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**Marzia Sciortino, Giuseppe Alonzo,
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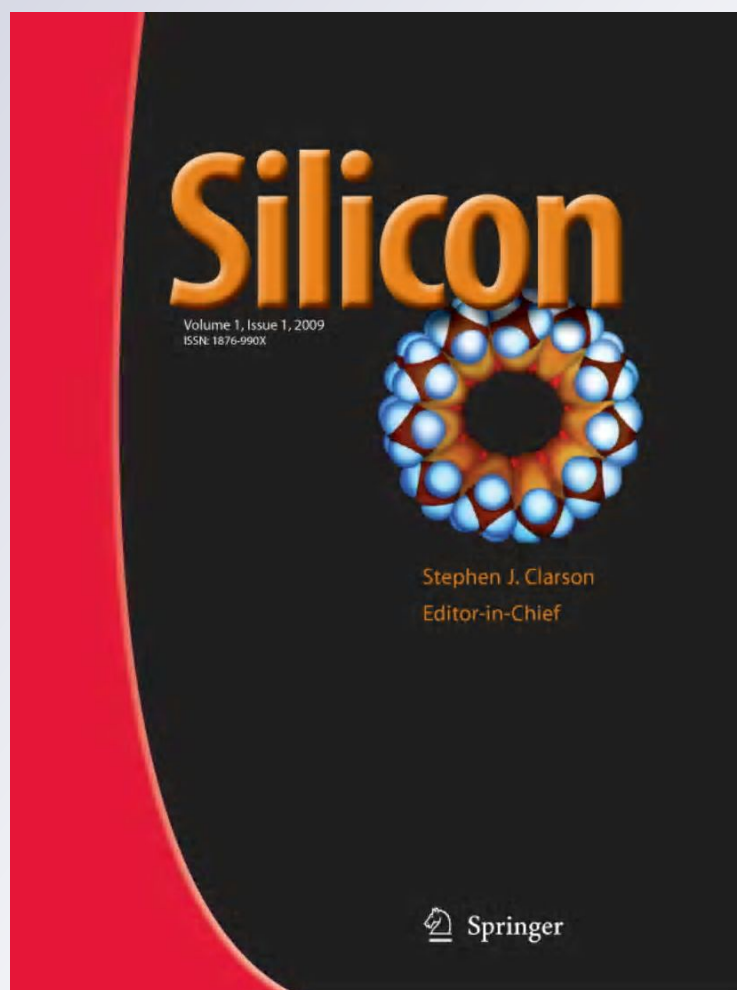
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Sol–Gel Microcapsulation in Silica-Based Particles: A Comparative Study

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Abstract Comparison between the two main sol–gel/emulsion methods to prepare microparticles made of organosilica doped with a lipophilic molecule shows that entrapment only takes place starting from O/W emulsions. In this case, however, formation of spherical microcapsules, observed when the sol–gel polycondensation is carried out in a W/O microemulsion, does not take place.

Keywords Microparticle · Sol–gel · Microencapsulation · Emulsion · Silica · Organosilica

1 Introduction

Silica and organosilica microparticles doped with functional molecules are increasingly important in a number of different applications [1] since in the research of chemical companies new molecules are still important but new effects, new systems and new functional materials are needed [2]. Basically, two main methods exist to produce silica-based microparticles doped with actives. Both use a combined microemulsion/sol–gel process. In one case the sol–gel process is combined with a water-in-oil (W/O) emulsion [3]; and in the other the sol–gel polycondensation is carried out in an oil-in-water (O/W) microemulsion [4].

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In this study we compare the two methods using different solvents and surfactants using in each case benzoyl peroxide (BPO) as an active dopant. In addition, we study the morphology of the resulting particles upon varying the nature of the organosilane and the pH of the sol–gel process. Our aim was twofold: first, to assess how much of a dopant is incorporated and which factors influence the materials structure. Second, to study the effect of the organic modification of the silica surface. The results point to a number of relevant findings of general value.

