

Example 11 - Encapsulation of BPO (BPO dispersed in squalane)

a) Preparing the oil phase: A mixture of 80.2 g BPO (75%), 93.5 g squalane (obtained from Lake Oil, Spain) and 5.38 g Span 20 and 42.07 g of TEOS were milled first by high shear at 10000 rpm for 1 minute and then by microfluidizer for 15 minutes.

b) Preparing the water phase: A water phase including 4.05 g CTAC (29 %), 61.51 g PVA (10 %) and 257.74 g of water, was prepared.

The oil phase (a) was added to the water phase (b) under shearing at 4000 rpm and then 61.42 g of Ludox TM 50 (50 %) was added and shearing at 5000 rpm continued for 1 minute. Then, 21.1 g of aluminum sulfate (50 %) were added and the resulted mixture was milled at 5000 rpm for 1 minute. The mixture was then transferred to reactor preheated at 41.2 °C and stirred at 103 rpm for 4 hours. Then, the temperature was cooled down to room temperature and stirring continued for 20 h.

Example 12: Formulation of encapsulated ATRA and encapsulated BPO (E-ATRA 0.1% / E-BPO 6%).

Ingredients:

(a) E-ATRA suspension: equivalent to 0.1% ATRA, (prepared according to the procedure in Example 1).

(b) E-BPO suspension: equivalent to 6% BPO (prepared according to the procedure in any one of Examples 2-11).

(c) Carbomer 980: 1.2% (Carbopol™ 980 NF from Lubrizol)

(d) Carbomer 1342: 0.3% (Pemulen™ TR-2 NF from Lubrizol)

(e) Sodium hydroxide (Sodium hydroxide pellets extra pure Ph Eur, BP, JP, NF, FCC, E 524 from Merck)

(f) Water

Formulation preparation:

Carbomer 980 & carbomer 1342 were dispersed in water to a lump-free, homogeneous suspension. E-ATRA suspension was added into the carbomers suspension. E-BPO suspension was added into the carbomers suspension. Sodium

hydroxide was added to achieve pH values of 5.0±0.1. Water was added to top 100% formulation weight. Formulation was finally mixed until homogeneity.

Example 13: Formulation of encapsulated ATRA and encapsulated BPO (E-ATRA 0.1% / E-BPO 6%).

Ingredients:

(a) E-ATRA suspension: equivalent to 0.1% ATRA, (prepared according to the procedure in Example 1).

(b) E-BPO suspension: equivalent to 6% BPO (prepared according to the procedure in any one of Examples 2-11).

(c) Carbomer 980: 1.0% (Carbopol 980 NF from Lubrizol)

(d) Hydroxyethyl cellulose: 0.7% (Natrosol® 250 HHX PHARM hydroxyethylcellulose from Hercules).

(e) Sodium hydroxide (Sodium hydroxide pellets extra pure Ph Eur, BP, JP, NF, FCC, E 524 from Merck)

(f) Water

Formulation preparation:

Carbomer 980 & hydroxyethyl cellulose were dispersed in water to a lump-free, homogeneous suspension. E-ATRA suspension was added into suspension. E-BPO suspension was added into the suspension. Sodium hydroxide was added to achieve pH values of 5.0±0.1. Water was added to top 100% formulation weight. Formulation was finally mixed until homogeneity.

Example 14: Formulation of encapsulated ATRA and encapsulated BPO (E-ATRA 0.1% / E-BPO 6%).

Ingredients:

(a) E-ATRA suspension: equivalent to 0.1% ATRA, (prepared according to the procedure in Example 1).

(b) E-BPO suspension: equivalent to 6% BPO (prepared according to the procedure in any one of Examples 2-11).

(c) Hydroxyethyl cellulose: 1.25% (Natrosol® 250 HHX PHARM hydroxyethylcellulose from Hercules).

(d) Hydroxypropyl cellulose: 0.5% (Natrosol® 250 HHX PHARM hydroxyethylcellulose from Hercules).

