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Si-based inorganic microencapsulation

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1 Introduction

Microencapsulation is a process of enclosing micrometer-sized particles of solids, liquids or gases in an inert shell, which serves to isolate and protect the particles from the external world [1]. The first microencapsulation process was invented in 1953 by B.K. Green and L. Schleicher [2] working in the laboratories of the National Cash Register Company, as a way to encapsulate leuco dyes for carbonless copy paper (CCP). Since then, many encapsulation methods have been developed:

- Physical: for example pan coating, air suspension coating, centrifugal extrusion, vibration nozzle and spray-drying.
- Physicochemical: e.g. ionotropic effects, gelation or coacervation.
- Chemical: for example *in situ* polymerization, matrix polymerization, interfacial polycondensation or interfacial crosslinking.

Today, predominantly organic materials, such as, gelatin, formaldehyde-urea, polyurea, polyacrylates, polystyrene, polysaccharides etc., are used to encapsulate actives of interest within a core-shell type microcapsule or a matrix microsphere. A short history of organic based microencapsulation technology has been compiled by C. Thies [3] and key milestones are shown in Table 1.

Table 1 Key milestones in physicochemical microencapsulation technology.

Year*	Inventor/Company	Wall Chemistry	Ref
1953	Green/NCR	Simple coacervation of gelatin with sodium sulfate	[2]
1953	Green and Schleicher/NCR	Complex coacervation of gelatin with gum arabic	[4]
1962	Miller and Anderson/NCR	Ethylcellulose/polyethylene wax with hot cyclohexane	[5]
1962	Ruus/Moore	Polyester, polyamide, polyurea,	[6]
1962	Vrancken/Gevaert	W/O/W microcapsules	[7]
1963	Mackinney/IBM	Interfacial polycondensation	[8]
1965	Chang/McGill University	Nitrocellulose	[9]
1965	Morgan/DuPont	Polyamide	[10]
1966	Matson/3M	Urea with formaldehyde (aminoplast)	[11]
1968	Vandegaer/Pennwalt	Polyurethane, polyurea, polyester, polycarbonate	[12]
1978	Scher/Stauffer	Polyurea produced in the oil dispersed phase	[13]
1979	Beestman/Monsanto	Polyurea and lignosulfonate emulsifiers	[14]
1981	Lim/Virginia University	Cell encapsulation with alginate and poly-L-Lysine	[15]

Prior article date.

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Until the end of the 20th century, the biggest microcapsules consumers were the CCP and agrochemical markets. The commercial decline of the former forced the development of new opportunities. Today microencapsulation is regaining interest by providing innovative solutions for fragrance-controled release in household care, self-healing in coatings, drug delivery in health care, adhesives in automotive etc.

Despite the various organic chemistries available to encapsulate, technical gaps such as shell permeability, mechanical strength, chemical stability, limited functionalization, poor toxicological profile and high cost in use are still frequent and unacceptable for some markets.

Interestingly, metal alkoxydes in general, and silicon alkoxides, in particular were never considered for microencapsulation purposes before the late 1980s. Silicon alkoxides have considerable advantage vs. other metal alkoxides in terms of cost and control of the rate of hydrolysis and condensation reactions. The genesis of Si-based inorganic microencapsulation finds its roots in the usage of surfactants that template the formation of metal oxides layers around their hydrophilic heads. Beck et al. [16] were the first group building ordered mesoporous material (MCM-41) from surfactant templating in alkaline conditions (Figure 1).

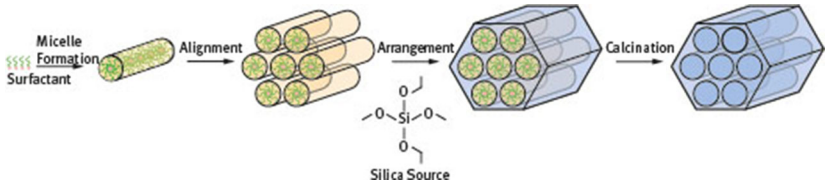

Figure 1: Synthesis of mobile composition of matter 41 (MCM-41). Source: Hermann Luyken.

The missing link between surfactant templating and microencapsulation was found by G.D. Stucky et al. in 1996 [17]. They combined long-range O/W emulsion and O/W interface physics with the shorter range cooperative assembly of silica and surfactants at the O/W interface to create ordered composite mesostructured phases that are also macroscopically structured. They also used acid-prepared mesostructures synthesized from very acidic solutions below the pH of the isoelectric point of silica. The oil phase comprised of a volatile organic compound (mesitylene) and tetraethyl orthosilicate (TEOS). They suggested a model for the formation of the shell where TEOS contained in the oil droplet is hydrolyzed under acidic condition at the interface and forms the mesostructure under the influence of the surfactant. This was the very first *in situ* way, i.e. mixing the active with shell precursors before emulsification to make silica-based core-shell microcapsules and, after mesithylene removal, silica hollow spheres. However, for that group, microencapsulation was not the ultimate goal but only a step before calcination to ultimately obtain highly structured mesoporous materials.

2 Chemistry

2.1 The water glass process

Sodium silicate, also known as water glass or liquid glass, are compounds with the formula $Na_2(SiO_2)_nO$. They are available in liquid or solid forms and obtained from sodium carbonate and silica (eq. 1).

$$Na_2CO_3 + SiO_2 \rightarrow Na_2SiO_3 + CO_2 \quad (1)$$

Its main applications are in detergents, paper, water treatment, and construction materials. Many authors are using sodium metasilicate, Na_2SiO_3, as a precursor to encapsulate actives into silica in the presence of a strong acid (eq. 2).

$$\text{Active} + Na_2SiO_3 + HCl - (x-1)\,H_2O \rightarrow \text{Active} + SiO_2 \cdot xH_2O + 2\,NaCl \quad (2)$$

This route is widely used and is very cost effective, but has major constraints in terms of pH and pI and can be a fatal flaw for biological stability.

3 The sol–gel process

More expensive, but more versatile and controlable than the water glass route, the so-called "sol–gel process" has been the topic of countless publications and text books, illustrating the specificity and the complexity of the process [18, 19]. This can be summarized as the hydrolysis and condensation of alkoxysilanes (eq. 3).

$$\text{Active} + \text{Si(OR)}_4 + 2\text{H}_2\text{O} \rightarrow \text{Active} + \text{SiO}_2 + 2\,\text{ROH} \quad (3)$$

Until the end of the 1990s, most of the fundamental understanding has been gained to support the manufacturing of silica gels, aerogels, glasses, organo-modified silicate, ceramics, enzyme immobilization and entrapment, membranes, coatings, etc. in water-depleted conditions. As a result, the sol–gel route found more and more applications as protective and smart coatings, for separative chromatography, catalysis, diagnostics, biotechnology, building waterproofing, optical lenses, restoration and controled release [20]. However, the fundamental understanding of the sol–gel route from metal alkoxides in the presence of a large excess of water was not been a center of interest and there is still a large gap existing today. Indeed, only a few publications can be found about the hydrolysis and condensation of alkoxysilane in an O/W emulsions such that a shell is specifically built at the O/W interface.

In order to obtain the tightest shell material possible with an acceptable toxicological profile and encapsulation kinetic, the usual choice is to start from tetraethylorthosilica (TEOS) instead of tetramethoxysilane (TMOS) as precursor. While TEOS is water-insoluble, its hydrolysis product, the orthosilicic acid ($Si(OH)_4$), is highly soluble in water. The total conversion of TEOS into silica (SiO_2) is sequentially obtained by hydrolysis (a) and condensation (b) in equation 4.

$$\begin{array}{rcl} (a)\ TEOS + 4H_2O & \rightarrow & Si(OH)_4 + C_2H_5OH \\ (b)\ Si(OH)_4 & \rightarrow & SiO_2 + 2\,H_2O \\ \hline \text{TEOS} + 2\,\text{H}_2\text{O} & \rightarrow & \text{SiO}_2 + 4\text{C}_2\text{H}_5\text{OH} \end{array} \quad (4)$$

The use of this chemistry is delicate because the structure and porosity of the silica produced depends on many physical parameters such as temperature, pH, ionic strength, etc. [18]. The hydrolysis and condensation reactions described above are further complicated by the presence of a surfactant to template the silica shell, as well as the presence of a dispersed oil phase in a large excess of water.