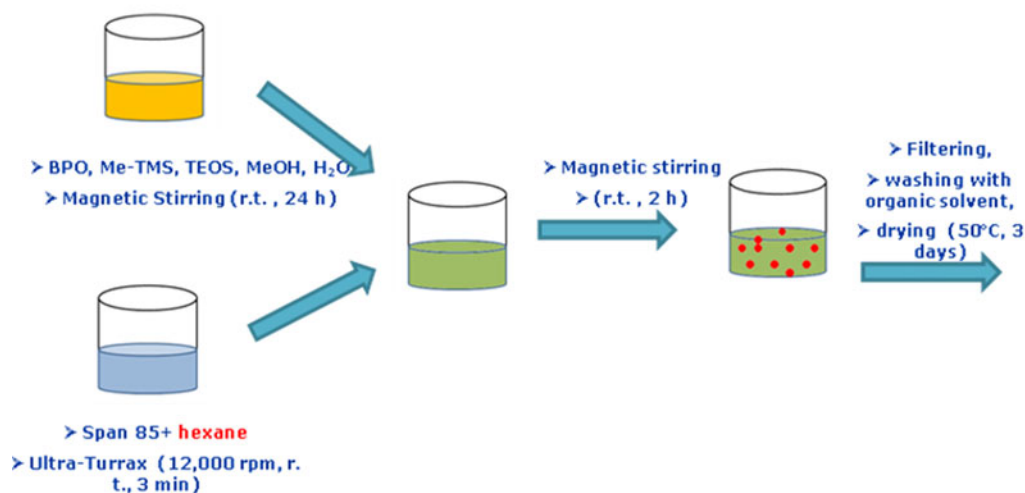
2 Experimental Section

Silica and organosilica materials doped with BPO were prepared by conducting the sol–gel process in W/O and in O/W emulsions (Scheme 1).

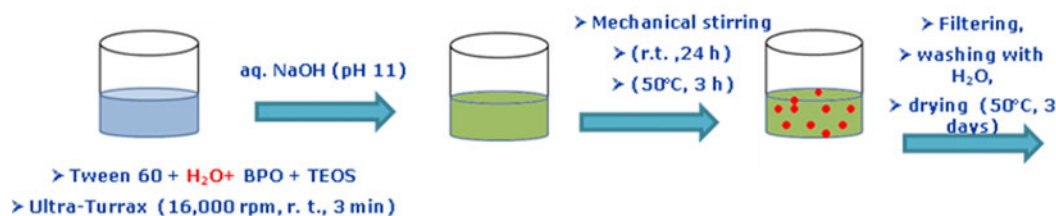
Several organosilica-based particles were first prepared according to the W/O polycondensation methodology, by changing both the organically modified alkoxide and the organic solvent (Table 1). We then prepared SiO₂ and 10% alkyl-modified silica materials under either basic conditions (Table 2) or acidic conditions (Table 3).

All chemicals were purchased from Aldrich and used without further purification. A typical preparation of organosilica doped particles in a water-in-oil (W/O) emulsion was prepared by mixing 50 mg of BPO dissolved in tetraethylorthosilicate (TEOS, 5.00 mL) along with MeOH (1.00 mL) and water (3.50 mL) (Si:MeOH:H₂O = 1:1:8 molar ratio). This mixture was added with methyltrimethoxysilane (MTMS, 350 µl). The resulting solution was stirred for 24 h at ambient temperature. Then a surfactant solution was prepared by dissolving a surfactant (e.g. Span 85) in 50 mL of non-polar solvent (e.g. hexane or cyclohexane) followed by homogenization using an

Sol-gel microcapsules (W/O)



Sol-gel matrix particles (O/W)



Scheme 1 Sol-gel routes to silica-based microparticles in different emulsions

Ultra-Turrax T-25 basic with S 25 KR-18G dispersing tool (IKA) at 19,000 rpm for 2 min to form a clear solution to which was added the sol-gel solution (800 μ l). The resulting emulsion was stirred for 60 min at 500 rpm resulting in the formation of a suspension of white microparticles. The filtrate was washed 4 times with the non-polar solvent and the material dried at 50 °C for 2 days.