(e) Glycerin: 15% (Glycerine 99.5% USP from Oleochemicals)

(f) Hydrochloric acid (Hydrochloric acid fuming 37% extra pure Ph Eur, BP, JP, NF from Merck)

(g) Water

Formulation preparation:

E-ATRA suspension was mixed with water. E-BPO suspension was added to E-ATRA suspension. Hydroxyethyl cellulose and hydroxypropyl cellulose were wetted with glycerin in a separate container. The wetted paste was added to the E-ATRA and E-BPO suspension. Hydrochloric acid was added to achive a pH level of 3.5±0.1. Reminder of water was added to top up formulation to 100%. Formulation was finally mixed until homogeneity.

Example 15: Formulation of encapsulated ATRA and encapsulated BPO (E-ATRA 0.1% / E-BPO 6%).

Ingredients:

(h) E-ATRA suspension: equivalent to 0.1% ATRA, (prepared according to the procedure in Example 1).

(i) E-BPO suspension: equivalent to 6% BPO (prepared according to the procedure in any one of Examples 2-11).

(j) Hydroxyethyl cellulose: 1.25% (Natrosol® 250 HHX PHARM hydroxyethylcellulose from Hercules).

(k) Hydroxypropyl cellulose: 0.3% (Klucel®).

(l) Glycerin: 5% (Glycerine 99.5% USP from Oleochemicals)

(m) Hydrochloric acid (Hydrochloric acid fuming 37% extra pure Ph Eur, BP, JP, NF from Merck)

(n) Water

Formulation preparation:

E-ATRA suspension was mixed with water. E-BPO suspension was added to E-ATRA suspension. Hydroxyethyl cellulose and hydroxypropyl cellulose were wetted with glycerin in a separate container. The wetted paste was added to the E-ATRA and E-BPO suspension. Hydrochloric acid was added to achive a pH level

of 3.5±0.1. Reminder of water was added to top up formulation to 100%. Formulation was finally mixed until homogeneity.

Example 16: Stability of formulations of encapsulated ATRA and encapsulated BPO (E-ATRA 0.1% / E-BPO 6%)

The following stability data was obtained from measurements of formulations of Examples 12 – 15 performed using Tretinoin assays were measured according to USP32, 2009 edition, page 3779 – Tretinoin cream.

Table 1 - Stability of Formulation in Example 12

Tests			Specification limits	Zero Time	Time			
					2w	1month	2month	3month
ATRA	Assay		0.09-0.11%	0.107	0.103	0.099	0.091	
	RSD, %		LT 3.0%	0.8	0.8	0.2	0.9	
	Sum of degradation products		collect data	0.42	0.83	1.22	1.47	
	degradation products	RRT 0.25		0.34	0.23	0.22	0.19	
		RRT 0.56				0.09	0.09	
		RRT 0.86				0.09	0.09	
		RRT 0.921			0.07	0.09	0.09	
		RRT 0.935				0.08	0.09	
		RRT 0.963		0.09	0.09	0.08	0.08	
		RRT 1.2				0.1	0.18	
		RRT 1.24			0.08	0.13	0.21	
		RRT 1.578			0.12	0.15	0.19	
		RRT 1.592			0.23	0.28	0.34	

Table 2 - Stability of Formulation in Example 13

Tests			Specification limits	Zero Time	Time			
					8days	1month	2month	3month
ATRA	Assay		0.09-0.11%	0.106	0.104	0.099	0.094	
	RSD, %		LT 3.0%	0.6	0.8	0.3	0.1	
	Sum of degradation products		collect data	0.51	1.0	1.57	1.91	
	degradation products	RRT 0.25		0.38	0.32	0.24	0.19	
		RRT 0.28						
		RRT 0.56						
		RRT 0.86				0.09		
		RRT 0.921				0.09	0.09	
		RRT 0.935						
		RRT 0.963		0.13	0.09			
		RRT 1.2				0.12	0.2	
		RRT 1.24			0.11	0.23	0.36	
		RRT 1.578			0.2	0.24	0.29	