Due to its sequential nature, the hydrolysis and condensation of TEOS can follow multiple pathways [18]. From TEOS to silica, no less than 13 different intermediates species belonging to the categories of ethoxysilanes, ethoxysiloxanes or ethoxyhydroxysiloxanes can be generated. Their structures and molecular weights determine the properties of the intermediates (SiO_2 sols) or final products (SiO_2 gels). The pathway starts from TEOS, a water-insoluble liquid that can hydrolyze into orthosilicic acid ($Si(OH)_4$) a highly water-soluble species. Condensation of the ortho-silicic acid leads to higher molecular weight species having reduced water solubility, eventually leading to the formation of precipitates. The water-insoluble condensate is a negatively charged polyelectrolyte at pH values above 4.5, the pKa of silanol [21]. The complete reaction, likewise an emulsion polymerization process, involves at least one phase transfer of the precursor. Because the hydrolysis of TEOS generates ethanol, a good solvent for both TEOS and water, TEOS becomes increasingly soluble into the water/ethanol continuous phase during the hydrolysis process. The three-dimensional (3D) structure of the resulting silica has been found to be dependent on a region in the ternary phase diagram in which the hydrolysis/condensation reaction was conducted.

The pH also influences the relative rates of the hydrolysis, condensation, and dissolution reactions and has been summarized in the familiar Iler graph [18]. It follows from this graph that the condensation rate in solution is at a maximum for pH ranging from 6 to 7 and at minimum for the pH ranging from 1.5 to 2. In alkaline media the condensation rate of silicic acid falls sharply and at pH above 11 a reverse depolymerization or hydrolysis of Si-O-Si bonds takes place. It can be anticipated that this differentiation of the reaction kinetic can lead to differentiated silica structures [22].

A key aspect of this chemistry is the combined impact of pH and ionic strength on the spatial organization of the silica produced [18]. Conducting the hydrolysis and condensation at basic pH and low pI leads to the synthesis of the so-called “Stober” silica [23]. Particles grow in size with a decrease in number leading to a colloidal silica sol of individual spherical nanoparticles. In acid solution or in the presence of flocculating salts, particles aggregate into 3D fractal networks and form gels [18].

Finally silica starts to solubilize at a basic pH of 10 at room temperature [18]. In contrast, silica is stable at very acidic pH which is an asset versus organic shell materials.

4 The main structures and their production process

The purpose of this paragraph is to describe the different processes that researchers have found to encapsulate actives with inorganic materials. The processes of producing hollow glass spheres at temperatures above 500 °C

is not part of this review as no active materials, except some metal oxides, can be usefully encapsulated [24] that way. On the contrary, both "water silica" and "sol–gel" routes are useful for the encapsulation of hydrophilic and lipophilic active materials.

The tracking of patents and publication literature in the field of Si-based inorganic microencapsulation is complex due to the number of terms used by authors to describe inorganic microencapsulation. The most-used attribute to describe the type of inorganic microcapsules is "sol–gel". However, other key words like ceramispheres can be found too. One way to approach the activity in the field is to conduct a literature search on silica microcapsules. As shown in Figure 2, the intellectual property and literature landscape is showing increasing activity which began in industry and is now endorsed by academia.

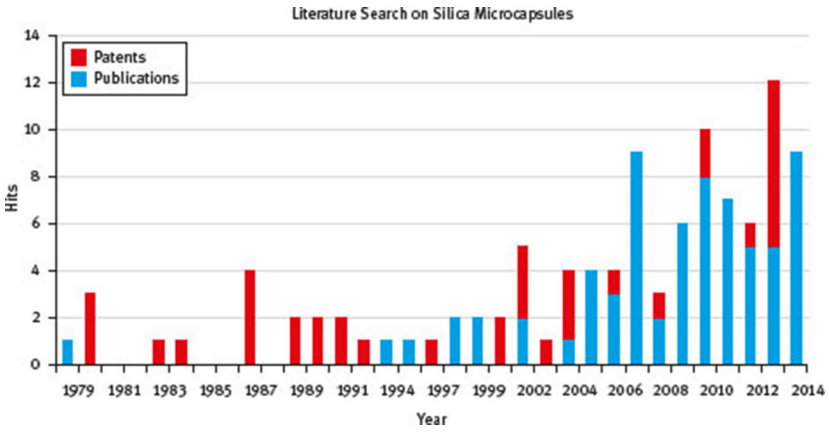

Figure 2: Literature search on "silica microcapsules". Source: Scifinder.

Depending on their production process, microcapsules adopt different types of morphologies. Generally we can distinguish microspheres, core-shell microcapsules, polynuclear microcapsules and hollow spheres (Figure 3).

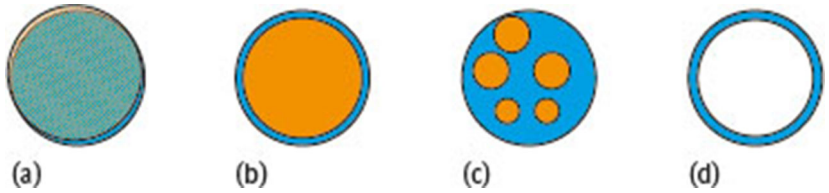

Figure 3: (a) Nano/microsphere, (b) core-shell nano/microcapsules, (c) polynuclear nano/microcapsule, (d) hollow spheres.

5 Active-containing silica microsphere: encapsulation of hydrophilic and lipophilic actives

Microspheres can be broadly defined as submicron spherical polymer particles wherein an active is homogeneously dispersed. Methods of preparation and use of silica microspheres for encapsulation purposes has been mostly reported in academic publications (Figure 4).

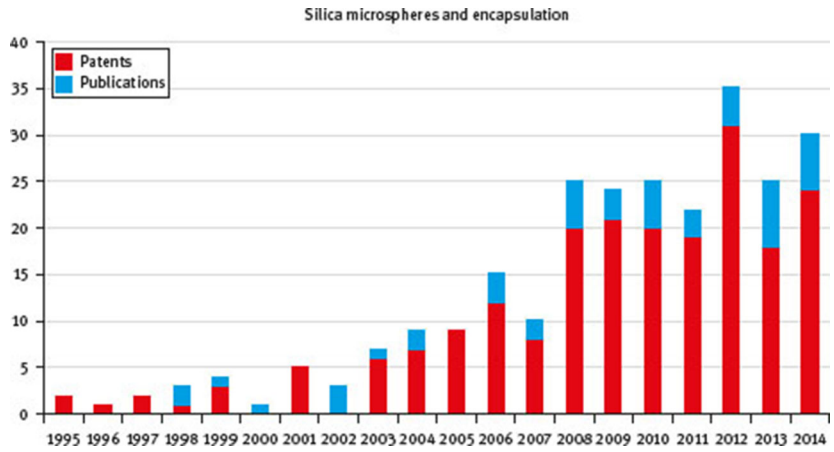

Figure 4: Occurrence of publications in the field of "silica microspheres and encapsulation". Source: SciFinder.

Generally microspheres are the easiest type of microcapsules to produce. The usual method of microspheres preparation consists in first solubilizing or dispersing the active to be encapsulated into the monomer or polymer matrix. Then this mixture is dispersed into an aqueous or an organic solvent phase with or without the help of an emulsifier [25]. However, for making silica microspheres, the phase behavior of precursors leads to different methods. Silica microspheres can be obtained from grinding of monoliths, inverse micelles or water in oil emulsions (W/O).

5.1 Silica microspheres from monoliths

These silica monoliths can be obtained by the "water glass" route or by the "sol–gel" process. The water glass route starts with a liquid sol that generally contains sodium silicate and the hydrophilic active material to be entrapped and leads to gels. The extreme pH starting condition and the final high ionic strength (pI) penalizes the use of that route.