A typical preparation of organosilica particles in a oil-in-water emulsion (O/W) was prepared by dissolving 665 mg of benzoyl peroxide in 16 mL TEOS and 1.15 mL MTMS. The organic phase was emulsified in 100 mL of aqueous solution containing the surfactant Tween 60 (1% w/w)

under high shear forces using an Ultra-Turrax T-25 basic with S 25 KR-18G dispersing tool (IKA) at 19,000 rpm. This emulsion was then poured into a flask containing 100 mL NaOH aqueous solution at pH 11.3. The solution was stirred at 400 rpm while the emulsion was added, and then the rate was set at 200 rpm. The mixture was stirred at room temperature for 24 h, followed by stirring at 50 °C for 3 h. The resulting suspension was washed with deionized water and freeze-dried.

SEM measurements were carried out using the Hitachi 5570 Scanning Electron Microscope. TEM experiments were done with a Hitachi H7650 Transmission Electron Microscope. The optical images were obtained with a Carl Zeiss optical

Table 1 Synthetic protocol for microparticles doped with BPO from W/O emulsions

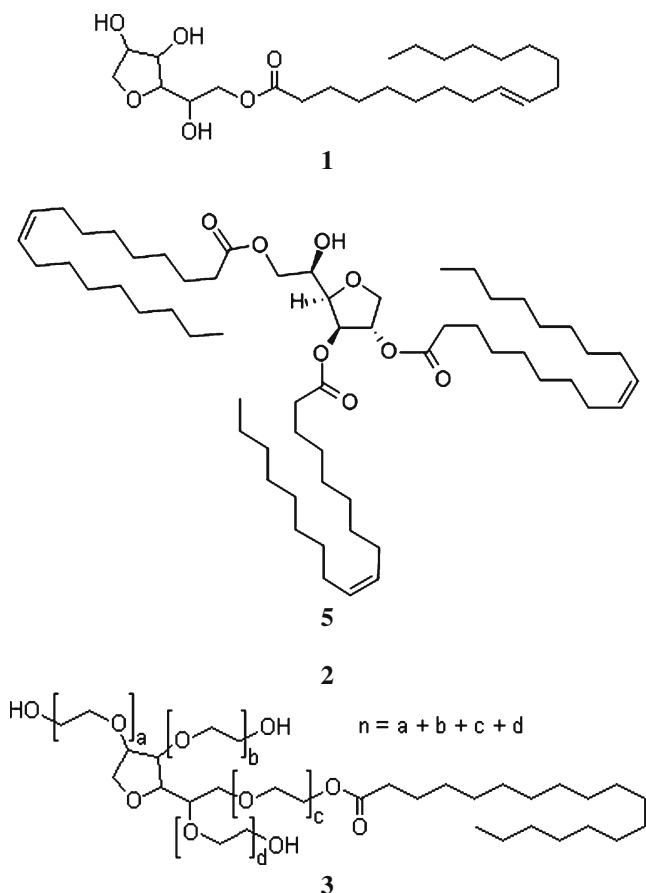
For each sample, except BPO@TMOS/MTMS (hexane), the amounts of BPO, MeOH, H₂O and Span 85 added were, respectively, 50 mg, 1 mL, 3.5 mL and 9.6 g. All preparation employed 50 ml of oil (hexane or cyclohexane)

BPO@TMOS/MTMS (hexane)	BPO@ TEOS/PTMS (hexane)
350 μ l MTMS	440 μ l PTMS
3,50 ml TMOS	5,00 ml TEOS
BPO@TMOS/MTMS (cyclohexane)	BPO@ TEOS/PhTMS (hexane)
350 μ l MTMS	470 μ l PhTMS
3,50 ml TMOS	5,00 ml TEOS
	3,46 g Span 20
BPO@ TEOS/MTMS (hexane)	BPO@ TEOS/MTMS (hexane)
350 μ l MTMS	350 μ l MTMS 350
5,00 ml TEOS	5,00 ml TEOS

microscope. DRIFT FTIR spectra were recorded with a Mattson RS1 spectrometer, with a wide range MCT detector, at 4 cm^{-1} resolution, resulting from 1,000 scans for the sample ratioed against the same number of scans for the background. The BET pore size and specific surface area were obtained on a Micromeritics ASAP 2050 V1.00 E sorption analyzer.