		RRT 1.592			0.46	0.66	0.77	

Table 3 - Stability of Formulation in Example 14

Tests			**Specification limits**	**Zero Time**	**Time**			
					2w	**1month**	**2month**	**9month**
	Assay		0.09-0.11%	**0.107**	**0.102**	**0.100**		
	RSD, %		LT 3.0%	**0.8**	2.5	0.9		
	Sum of degradation products			**0.44**	**0.6**	**0.7**		
ATRA	**degradation products**	**RRT 0.25**		0.24	0.15	0.21		
		RRT 0.28						
		RRT 0.56						
		RRT 0.86						
		RRT 0.921	collect data	0.1	0.09	0.12		
		RRT 0.935		0.1	0.09			
		RRT 0.963						
		RRT 1.2						
		RRT 1.24						
		RRT 1.52						
		RRT 1.578			0.11	0.16		
		RRT 1.592			0.18	0.24		

Table 4 – Stability of Formulation in Example 15

Tests			**Specification limits**	**Zero Time**	**Time**			
					2w	**1month**	**2month**	**9month**
	Assay		0.09-0.11%	**0.109**	**0.107**	**0.105**	**0.104**	
	RSD, %		LT 3.0%	**0.7**	0.4	0.2	**0.5**	
	Sum of degradation products			**0.35**	**0.8**	**0.88**	**0.93**	
ATRA	**degradation products**	**RRT 0.25**		0.25	0.34	0.27	0.13	
		RRT 0.28						
		RRT 0.56						
		RRT 0.86					0.08	
		RRT 0.921	collect data		0.09	0.12	0.1	
		RRT 0.935						
		RRT 0.963		0.10	0.08			
		RRT 1.2						
		RRT 1.24						
		RRT 1.52						
		RRT 1.578			0.12	0.21	0.26	
		RRT 1.592			0.18	0.28	0.37	

Table 5 – Stability results of Formulations 12-15 (Zero time and 40C)

Formulation	Zero time			40C 1 week			
	Assay	RSD	% degrad prod	Assay	RSD	% degrad prod	% of degrad from t0
Example 12	0.107	0.8	0.42	0.092	1	1.88	**14.0**
Example 13	0.106	0.6	0.51	0.09	0.2	2.8	**15.1**
Example 14	0.107	0.8	0.44	0.098	1.2	0.9	**8.4**
Example 15	0.109	0.7	0.35	0.104	0.9	0.7	**4.6**

Table 6 – Stability Results of Formulations 12-15 (25C)

Formulation	25C 2 weeks				1 month				2 month			
	Assay	RSD	% degrad prod	% of degrad from t0	Assay	RSD	% degrad prod	% of degrad from t0	Assay	RSD	% degrad prod	% of degrad from t0
Example 12	0.103	0.8	0.83	**3.7**	0.099	0.2	1.22	**7.5**	0.091	0.9	1.47	**15.0**
Example 13	0.104	0.8	1.0	**1.9**	0.099	0.3	1.57	**6.6**	0.094	0.1	1.91	**11.3**
Example 14	0.102	2.5	0.6	**4.7**	0.100	0.9	0.7	**6.5**				**100.0**
Example 15	0.107	0.4	0.8	**1.8**	0.105	0.2	0.88	**3.7**	0.104	0.5	0.93	**4.6**

CLAIMS:

1. A process for preparing microcapsules having a core encapsulated within a metal oxide shell, said process comprising:

(a) preparing an oil-in-water emulsion by emulsification of an oily phase comprising at least one active agent and at least one phase changing material, in an aqueous phase, wherein at least one of said oily phase and aqueous phase comprise a sol-gel precursor;

(b) subjecting said emulsion to microcapsule forming conditions; thereby obtaining said microcapsules,

wherein said core of said microcapsules is solid or semi-solid at room temperature and has a viscosity of about 300cP to about 1,000,000cP.

2. The process according to claim 1, wherein said at least one active agent is a pharmaceutical agent or cosmetic agent.

3. The process according to claim 1, wherein said at least one active agent is a dermatological agent.

4. The process according to claim 3, wherein said dermatological agent is selected from anti-fungal agents, anti-bacterial agents, anti-inflammatory agents, anti-puritic agents, anti-psoriatic agents, anti-acne agents, anti-rosacea agents, and any combinations thereof.