The "sol–gel" route is more robust and less demanding for labile molecules like enzymes or living bodies if the released alcohol can be rapidly eliminated from the reaction environment. First the active is mixed with Si alkoxide precursors and after their hydrolysis and condensation process, a monolith silica or organically modified silica (Ormosil) matrix is obtained [26]. Next, the monolith is ground into microspheres. The main issue with that approach is that the entrapped active can be exposed to the environment and lose its protection. Another constraint of this encapsulation approach is that the molecular conformation of the active can change due to the shrinkage of the xerogel upon the drying process of the wet gel. However, shrinking can be reduced by reducing the amount of silanol-silanol interactions by hydrophobization to obtain an ambigel. Another strategy is the use of supercritical drying by CO_2 at 31 °C and 1072 PSI to obtain an aerogel (Figure 5).

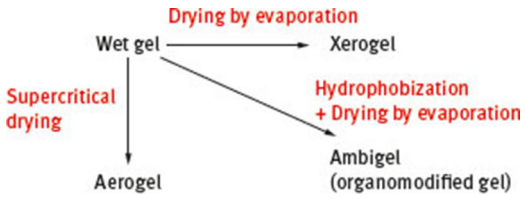

Figure 5: Strategies to reduce shrinkage of wet gels.

The encapsulation of enzymes by this route found many industrial applications in medical diagnostics [27] as biosensors for glucose, cholesterol, urea, lactate, assays, etc. The end-points can be electrochemical or optical. In the former case the gel contains additional conducting particles like graphite, metal powders, mediators or co-reagents and a current is measured. In the latter case the enzymes are labeled with chromophoric or fluorescent groups or a molecule reacting to changes in pH or O_2 levels and a light emission or absorption is measured. The technology is also used for the synthesis of chiral compounds, chromatographic columns, and biocompatible implants and even in ammonia-free hair colorants [24]. However, gels have constraints in terms of loading of active ingredients and the small surface of exchange significantly reduces their controled delivery kinetic. To respond to these limitations, the use of a colloidal delivery system like microspheres attracted attention.

5.2 Silica microspheres from inverse micelles templating

While Nakahara synthesized spherical porous silica particles from nonionic surfactant micelles back in 1978, it was only in 1995 that he applied the preparation method to make active-containing inorganic microspheres [28]. The hydrophilic core materials were released at a rate controled by the size of micropores in the outer wall of microcapsules.

5.3 Silica microspheres from W/O emulsions templating

Another route to entrap water-soluble actives into a silica microsphere is to start from a W/O emulsion, wherein the water phase contains the active to be entrapped and the hydrolyzed Si alkoxide precursors [29]. Pope et al. encapsulated living tissue cells into a silica microsphere in the absence of surfactant. Using surfactant-made W/O emulsions as a template to entrap hydrophilic or hydrophobic actives opens additional features such as smaller and narrower distribution microcapsules sizes as well as higher content in the slurry.

The W/O route to entrap active materials has been extensively studied and patented in 2000 by Barbé et al. [30]. In that process the sol–gel precursors are dispersed into the drug containing water (Figure 6).

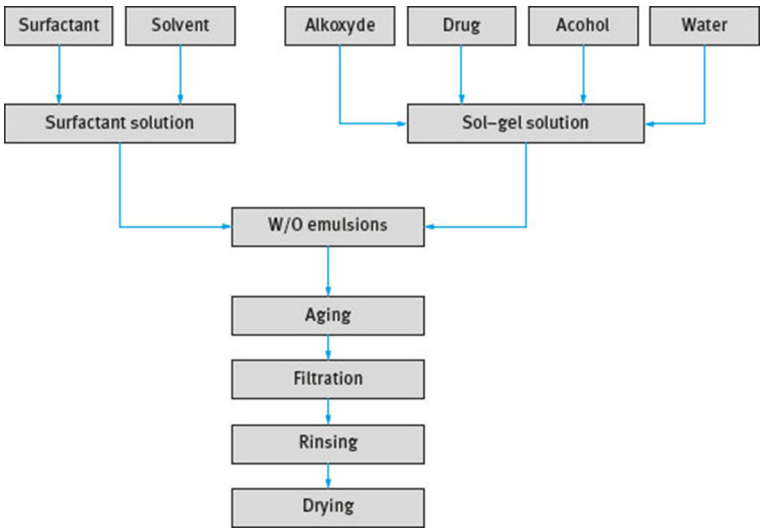

Figure 6: Reproduced from EP 1257259B1 (assignee: ANSTO/Ceramispheres).

Nonionic surfactants with a hydrophilic-lipophilic balance (HLB) fewer than 10 are used to orientate the interface in the W/O direction. When the hydrolysis and condensation of alkoxides occurs in the water phase, a gel, i.e. a tridimensional network of silica or organo-modified silica (Figure 7), will homogeneously entrap the drug in the network.

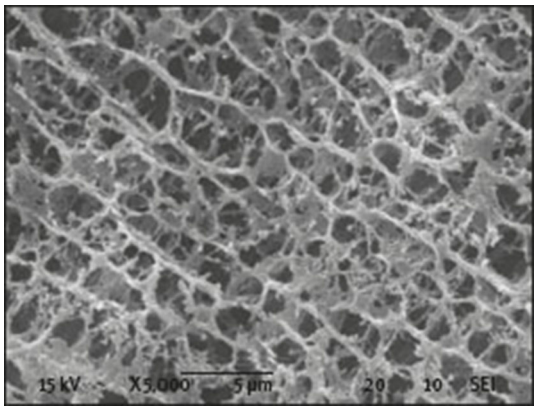

Figure 7: Tridimensional colloidal silica gel network obtained at acidic pH.

The size of the microcapsules can be controled by the amount of water and the solvent/surfactant ratio, such that a size range 10–100 µm is claimed. In a later publication Barbé et al. discovered that at acidic pH, where the hydrolysis rate is fast and condensation is the limiting step, this process leads to homogeneous silica particles

with mesopore sizes 2–6 nm [31]. In basic conditions the limiting hydrolysis step followed by fast condensation produces an in homogeneous system, characterized by large silica micropore size distributions from 3 to 11 nm.

If the hydrolysis and condensation of alkoxides is located at the W/O interface then the process leads to hollow silica or organo-silica spheres. In 2008, Wang and co-workers published a paper describing the direct microencapsulation of two water-soluble model drugs, gentamicin sulfate (GS) and salbutamol sulfate (SS), into silica microcapsules using a sol–gel process and TEOS as precursor in W/O emulsion [32]. The water phase was acidified with an aqueous solution of hydrochloric acid (HCl) and contained Tween 80, GS and SS. The oil phase was a cyclohexane solution containing Span 80. After 24 h of encapsulation the microcapsules have been filtrated and washed with cyclohexane. The silica microcapsules were uniform spherical particles with a size range of 5–10 μm, and had a specific surface area of about 306 m^2/g. *In vitro* release behavior of drugs in simulated body fluid revealed that the system exhibited excellent sustained release properties.

6 Core-shell micro and nanocapsules from O/W emulsions templating: encapsulation of lipophilic actives

After the first publication Stucky et al. [17] describing the use of O/W emulsions to template the building of water-insoluble liquid-containing core-shell microcapsules by mainly industrial developments took place to encapsulate lipophilic actives up to 2002 before being endorsed by academics (Figure 8).

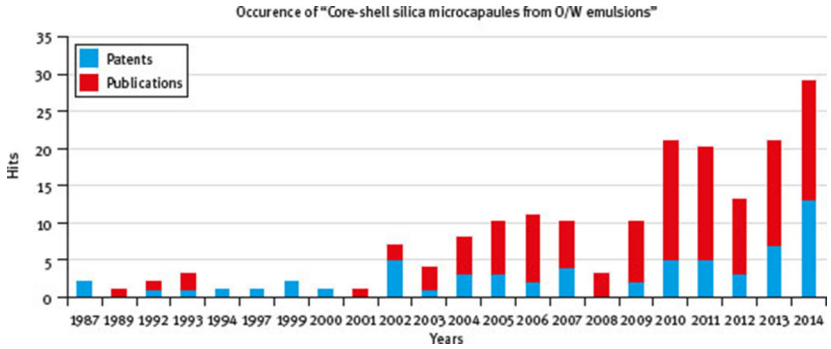

Figure 8: Occurrence of publications in the field of "silica microspheres and encapsulation". Source: SciFinder.