3 Results and Discussion

The selection of the surfactant is critical in controlling the interfacial tension between the non-polar and polar phase. In the case of W/O reactions, surfactants Span 80 (Sorbitan monooleate, **1**) and Span 85 (Sorbitan trioleate, **2**) were selected as emulsifying agents because their HLB¹ (4.3 and 1.8, respectively) is suitable for water-in-oil emulsion. Surfactant Tween 60 (Polyethylene glycol sorbitan mono-stearate, **3**; HLB = 14.9) was chosen for the O/W syntheses.



¹ The HLB number is used as a measure of the ratio of these groups. It is a value between 0 and 60 defining the affinity of a surfactant for water or oil. HLB numbers are calculated for nonionic surfactants, and these surfactants have numbers ranging from 0 to 20. HLB numbers >10 have an affinity for water (hydrophilic) and number <10 have an affinity of oil (lipophilic). Ionic surfactants have recently been assigned relative HLB values, allowing the range of numbers to extend to 60. See also: Myers [5].

Table 2 SiO₂ and 10% alkyl-modified silica particles prepared from O/W emulsions at pH 11

Sample	TEOS (mL)	Organosilane (mL)	Yield (g)
BPO 4	100% (17,5)	–	6,18
BPO 5	90% (16)	10% MTMS (1,55)	4,554
BPO 6	90% (16)	10% MTMS (1,15)	4,829
BPO 7	90% (16)	10% PTMS (1,4)	5,129

Tween 60 is the surfactant employed. *MTMS* methyltrimethoxysilane; *PTMS* propyltrimethoxysilane

In general, the method gave nice spherical microparticles. For example, the optical microphotograph in Fig. 1 shows the particles obtained from a 10% methyl-modified silica sample obtained using hexane as organic solvent (BPO@TMOS/MTMS).

The “ghost shell” in the image is a common optical artifact with glass spheres, and does not point to a core shell structure. Indeed, the SEM picture (Fig. 2) of the same materials clearly shows the formation of full organosilica matrix particles of varying diameter, around 100 μm .

What is remarkable from an applicative viewpoint, however, is that no BPO was entrapped in the resulting materials pointing to complete leaching of the hydrophobic molecule into the oil phase, in which it is much more soluble, eventually affording empty microparticles. Accordingly, the FTIR spectrum of the material (Fig. 3) displays the typical vibrational modes of an organically modified silica: the broad νOH ($\sim 3,300\text{ cm}^{-1}$), the $\nu_{\text{as}}\text{CH}_3$ and $\nu_{\text{s}}\text{CH}_3$ (at $2,964$ and $2,887\text{ cm}^{-1}$, respectively), the $\delta\text{Si-C}$ ($1,254\text{ cm}^{-1}$), the $\nu_{\text{as}}\text{Si-O-Si}$ ($1,080\text{ cm}^{-1}$), the $\nu\text{Si-O}$ (950 cm^{-1}), and the $\nu_{\text{s}}\text{Si-O-Si}$ (800 cm^{-1}) partially overlapped with the $\rho(\text{O})-\text{CH}_3$ (830 cm^{-1}). The main bands of benzoyl peroxide would be the in-phase and out-of-phase $\nu\text{C=O}$ modes (a doublet at $1,780/1,760\text{ cm}^{-1}$), the aromatic ring $\nu\text{C-C}$ modes ($1,455\text{ cm}^{-1}$) and the $\nu\text{O-O}$ (700 cm^{-1}), all in wavenumber ranges of very low absorption from the matrix. Since they are absent, it is evident that BPO is not present within these microcapsules.