5. The process according to claim 4, wherein said anti acne agent is selected from benzoyl peroxide, retenoid, and mixtures thereof.

6. The process according to any one of claims 1 to 5, wherein at least one metal oxide nanoparticle is added to said aqueous phase prior, during or after preparation of oil-in-water emulsion of step (a).

7. The process according to claim 6, wherein said at least one metal oxide nanoparticle is selected from Silica, Titania, Zirconia, ZnO nanoparticles and any mixtures thereof.

8. The process according to claims 6 or 7, wherein said at least one metal oxide nanoparticle has a particle size diameter (d50) in the range of 1-100 nanometer.

9. The process according to any one of claims 6 to 8, wherein the weight ratio between said at least one metal oxide nanoparticle and oily phase is in the range 1:99 to 3:2.

10. The process according to any one of claims 6 to 9 wherein the mole ratio between the metal oxide produced from said sol-gel precursor and said metal oxide nanoparticles is in the range 1:99 to 1:1.

11. The process according to any one of claims 1 to 10, wherein said at least one phase changing material is selected from natural or synthetic paraffin, aliphatic alcohols, fatty acids or any combination thereof.

12. The process according to any one of claims 1 to 11, wherein said at least one phase changing material is in a liquid state in said emulsion.

13. The process according to any one of claims 1 to 12, performed under a temperature wherein said at least one phase changing material is in a liquid state.

14. The process according to any one of claims 1 to 13, further comprising a step of cooling the obtained microcapsules to room temperature.

15. The process according to any one of claims 1 to 14, further comprising adding a metal oxide salt to said aqueous phase prior, during or after emulsification of step (a).

16. The process according to claim 15, wherein said metal oxide salt is selected from sodium silicate, potassium silicate, sodium titanate, potassium titanate, sodium zirconate, potassium zirconate, and any mixtures thereof.

17. The process according to any one of claims 1 to 16, further comprising adding a binding or cross-linking additive selected from a polymeric agent, a di- or trivalent metal salt, a polyelectrolyte, and mixtures thereof, to said aqueous phase prior, during or after emulsification of step (a).

18. The process according to claim 17, wherein said polymeric agent is selected from sodium alginate, polyvinyl alcohol, carboxymethyl cellulose, polyvinyl pyrrolidone, and mixtures thereof.

19. The process according to claim 17, wherein said di- or trivalent metal salt is selected from aluminum sulfate, sodium aluminate, sodium borate, calcium chloride, and mixtures thereof.

20. The process according to claim 17, wherein said polyelectrolyte is selected from Polyquaternium-7, Polyquaternium-1, Polyquaternium-10, Chitosan, Polylysine and mixtures thereof.

21. The process according to claim 1, wherein said oily phase comprises a sol-gel precursor.

22. The process according to claim 1, wherein said sol-gel precursors are selected from metal alkoxide monomers, semi-metal alkoxide monomers, metal ester monomers, semi-metal ester monomers and from monomers of the formula $M(R)_n(P)_m$, wherein M is a metallic or semi metallic element, R is a hydrolysable substituent, n is an integer from 2 to 6, P is a non polymerizable substituent and m is an integer from 0 to 6, a partially

hydrolyzed and partially condensed polymer of any of the above, and mixtures of any of the above.

23. The process according to claim 22, wherein said metallic or semi metallic element is selected from Si, Ti, Zr, Al, and Zn.

24. The process according to claim 22, wherein said sol-gel precursors are selected from silicon alkoxide monomers, silicon ester monomers, monomers of the formula $Si(R)_n(P)_m$, where R is a hydrolysable substituent, n is an integer from 2 to 4, P is a non polymerizable substituent and m is an integer from 0 to 4, a partially hydrolyzed and partially condensed polymer of any of the above, and mixtures of any of the above.