In February 1998 Yoshioka et al. encapsulated organic sunscreens by using surface-active hydrolyzed protein functionalized silanes [33]. No surfactant templating per se was used, instead the surface-active silanes play both the role of emulsifier and shell precursor and formed a capsule after the hydrolysis and condensation at the active/water interface.

One month later, Dauth et al. filed a patent [34] describing the encapsulation of a nonionic surfactant stabilized emulsion. However, they obtained poor microencapsulation yields from 38 to 87%.

In August 1998, Sol-Gel Technologies Ltd., a spin-off of the Hebrew University of Jerusalem, filed a patent application for a process of making sol–gel microcapsules [35]. The process consists of blending the lipophilic active to be encapsulated with sol–gel precursors to make core-shell microcapsule (Figure 9).

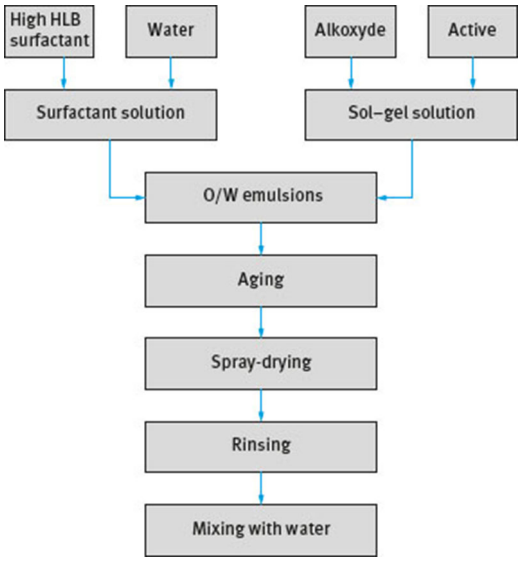

Figure 9: *In situ* process of making core-shell microcapsules. (Reproduced from US 6303149B1.)

This technique is useful for the entrapment of a water-insoluble liquid material called the dopant. The dopant is first mixed with the sol–gel precursor. The sol–gel solution is first emulsified with the help of cetyltrimethyl ammonium chloride. The volume fraction of the emulsion droplets is in the range of 10%. The hydrolysis and condensation of the sol–gel precursor at the O/W interface is building an amorphous silica shell. The microencapsulation process is first conducted at acidic pH to accelerate the hydrolysis and then the pH is increased to complete condensation. A film-forming polymer like polyvinylpirolidone is added to the suspension. In a third step, the suspension of core-shell microcapsules is spray dried or freeze dried. The microcapsule powder is washed and dispersed in water to obtain a final volume fraction of about 30%. This process is a true sol–gel process in the sense that it goes through a gelation step and the removal of the mother liquor. In this case, one deals with an *in situ* route, i.e. the shell precursors are added into the dispersed phase before emulsification. The hydrolysis and condensation of the alkoxysilane occurs at the O/W interface. Consequently, the shell layers are built from the outside to the inside of the oil droplet.

In 2002, the *ex situ* route, i.e. the shell precursors are added in the continuous phase, was filed by Dow Corning Corporation in EP1471995B1 [36]. This is generated from a positive zeta potential O/W emulsion in a one-step process without gelation and without removal of the mother liquor (Figure 10).

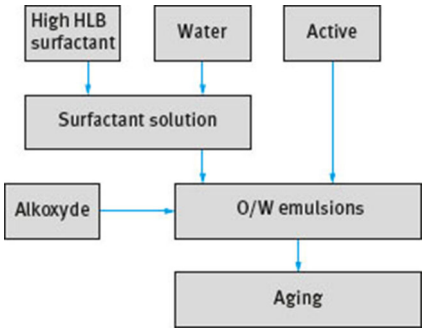

Figure 10: Ex-*situ* process of making core-shell microcapsules. (Reproduced from EP 1471995B1.)

Optionally, the core-shell microcapsules can be harvested in a powdery form by, for example, spray-drying or freeze-drying (Figure 11).

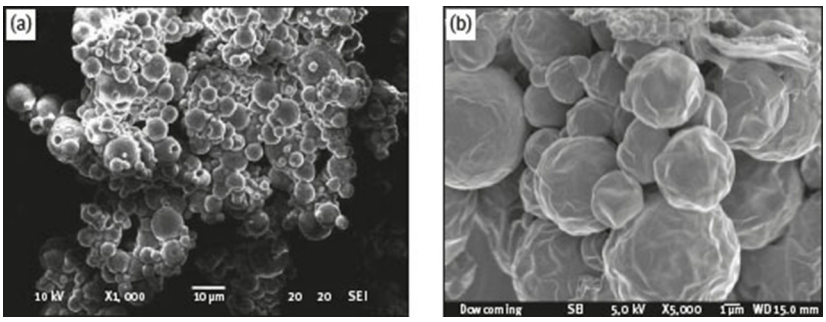

Figure 11: Scanning electron microscope (SEM) of (a) spray-dried (a), (b) freeze-dried microcapsule suspensions.

In 2003, Unitech Co. Ltd., a spin-off of the Korean Reasearch Institute of Chemical Technology, disclosed a process for preparing silica microcapsules [37]. The process is comprised of the following steps: (i) dissolve TEOS into an aqueous solution containing a hydrolysis catalyst; (ii) dissolve the active to be encapsulated; and (iii) add aminopropyltrialkoxysilane (APS) as a gelling agent. Then, emulsify in a separate container with the active in a nonionic surfactant in a solution of opposite polarity. This process is a two kettle *ex situ* process with an O/W cationic interface provided by the APS. The exemplified actives are UV sunscreens.

In March 2005, Aquea Scientific corporation disclosed body wash compositions containing cationic *in situ* sol–gel microcapsules [38].

In 2005, the Australian Nuclear Science & Technology Organization disclosed a process of making particles comprising a releasable dopant [39]. They describe an *ex situ* method using trialkoxysilanes followed by the addition of aminopropyl trimethoxysilane.

In 2007, BASF disclosed UV sunscreens containing microcapsule compositions made by the *in situ* method [40].

In 2008, the company Ets Robert Blondel filed an *ex situ* process using a polymeric cationic emulsifier, claiming a faster microencapsulation kinetic using mixture of formic acid and acetic acid [41].

Still in 2008, Dow Corning disclosed a process for preparing cationic silicate shell microcapsules by adding a water reactive silicon compound to an O/W emulsion, comprising of a tetraalkoxysilane and an alkoxysilane with an amino or quaternary ammonium substituted alkyl group [42]. The purpose is to improve the deposition of the microcapsules onto negatively charged surfaces like textiles fabrics, hair fibres and skin.

Five days later, Microcapsules Technologies disclosed a process of making microcapsules composed essentially from silsesquioxane homo or copolymers [43]. In this application, methyltriethoxysilane (MTES) and methyltrimethoxysilane (MTMS) are used as *in situ* sol–gel precursors optionally in combination with ethylpolysilicate pre-polymers. The O/W emulsion is made from nonionic or anionic protective colloids. The option to use quaternary ammonium is disclosed in the application.

In 2008, IFF disclosed fragrance containing microcapsules obtained by the *in situ* and *ex situ* method [44].

In 2009, Biosynthis basically utilized the same process of making microcapsules as Microcapsules Technologies, but added polyquaterium 80 at the end, a silicone-based quaternary ammonium acetate ABA copolymer to reduce skin permeation of organic sunscreens [45].

In July 2009, Altachem disclosed an *ex situ* method for the preparation and the use of leach-proof microcapsules [46]. The inventor found that the partial alkylation of the silica shell from 2% to 25% improves the imperviousness of the benzoyl peroxide (BPO) catalyst containing microcapsule useful for the preparation of one component PU foam.