BPO is poorly soluble in water but it soluble and stable in a mixture of water and hydric solvents such as MeOH [6], in which we dissolved the substance for the sol-gel encapsulation. The reason for its absence from the sol-gel

Table 3 SiO₂ and 10% methyl-modified silica particles prepared from O/W emulsion at pH 2

Sample	TEOS (mL)	Organosilane (mL)	Yield (g)
BPO 8	90% (16)	10% MTMS (1,15)	3,42
BPO 9	100% (17.5)	–	4,10 g

Tween 60 is the surfactant employed

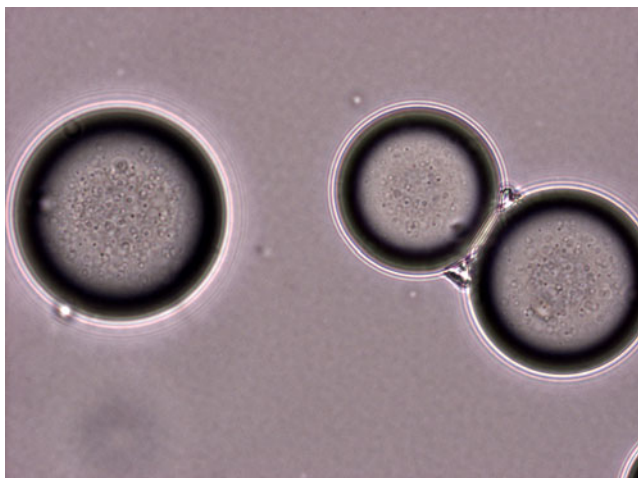


Fig. 1 Optical micrograph of BPO@TMOS/MTMS (hexane), a sol-gel 10% methyl-modified silica matrix particles obtained using a water-in-oil emulsion with hexane as organic solvent and Span 85 as surfactant

particles is that BPO is highly lipophilic, a favorable characteristic for penetration into sebaceous follicles in the anti-acne treatment with silica microcapsules with BPO² when all released BPO molecules migrate from the polar emulsion droplets to the follicles.

This result shows that the W/O approach to silica microparticles is suitable exclusively for the microencapsulation of hydrophilic molecules, beyond the requirement of solubility in water or in protic solvents [7]. In other words, not only a molecule must be soluble in the water/alcohol original sol, but it must not be lipophilic. Otherwise, no entrapment will take place.

We thus attempted microencapsulation using the oil-in-water (O/W) methodology developed by Avnir and coworkers [4]. Both acid and basic catalysis were employed. In each case, the method afforded particulate materials with high loads of entrapped BPO, which led us to encapsulate about 600 mg in 4–6 g of final materials.³ Actual entrapment was directly proved by extraction of the entrapped BPO with ethyl acetate under reflux and further GC-MS analysis of the extract.

Micrographs in Fig. 4 show the SEM and TEM pictures of a 10% methyl-modified sample (BPO 4 in Table 2). Obviously, no microcapsule formation has taken place

² The Israeli company Sol-gel Technologies has developed in 2008 the technology for the manufacture of Cool Pearls BPO, a non-irritating acne therapeutic agent made of silica capsules doped with benzoyl peroxide that was recently commercialized in the US. See also at: www.sol-gel.com.

³ The amount of entrapped BPO was assessed by dissolving each sample particles in strong base (NaOH 3M) followed by extraction of BPO with ethyl acetate. In each sample the percentage of entrapped BPO was higher than 90% of the amount initially added.

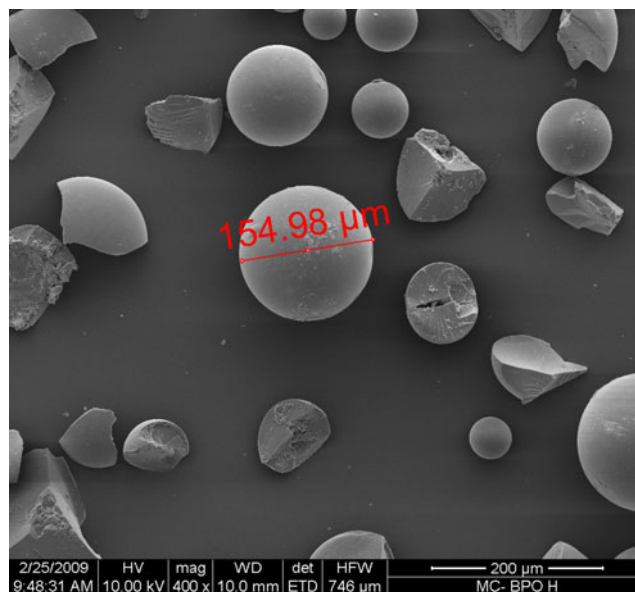


Fig. 2 SEM image of BPO@TMOS/MTMS (hexane), a sol-gel 10% methyl-modified silica matrix particles obtained using a W/O emulsion

using the alkaline O/W materials synthesis. Matrix particle aggregates are instead formed resembling a classical sol-gel precipitate resulting from an unstable emulsion.