25. The process according to claim 24, wherein said silicon alkoxide monomer is selected from tetramethoxy silane, tetraethoxy silane, and mixtures thereof.

26. The process according to claim 24, wherein said monomers of the formula $Si(R)_n(P)_m$ are selected from methyl trimethoxysilane, dimethyl dimethoxysilane, and mixtures thereof.

27. The process according to any one of claims 1 to 26, wherein the pH of said aqueous phase is in the range of between 2 to 9.

28. The process according to claim 27, wherein the pH of said aqueous phase is in the range of between 2 to 7.

29. The process according to any one of claims 1 to 28, wherein said microcapsule forming conditions comprise isolation of said microcapsules through procedures selected from at least one of: separation by centrifuge, filtration, evaporation, re-suspension in aqueous medium, and dialysis.

30. The process according to any one of claims 1 to 29 , wherein said microcapsule forming conditions comprise altering the pH level of said emulsion to a range of between 2 to 9.

31. The process according to any one of claims 1 to 30, wherein said microcapsule forming conditions comprise stirring of said emulsion.

32. The process according to any one of claims 1 to 31, wherein said microcapsule forming conditions comprise drying the obtained microcapsules in suspension.

33. The process according to any one of claims 1 to 32, wherein said microcapsules are stable for a period of between 2 weeks to 2 years at room temperature.

34. The process according to any one of claims 1 to 33, wherein said microcapsules encapsulating said at least one active agent and at least one phase changing material have a viscosity of between 300cP to 1,000,000cP.

35. Microcapsules obtained by the process according to any one of claims 1 to 34.

36. Microcapsules comprising a core encapsulated by a metal oxide shell, wherein said core has a viscosity of between 300cP to 1,000,000cP and comprises at least one active agent and at least one phase changing material; wherein the thickness of said metal oxide shell is in the range 0.1-10 micron; and wherein said shell is obtained from (a) metal oxide nanoparticles, and (b) a hydrolyzed and polymerized sol gel precursor.

37. The microcapsules according to claim 36, wherein said at least one phase changing material is selected from natural or synthetic paraffin, aliphatic alcohols, fatty acids or any combination thereof.

38. The microcapsule according to claims 36 or 37, wherein said at least one active agent is selected from a pharmaceutical agent, a cosmetical agent and an agrochemical agent.

39. The microcapsules according to claims 36 or 37, wherein said core comprises a dermatological agent.

40. The microcapsules of claim 39, wherein said dermatological agent is selected from anti-fungal agents, anti-bacterial agents, anti-inflammatory agents, anti-puritic agents, anti-psoriatic agent, anti-acne agents, anti-rosacea agents, and any combinations thereof.

41. The microcapsules of claim 40, wherein said anti-acne agent is selected from benzoyl peroxide, retenoid, and mixtures thereof.

42. The microcapsules according to any one of claims 35 to 41, wherein said microcapsules are stable for a period of about 2 weeks to about 2 years at room temperature.

43. A composition comprising microcapsules according to any one of claims 35 to 42.

44. Use of a composition according to claim 43 for treating a surface condition in a subject, wherein said composition if formulated for topical administration to said subject.

45. Use of a composition according to claim 43 for the manufacture of a medicament for treating a surface condition in a subject, wherein said composition if formulated for topical administration to said subject.

46. The use of claim 44 or 45, wherein said surface is skin or mucosal membrane.

47. The use of claim 44 or 45, wherein said surface condition is a skin disease, disorder or condition selected from acne, infection, inflammation, puritis, psoriasis, seborrhea, contact dermatitis, rosacea, and a combination thereof.

48. A composition according claim 43, for the treatment of a disease, disorder or condition selected from acne, infection, inflammation, puritis, psoriasis, seborrhea, contact dermatitis, rosacea, and a combination thereof.

49. Use of microcapsules according to claim 35 to 42, for the preparation of a topically administered composition.

50. The use according to claim 49, wherein said composition is for the treatment of a disease, disorder or condition selected from acne, psoriasis, seborrhea, contact dermatitis, infection, rosacea, inflammation, and a combination thereof.