In July 2009, the CNRS filed a method for preparing core-shell materials and the use thereof for the thermos-stimulated generation of substances of interest [47]. The core material predominantly contains crystallizable oil, having a melting temperature below 100 °C, emulsified with the help of amphiphyle nano-silica. The Pickering emulsion obtained is further encapsulated with TEOS at strongly acidic pH of 0.2 in presence of cetyltrimethylammonium chloride.

In 2009, Sol-Gel Technologies Ltd. filed a patent disclosing the use of metal alkoxide nanoparticles, typically Ludox®™ 50, colloidal silica along with a sol–gel precursor to make thicker and therefore more impervious shell walls [48]. Ludox®™ 50 colloidal silica particles have a nominal particle size of 22 nm and are negatively charged.

In 2010, BASF disclosed a patent describing the microencapsulation of fragrances, perfumes or flavors first dissolved in paraffin or polyvinylether waxes [49]. The blend is later mixed with sol–gel precursors and emulsified. This *in situ* process is making core-shell microcapsules that have a payload smaller than 80%, wherein the core material comprises at least one fragrance, perfume or flavor and the shell at least one inorganic/hybrid material.

Still in 2010, the University of Tours François Rabelais patented an improvement of the shell imperviousness compared to the Robert Blondel's process [50]. This is obtained by (i) emulsifying the active-containing oil phase in an acidic aqueous phase at 50 °C, (ii) increasing pH, (iii) decreasing pH and (iv) finally increasing the pH to obtain a better condensation. Optionally, a hydrolyzed silane can be added before the last pH increase to form double layer shells.

In 2011, Givaudan filed an *ex situ* route to encapsulate perfume [51]. In order to confer positive zeta potential to the O/W interface, aminopropyltriethoxysilane is systematically added.

In 2012, Les Innovations Materium filed an *in situ* process able to build thick silica or organo-modified shells from 50 nm to about 500 μm [52]. The templating can be achieved by a nonionic surfactant like polyoxyethylene (20) sorbitan monooleate. The shell can be further functionalized by a trialkoxysilane.

7 Core-shell micro and nanocapsules from O/W/O emulsions templating: encapsulation of lipophilic actives

In 2006, Barbé and co-workers disclosed a process of preparing particles with hydrophobic material therein [53], using an O/W/O multiple emulsion. The hydrophobic material to be encapsulated is micellized in high HLB surfactants like Tween 21®. The swollen micelles are mixed with the hydrophilic phase containing the sol–gel precursor. Low HLB surfactants like Span 80 are used to emulsify the O/W emulsion into cyclohexane. After the ageing, i.e. the complete hydrolysis and condensation of the sol–gel precursors, the O/Silica/Cyclohexane suspension is filtrated and the recovered microcapsules washed with NaCl and water solutions.

8 Core-shell micro and nanocapsules from W/O/W emulsions templating: encapsulation of hydrophilic actives

Because of the limited surfaces developed by sol–gel monoliths, they found limited industrial applications wherein transformation rates are critical. One way to meet this requirement is to significantly increase the interfacial exchange surface between the biocatalyst and its substrate medium. An option is to microencapsulate the hydrophilic active into a nano or microcapsule in suspension in the substrate media. One solution could be a W/O/W multiple emulsion as the template. However, W/O/W multiple emulsions are very unstable. Indeed, on top of the intrinsic entropic instability of emulsions they have to face an osmotic pressure gradient between the internal and the external water phases. One way to mitigate the later is to increase the elastic modulus (G′) of the oil phase.

In 2006, Nakahara et al. [54] disclosed a method of making hollow silica particles via the water glass route, comprising of a silicon shell with macropores starting from a W/O/W emulsion. The internal water phase is composed of water-soluble silicates and the actives to be encapsulated and is emulsified into a continuous oil phase. The obtained W/O emulsion is further emulsified into a water external phase. Huge bio-molecules, cells, or viruses can be included and claimed to be preserved for a long time in the hollow particle.

Another approach disclosed by Dow Corning Corporation [55] is to use sol-gel precursors like alkoxysilanes as the initial oil phase. They start from a W/Alkoxysilane/W multiple emulsion and end with a W/silica or organo-modified silica/W polynuclear microcapsule suspension (Figure 12).

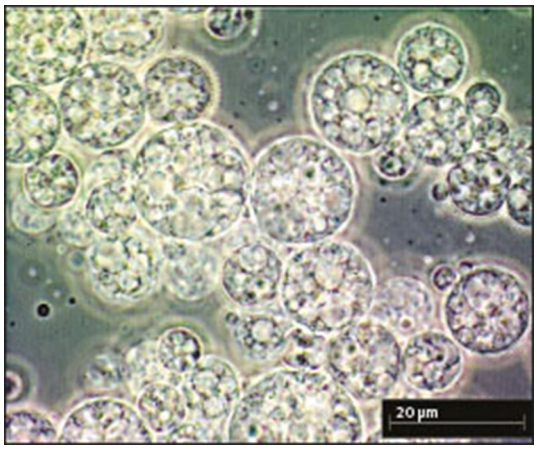

Figure 12: W/Silica/W polynuclear microcapsule suspension.

The inventors describe the use of this process to encapsulate biocatalysts. The internal water phase contains the biocatalyst, preferably water-soluble enzymes and its co-factor, and the external phase, the substrate. The goal is that the polynuclear microcapsule is acting as a microbioreactor, wherein the substrate can diffuse in the internal water phase and be transformed by the biocatalyst in a product that can diffuse out to the external water phase. The internal water phase contains *Aspergillus niger* catalase, an oxido-reductase enzyme, catalyzing the transformation of hydrogen peroxide into water and oxygen (eq. 5):

$$\begin{array}{rl} H_2O_2 + FE\,(III) - C & \rightarrow \; H_2O + O = Fe\,(IV) - C \\ H_2O_2 + H_2O + O = Fe\,(IV) - C & \rightarrow \; O_2 + Fe\,(III) - C \\ \hline 2H_2O_2 & \rightarrow \; 2O_2 + O_2 \end{array} \tag{5}$$

Catalase contains four sub units of polypeptide chains and four porphyrin hemes for a total Mwt. of about 345,000 g/mole (Figure 13). Its Stokes radius is 5.83 +/−0.49 nm. Its reaction rate is only limited by substrate diffusion allowing ~200.000 reactions/s.

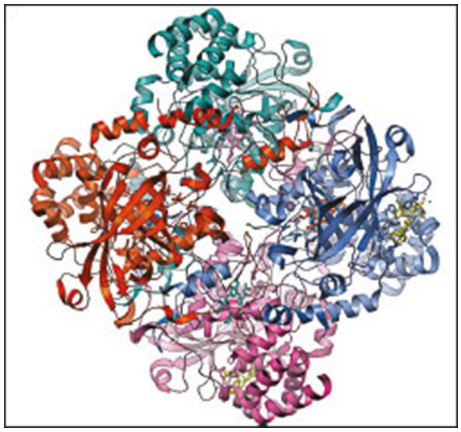

Figure 13: Catalase from human erythrocyte. Source: Vossman.

The authors observed non-measurable loss of catalase from the internal water to the external water phase upon ageing. All the microencapsulated catalase was fully encapsulated at pH 4, 7 and 8.9. The enzymatic activity of the suspensions obtained at pH 4, 7 and 8, 9 have been monitored upon shelf life. The inventors found that the microencapsulation of catalase from *A. niger* into silica polynuclear microcapsules extends its half-life time from 2 weeks RT to 1 year RT.

9 Triggers

The technical potential and utility of a microencapsulation technology resides in the triggers that can be used to release the encapsulated active. Silica and organo-modified silica have, in that respect, many advantages vs. organic shell materials. Some triggers developed in this chapter are useful for the delivery of actives from all type of Si-based nano and microcapsules. Others are specific to core-shell structures.

10 Trigger mechanisms for breaking capsules

10.1 Shear

Shear sensitivity of microcapsules is mainly correlated to their sizes and their mechanical strength. The latter depends, among other parameters, on the payload, the viscosity of core material and the mechanical strength of the shell material. It is generally acknowledged that microcapsules with sizes below 10 μm are not shear-sensitive. Using shear as a trigger is therefore easily accomplished, providing that large microcapsule sizes are acceptable in the application. One illustration of this phenomenon can be observed under an optical microscope with a vitamin A palmitate containing microcapsules suspension. The compression of the cover slip breaks the microcapsules standing between the microscope slide and the cover slip (Figure 14).