We then investigated the morphology of matrix particles made of a 10% methyl-modified sample obtained under acidic conditions (BPO 8 in Table 3). This time the SEM and TEM pictures in Fig. 5 show the typical branched

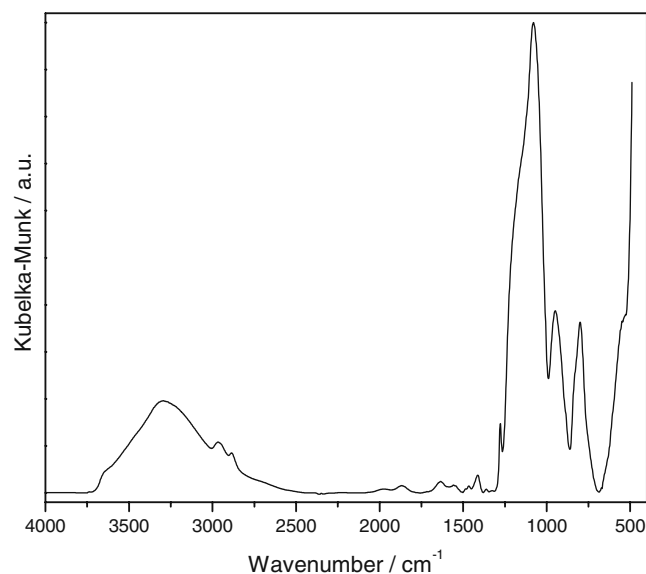
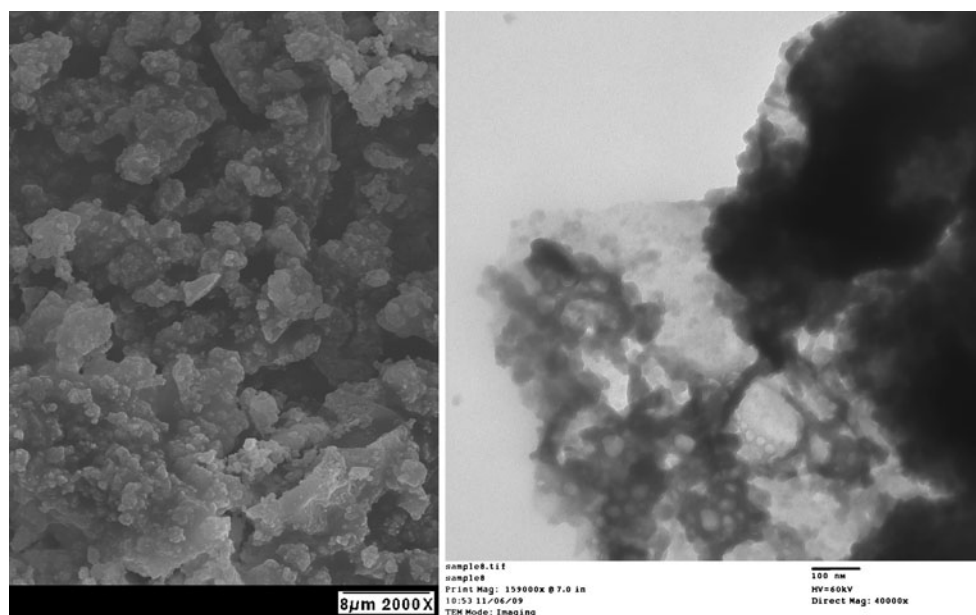


Fig. 3 DRIFT spectrum of a droplet of 10% methyl-modified silica (BPO@TMOS/MTMS). Despite attempt to dope it with BPO, the spectrum clearly indicates that all the BPO was leached in the oil phase

Fig. 4 SEM pictures of samples **BPO 4** organosilica samples obtained under alkaline conditions. Pictures of **BPO 5**, **BPO 6** and **BPO 7** samples, not shown, are similar



structure of sol–gels formed at acidic pH due to the lower condensation rate of the silane monomers and oligomers [8]. The TEM picture shows that material in this case could be made by microparticles although they are heavily aggregated/fused together (3 smaller particles, in the image at the bottom of Fig. 5).

Finally, the BET average pore diameter obtained from the BET interpolation is 92 Å whereas the extremely low specific surface area (0.15 m²/g) excludes any kind of porosity.

Based on these findings a mechanism for formation of the solid organosilica particles in the O/W microemulsion is proposed in Scheme 2. In practice, the TEOS/MTMS oil droplets in the water phase stabilized by the Tween 60 surfactant become unstable after addition of the basic (NaOH) and acid (HCl) catalysts of the sol–gel hydrolytic polycondensation. Both TEOS and the organosilane are now hydrolyzed and assembled, but the process instead than taking place at the oil–water interface, occurs at the interface of nucleated silane oligomer particles giving rise to the formation of irregular solid, matrix particles.

This process is accelerated under basic conditions, when condensation is much faster than under acidic condition, resulting in the formation of aggregates that are typical of sol–gel unstable mixtures of Si alkoxides. Under acidic conditions, condensation is slow and the typical branched structure of sol–gels formed at acidic pH occurs, resulting in compact, microporous materials of very low surface area. Supporting our hypothesis, Teng and co-workers have recently reported that in the synthesis of silica-based microparticles stabilization of the metastable emulsion

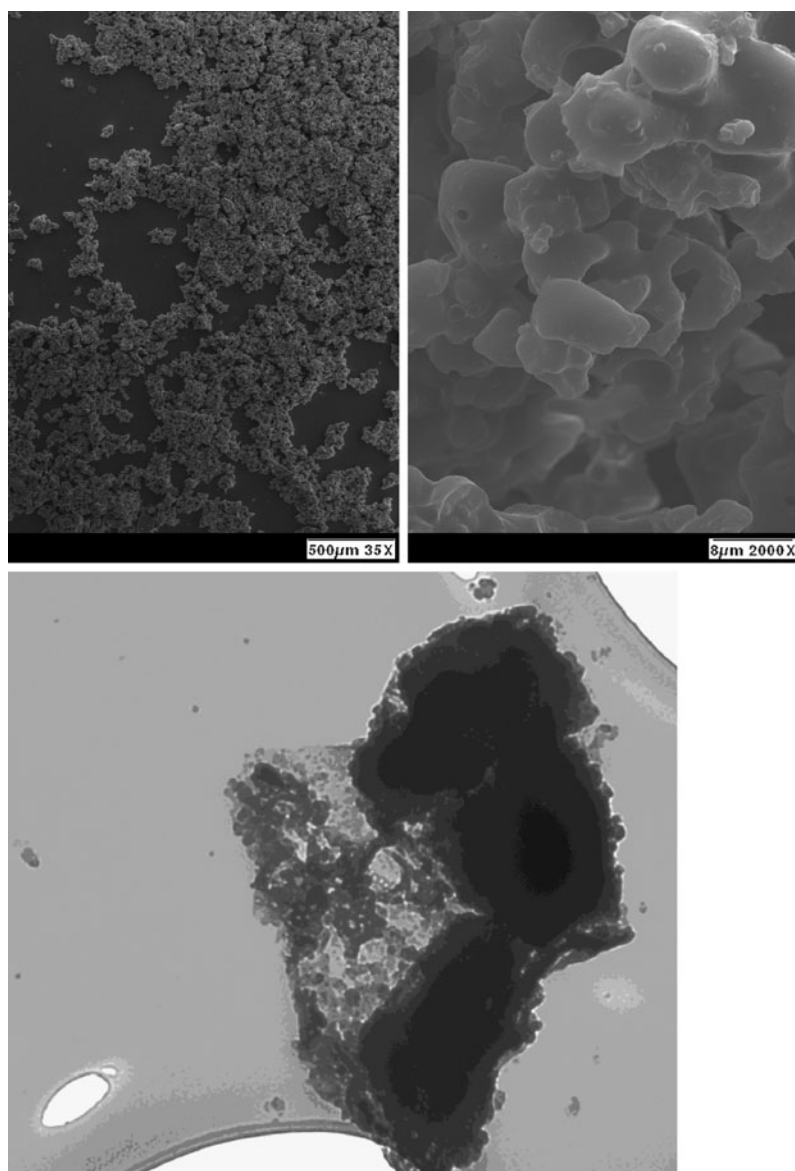
phase is often required using a water/ethanol mixture in place of water only [9].