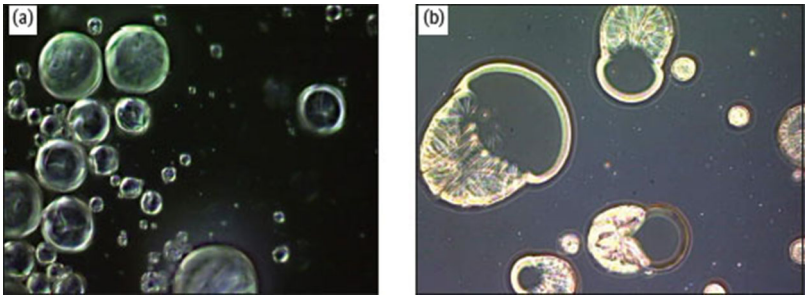

Figure 14: Vitamin A Palmitate containing microcapsules (a) before and (b) after glass slides compression (average microcapsule size = 60 μm).

10.2 pH > 10 (silica dissolution)

The silica dissolution at basic pH [18] can be used as a trigger mechanism to release an active. Such a trigger can be used in cementitious matrices in the construction industry.

10.3 Osmotic pressure

In colloidal systems at equilibrium, such as microcapsule suspensions, chemical potentials always tend to equalize. Because of the chemical composition difference between each side of the microcapsule shells, the overall chemical potential must be compensated by the osmotic pressure. The later can be stronger than the mechanical resistance of the shell. Depending on the gyration radius of the active molecule, the silica shell porosity can be designed as an impervious, semi-permeable or permeable membrane.

When a low Mwt solvent is added to the suspension of microcapsule core material and continuous phase, the solvent is able to diffuse quickly through the shell and burst the microcapsule rapidly. As observed (Figure 19) this can be done with the use of ethanol in an organic sunscreen containing microcapsule suspension. Indeed, ethanol does fulfil the requirements for microcapsule breakage by osmotic pressure as it is a smaller molecule than the silica shell pores estimated in the range ~2–3 nm and soluble in both water and the organic sunscreen. For instance, post-addition of only 10% ethanol to porous ethylhexylmethoxycinnamate (EHMC) containing silica shell microcapsule leads to a significant leakage of the encapsulated EHMC as measured by dialysis (Figure 15).

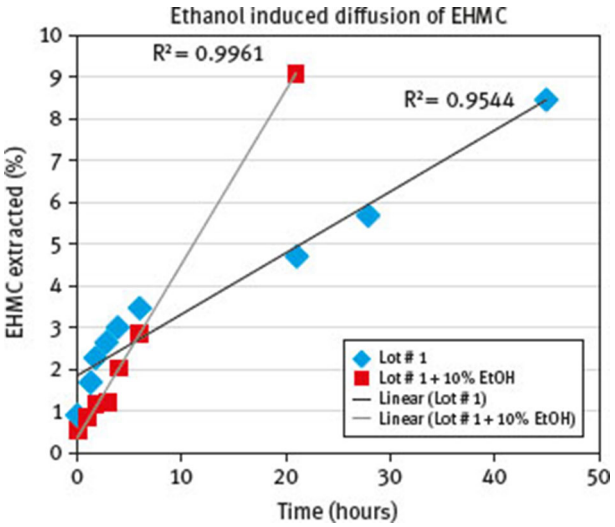

Figure 15: Impact of a post addition of EtOH to core-shell microcapsule suspension.

11 Specific to core-shell nano and microcapsules

11.1 Drying of the microcapsule suspension

The drying of the microcapsule suspension by evaporation of the continuous hydro-alcoholic phase is a very useful trigger. The drying process leads to the concentration of the core-shell microcapsules until their close packing and aggregation (Figure 16). At that stage a Laplace pressure due to the capillary forces occurring between them can be stronger than the mechanical strength of the silica or organo-modified silica shell. In that case the drying ends with the breakage of the shell and the release of the encapsulated active.

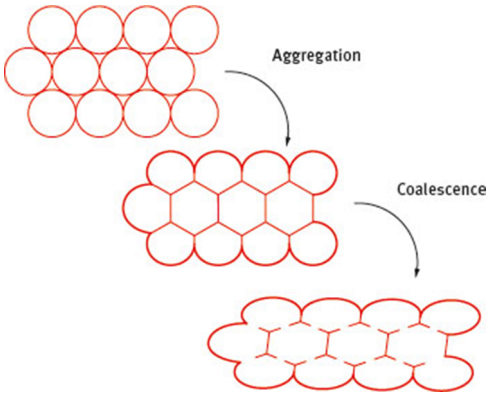

Figure 16: The coalescence process.

The process can be easily observed under an optical microscope (Figure 17).

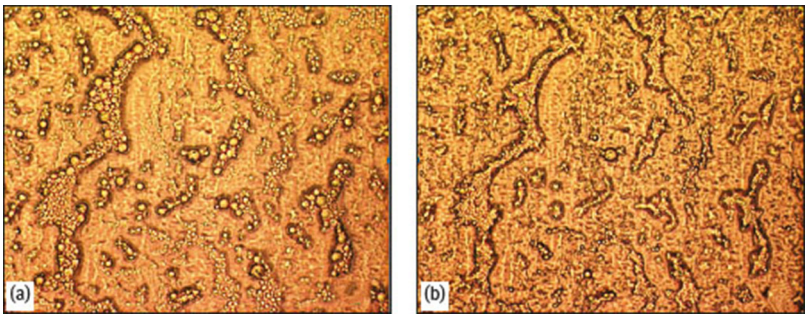

Figure 17: Coalescence of core-shell microcapsules from O/W emulsion (a) before and (b) after drying of a 120 μm film on glass.

This concept has been further developed by the Dow Corning Corporation [56], where curable compositions have been separately encapsulated in silicate shell microcapsules and mixed together as a one part water-based slurry. The latter shows extended bath-life times and when it dries, the two compositions react to form a cured siloxane composition.

11.2 Heat

Another important trigger that can be used in different settings is heat. As metal oxides in general, and silica in particular, have high T_g in the range of 520–600 °C [32] they are not able to melt at low temperatures like waxes or low T_g organic polymers.

Another patented [57] strategy for rendering the microcapsules heat sensitive is to co-encapsulate the active of interest with a "blowing aid" that has a low boiling point (Figure 18a). As expected, the burst temperature of the microcapsule, measured by headspace GC/MS, depends on the vapor pressure of the blowing aid and is thus strongly correlated to its boiling point, i.e. the temperature the co-encapsulated blowing aid starts to boil at atmospheric pressure (Figure 18b).

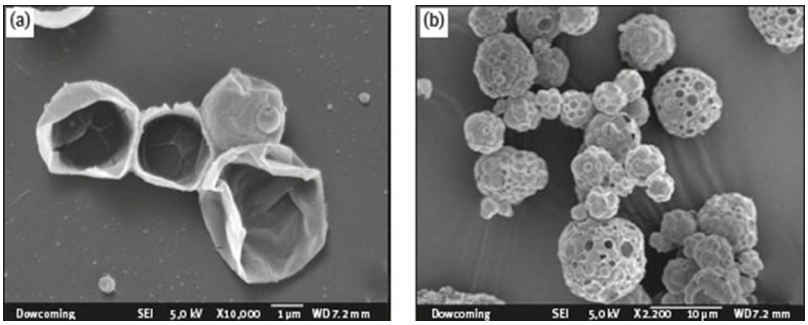

Figure 18: Scanning electron microscope (SEM) imaging of burst core-shell microcapsules containing (a) hexamethyldisiloxane and (b) vinylterminated polydimethylsiloxane in scanning electron microscope (SEM).

11.3 Good solvents

If the silica shell porosity is designed such that the core material can diffuse throughout it, then a passive diffusion can be triggered by the presence of a good solvent for the core material. One example to illustrate that trigger is the extraction of microencapsulated ethylhexylmethoxycinnamate, a UV-B sunscreen, from a core-shell microcapsule aqueous slurry by light mineral oil (Isopar L) by dialysis. As anticipated from a core-shell microcapsule, EHMC shows a zero order controled delivery kinetic (Figure 20).