4 Outlook and Conclusions

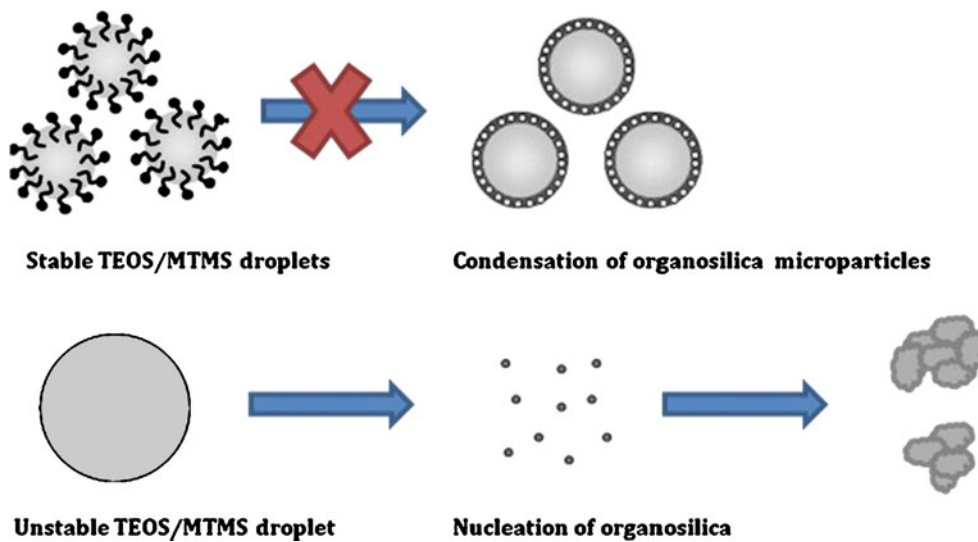
In conclusion, microencapsulation of a lipophilic substance such as BPO in organosilica-based microparticles requires the employment of a O/W emulsion to compartmentalize the active inside the oil droplets. If the W/O approach is used, no encapsulation occurs as the BPO molecules migrate from the polar droplets to the emulsion organic phase.

Whereas in the case of the W/O emulsion, spherical microparticles of solid organosilica are obtained, no microcapsule formation occurs using O/W sol–gel polycondensation even if high loads (ca. 10% in weight of microparticles) could be entrapped in the particulate materials. We make the hypothesis that both acid and basic catalysts employed to catalyze the sol–gel polycondensation destabilize the metastable emulsion. The hypothesis is reinforced also by the observation of the disordered aggregate particles typical of precipitate from unstable sol–gel precursor mixtures that is due to rapid condensation of the silane monomers and oligomers under basic conditions. For industrial applications efficient microencapsulation must be accompanied by a good degree of control over the particle size. Hence, we are now studying methods to stabilize the emulsion system. The results of this report are in any case of relevance to academic and industrial researchers working for example in heterogeneous catalysis.

Fig. 5 SEM (*top*) and TEM (*bottom*) pictures of organosilica sample **BPO 8** obtained from O/W emulsion under acidic conditions. Top: 35× (*left*) and 2000× (*right*)



Scheme 2 Schematic illustration of the formation processes of solid silica matrix particles (*bottom*). Hollow microparticles are not formed (*top*) due to emulsion droplet lack of stability



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