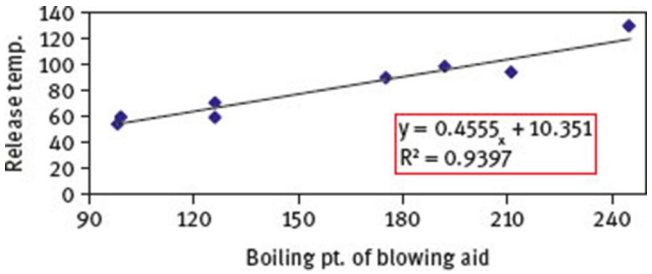

Figure 19: Correlation between burst temperature and the boiling point of blowing aid.

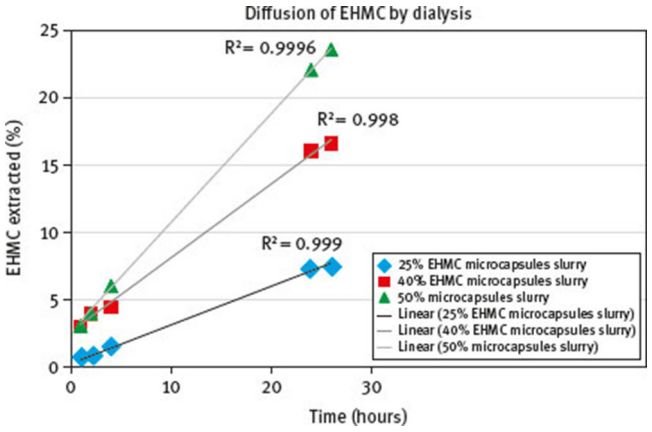

Figure 20: Zero order delivery of EHMC from core-shell aqueous slurry induced by mineral oil in a dialysis device.

11.4 Sonication

Sonication, in addition to a low Mwt. good solvent for the core material, is a common method used to break microcapsules and quantitatively recover their content. Sonicating for about 15 min with an ultrasonic probe like Bioblock Scientific, 88169, Type T460H at a HF-Frequency of 35 kHz, leads to the complete breakage of the shell.

11.5 Vacuum

Even though using vacuum is not considered as a common trigger, microcapsules have been shown to burst following application of vacuum.

12 Industrial examples

12.1 Core-shell microcapsules from O/W emulsions

12.1.1 Sun protection

The first commercial application for silica-based microcapsules was to encapsulate organic sunscreens (OS). OS have an unpleasant greasy feel and there is a need to prevent direct contact between the skin and potentially

irritant OS. As they are well known to penetrate the skin, entrapping them into a larger object significantly reduces the risk of percutaneous permeation [33]. More specifically, the mixture of ethylhexylmethoxycinnamate (EHMC) – the most widely used UV-B sunscreen – and benzyldimethoxybenzoylmethane (BMBM) – the most widely used UV-A sunscreen – is photo instable. All of these technical challenges can be overtaken by a silica-based core-shell microcapsule. Indeed OS are polar oils that are good solvents for organic based polymers and wall material in general. Their dosage level in a sun protection product is in the range 5–15%. As a consequence, only high payload microcapsules like core-shell type can be envisaged. The shell must be thin, to allow a UV beam to cross it and be absorbed by the OS, and impervious at the same time.

In 2002, Seiwa Kasei launched Silasoma, an encapsulated EHMC and BMBM. Microcapsule size is typically 2 μm and they are useful for protecting both skin and hair.

In mid-2002, Merck launched Eusolex® UV-Pearls™ under license from Sol-Gel Technologies Ltd. The Eusolex® UV-Pearls™ product range is composed of Eusolex® UV-Pearls™ OMC and Eusolex® UV-Pearls™ 2292 containing EHMC and preserved with parabens and chlorphenesin, respectively. Eusolex® UV-Pearls™ BO-2 and Eusolex® UV-Pearls™ BO contain a blend of Octocrylene and BMDBM preserved with parabens and chlorphenesin, respectively. Eusolex® UV-Pearls™ suspensions typically contain 40% of OS and microcapsules sizes are typically one micron.

Additional patent applications from key OS manufacturers like DSM and BASF emphasizes the good fit of Si-based microencapsulation for safer sun protection.

12.2 Construction chemicals

The encapsulation in acrylic polymers of phase change materials (PCM) that mitigate brutal temperature change thanks to their enthalpy of fusion, reached the market. Micronal PCM™ from BASF is one example. Zhang et al. used TEOS to encapsulate n-octadecane [58]. They proved by FTIR that a silica shell was successfully built onto the core of PCM material. They synthetised at pH 2.45 PCM microcapsules in the 7–16 μm range. X-ray scattering indicates that the n-octadecane retains a good crystallinity. Thermogravimetric analysis shows that the silica microcapsules have good thermal stability. By controling the loading of the core material and the acidic pH of the reaction solution during the sol-gel process, the silica-microencapsulated PCM can achieve good phase-change performance, high encapsulation efficiency, and good antiosmosis properties. During the cooling process, the authors observed that the silica shell contribute to an improvement of the melting temperature and a widening of phase transition temperature range.

Shi and co-workers assessed in the lab new self-healing materials, called passive smart microcapsules, which hold promise for "crack-free" concrete or other cementitious composites [59]. Cement healing agents and catalysts in methylmethacrylate monomer and triethylborane, respectively, have been encapsulated separately from TEOS in an O/W emulsion. Sulfonated polystyrene particles are used as the template for an interfacial self-assembly process of the TEOS/Core mixture. The microcapsules are then dispersed in fresh cement mortar along with carbon microfibers. Microcapsule breakage is triggered by crack propagation, releasing the healing agent and the catalyst into the microcracks.

Lecomte et al. disclosed two patents covering processes for increasing hydro-phobicity of porous materials, clay, bricks, gypsum or lime substrates [60, 61]. The inventions disclosed the treatment of construction substrates with *ex situ* prepared core-shell microcapsules to provide superior water-repellent performances compared with existing organopolysiloxane or alkoxysilane emulsions. Core materials are orga-nopolysiloxane for porous material treatment and organosilane (e.g. aminoalkylalkoxysilane, octyltriethoxysilane, or tetraalkoxysilane) and a branched siloxane resin for cementitious substrates, clay-based bricks, gypsum-based substrates, lime-based substrates or wood-based substrates.

De Schijver et al. disclosed a method of making hollow mesopous silica spheres containing benzoyl peroxide, a catalyst for two component PU foam. The purpose is to formulate a one component PU foam formulation wherein the encapsulated BPO is released by burstingthe leach-proof organically modified silica microcapsule upon dispensing out of a pressurized can.

12.3 Textiles

Dow Corning Corporation launched the DS 9000 Multifunctional Additive, a polydimethylsiloxane-containing microcapsule suspension for textile treatment obtained by the *ex situ* process. The suspension is claimed to provide the treated fabric with superior hydrophobicity, quick drying, softness and luxurious hand product by cold activation treatment. The treatment is of particular interest to reduce the harshness of flame retardant treated fabrics without impacting their fire resistance (Figure 21).

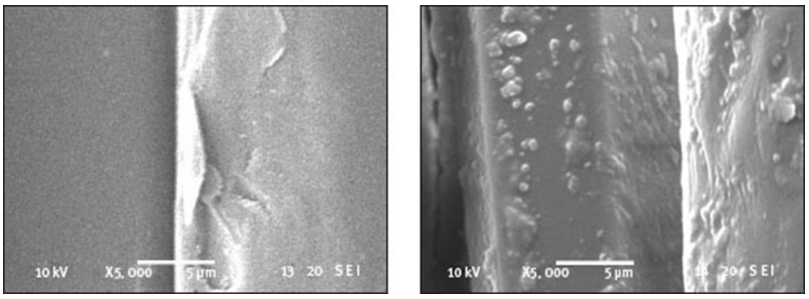

Figure 21: Multifunctional Additive Trevira® CS polyester fibers. (a) Untreated and (b) treated with 40 g/L of DS 9000.

12.4 Pharmaceuticals

Sol-gel Technologies Ltd. is very active in the field of the skin acne and rosacea therapy. Therefore, they use their patented *in situ* process to microencapsulate benzoyl peroxide (BPO) crystals. BPO is a skin irritant and the porosity of the silica shell of the microcapsule is designed to limit its direct contact while controling its delivery. The latter is claimed to be due to a slow dissolution of the BPO crystals by the skin lipids to the sebaceous follicles. A first product, Cool Pearls BPO anti-acne kit, was commercialized in 2009 by a dermo-pharmaceutical company in the U.S. The BPO-based product aimed to treat rosacea obtained positive results in a phase II clinical trial.

13 Core-shell microcapsules from W/O emulsions

13.1 Coatings

Based on US20120085261 [62], Ceramispheres launched Inhibispheres™ submicron particles providing specific functionalities to coating formulations. Active materials, such as corrosion inhibitors, biocides, fungicides, etc., can be incorporated inside sol–gel micro particles that can be mixed into a paint or coating formulation. The particles are shear-resistant and survive most paint processing techniques, such as milling and extrusion and do not adversely affect the key properties of the coating. Both water-soluble and poorly water-soluble active materials can be encapsulated, and Inhibispheres™ provides sustained release of the active from the coating over extended periods of time. Inhibispheres™ are compatible with both solvent- and water-based paint as well as powder coating.

13.2 Fermentation

Biotech applications in general, and in fermentation processes in particular, should attract more attention in the future. In addition to enzyme stabilization [51], the publications demonstrating the interest to microencapsulate living cells and organites by sol–gel precursors are growing fast. For instance Mellati and co-workers [63] used a W/O emulsion wherein living *Saccharomyces cerevisiae* (S.c.) was first mixed with ™OS as a precursor and emulsified into a vegetable oil. Bioactivity of immobilized yeast in microcapsules was investigated by measuring the amount of CO_2 released. The fermentation kinetic expressed by the production of CO_2 by encapsulated yeast increased about 150% more than free yeast. Repetition of the tests has proved that microcapsules saved their bioactivity for a month. Conversely, particle size was decreased from 175 to 110 µm by increasing the mixer rate from 600 to 1200 rpm during gelation and smaller particles showed more bioactivity up to 30%.

14 Key features of Si-based microcapsules

The key features of the main Si-based microcapsules and the most representative organic based microencapsulation technologies are compared in Table 2.

Table 2 Key features of main Si-based microencapsulation technologies vs. main organic ones.

	Complex coacervation	Interfacial polymerization	Urea-formaldehyde	Core-shell microcapsules	Polynuclear from W/O/W
Core					
H_20 soluble solids	No	No	No	No	Yes
Insoluble solids	No	No	SOME	Yes	No
Sherical MICS	THIN CORNERS	Yes	Yes	Yes	Yes
Polar liquids	Yes	No	No	Yes	Yes
Non-polar liquids	No	Yes	Yes	Yes	No
Labiles, e.g. ENZ, fragrances.		Yes	No	Yes	Yes
Gas	No	No	No	No	No
Mic size (μm)	2–200	2–200	2–200	0.2–200	2–200
Wall	Gelatin and arabic gum	PA, pUREA PU, PE, PC	Urea and formaldehyde	Silica or organo-modified	Silica or organo-modified
Melt	No	No	No	No	No
Water-soluble	No	No	No	No	No
Capsules					
Payload over 90 % Size distribution	Yes	Yes	Yes	Yes	
Process	Polydisperse	Polydisperse	Polydisperse	Monodisperse	Monodisperse
Batch/continuous	Batch	Batch	Batch	Both	Both
Largest batch	1000 kg	20 tons		>1 tonne	>1 tonne
Batch time	16 h	10 min – 2 h	1–4 h	<16 h	<16 h
Issues	Aggregation Core wetability. RM cost and supply Process control Gas permeability	Few wall mat. Core wettability Gas permeability	Few wall mat. Aggregation Gas permeability	Gelation gas permeability	Gelation gas permeability
Cannot do	H_2O soluble core Polar liquid Gas	Solid cores Thick walls Melt walls Polar oils Gas pH-sensitive cores	H_2O soluble cores Polar liquids Gas	H_2O soluble cores Gas	Gas
Advantages	In sol. Hydroph-imper. wall Proven process Good barriers	Well developed process Large batches	Well developed process Easy process	Liquid cores Easy process	LIQUID cores
Excellent for	Hydrophobic liquid core Core < 20 MIC	Drop below 20 MIC. Hydrophobic liq. Compl. Insol. Wall Flexible walls	Drop below 20 MIC Hydrophobic liq. Compl. Insol. Wall Thin wall	Labile mat Big part and large walls	Water-soluble actives
Toxicological profile	Glutaraldehydes	Organic monomers	Therm. Stable wall [FORMALDEHYDE] >80 PPM	Ethanol Silica IS Gras by FDA	Ethanol Silica IS Gras by FDA
Energy consumption	Heating (50 °C) and cooling (5 °C)	Cooling or heating	Heating to 55 °C for 2 h;	None	None
Triggers	Shear/pressure	Shear/pressure release Good solvent for wall material	Shear/pressure	Shear/pressure T° drying, good solvents, Vacuum and U.S.	Shear Water T°

Usage	CCP	Pesticides, CCP, insecticides	Pesticides Fragrances Adhesives, CCP	Textiles UV protection	Enzymes

15 Conclusions and perspectives

Inorganic microencapsulation with silicon-based materials obtained by the water glass route or the sol–gel route has unique features. Different types of microspheres, hollow particles, core-shell or polynuclear microcapsules with size ranges from 10 nm to 80 μm can be obtained. Therefore, shear-resistant or shear-sensitive microcapsules can be designed. In the case of porous silica shells, the wide range of reservoir sizes enable the fine controled delivery of active material over an extended period of time. As it can be run at room temperature and neutral pH, the sol–gel route is a mild encapsulation process particularly adapted for volatile compounds and labile molecules like proteins, enzymes and living cells. To complete this environmentally friendly profile, it is worth mentioning that no aldehydes are generated in that chemistry. The hydrolysis and condensation of alkoxysilane has no effect on the molecular structure of organic actives to be protected, which is an asset when active pharmaceutical ingredients are involved. The use of surfactants to template the microcapsules is a way to ensure high encapsulation yield. Basically, all the emulsified actives are encapsulated and the process is very efficient to separate incompatible compounds. The multiple processes that we have reviewed demonstrate the flexibility in the type of actives that can be entrapped. From water-soluble actives like enzymes to apolar oils such as polydimethylsiloxane via polar oils like OS and volatile compounds such as fragrance, the range of active that can be encapsulated seems to be endless. The payload for the core-shell type of microcapsule is usually above 95%. Depending on their molecular weight and the porosity of the shell the encapsulation can be permanent or the active release according to a zero order delivery. In that case the amount of active diffusing out of the shell is constant upon time until the reservoir is nearly empty. Triggers like water evaporation, heat, osmosis, pH, sonication and vacuum can be used to burst microcapsules or to onset active release. The active content in the suspension can reach high solid content in the range of 50%. The limitation is the potential shear sensitivity of the capsules against high viscosity slurries. Finally, the suspensions can be spray or freeze dried to obtain microcapsule in powdery form. All these features put together draw a microencapsulation technology profile which should be taken into account by researchers at the forefront of technological challenges to be overcome.

As the prior article search indicates, and despite the fact that interest is steadily growing, inorganic microencapsulation is still a juvenile topic that is lacking fundamental understanding and deep characterization of the encapsulant material. Indeed, the literature search indicates that encapsulation performances, when assessed, are generally obtained indirectly by a dosage of the released active and/or an overall performance of the material containing the capsules vs. the reference. Too often authors jump from the method of making the capsules to the performance of the final material without a deep characterization of the capsules. There is a need for developing analysis techniques to enabling the study of the molecular architecture of the barrier material *in situ* and online.

Acknowledgments

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