MATERIAL PROCESSING USING SUPERCRITICAL CO$_2$ TECHNOLOGY FOR APPLICATION IN COSMETICS

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Titanium dioxide (TiO$_2$) nanoparticles are essential components in many formulations used in the cosmetics industry, because of their properties as UV-filter and consequent ability to protect the skin of sun light. Nanoparticles dispersibility in the oil phases often used in cosmetics can be enhanced by TiO$_2$ surface hydrophobization, fi., by nanoparticles silanization. Moreover, the encapsulation of TiO$_2$ nanoparticles into lipidic compounds facilitates the incorporation of the UV-filter in oil-in-water cream formulations. Supercritical carbon dioxide (scCO$_2$) was used in this work as the reaction medium for surface silanization of TiO$_2$ nanometric particles. Next, silanized TiO$_2$ nanoparticles were encapsulated into solid lipid material by using the Particles from a Gas Saturated Solution (PGSS) process. Finally, the preparation of a sustained delivery system consisting on lipid-based particles loaded with silanized TiO$_2$ and caffeine was attempted using also the PGSS process.

1. INTRODUCTION

Titanium dioxide (TiO$_2$) is widely used in the industry of cosmetics as a filter to protect the skin against UV-light in combination with organic UV-absorbers. TiO$_2$ is often used in the form of nanometric particles with a high surface area, since the nanopowder confers enhanced UV-protection effect to the mixture and reduces the whitening effect of coarse TiO$_2$ particles when rubbed on the skin. On the other hand, the risk of nanoparticles to penetrate into the body through the skin is a concern to take into account nowadays. This can be avoided by entrapping the nanoparticles into micrometric lipidic particles [1]. However, the intrinsic hydrophilic character of non-treated TiO$_2$ surfaces makes difficult the dispersion of the nanoparticles in both lipids and the organic media used in cosmetics. Hence, the two objectives of this work were first the surface hydrophobization of nanosized TiO$_2$ achieved by silanization, and second its encapsulation in lipidic microparticles.

Octyltriethoxysilane (C$_8$H$_{17}$Si(OEt)$_3$) was chosen in this work as the surface modifier of TiO$_2$ nanoparticles using scCO$_2$ as a solvent [2]. Moreover, use of scCO$_2$ as polymer plasticization agent has appeared as a promising method for developing a general lipid carrier system able to encapsulate active inside solvent-free particles [3]. scCO$_2$ allows the formation of lipid-based particles under mild temperature conditions, since scCO$_2$ dissolves in lipids leading to a decrease in the melting point of the lipids. The precipitation of lipid particles with silanized TiO$_2$ was performed using the PGSS process. Finally, composite particles were also loaded with and active molecular compound (caffeine) using the PGSS technique. Caffeine was chosen as model compound, since its capacity to stimulate the metabolism of fats and subsequent anti-cellulite activity have been stated [4].

2. MATERIALS AND METHODS
2.1. Materials

TiO$_2$ nanometric powder (~ 20 nm diameter) was supplied by Degussa (P-25S). Octyltriethoxysilane (Fluka) was used for surface coating. Lumulse GMS-K (GMS, Lambent Technologies) and Cutina HR (HCO, José M. Vaz Pereira S.A.) lipids were used for encapsulation. Caffeine (Sigma-Aldrich) was used as the active compound.

2.2. Equipment and procedure

The nanometric TiO$_2$ powder was silanized using the equipment depicted in Fig. 1a. The main component was a 100 mL high-pressure autoclave (Thar Design, *Re1*) magnetically stirred (300 rpm) and heated using resistances. A syringe pump (Thar Design, *P1*) was used to increase the working pressure. The equipment was operated in the batch mode. In a typical experiment, the autoclave was charged with 1 mL of liquid silane added at the bottom of the reactor and ~0.6 g of TiO$_2$ powder suspended on the top. The equipment was heated at 348 K and pressurized at 10.0 MPa during a running time of 50 min. The silanized TiO$_2$ (sample Ti-SCsil) was further washed by using a continuous flow of scCO$_2$ (2-4 g min^{-1}) at 318 K and 22.5 MPa during 30 min.

The lipid- and lipid+caffeine-based particles were produced using the PGSS technique [5]. A schematic representation of the used equipment is shown in Fig. 1b. CO$_2$ was supplied by a high-pressure piston pump (*P1*, Haskel MCPV-71) to a 500 cm^3 stirred vessel (*Ve1*, Parr) heated using a thin band heater (Watlow STB3J2J1). Raw materials were added to the reactor that was heated at 345 K and pressurized at 13.0 MPa. After a certain equilibration time, the mixture was depressurized through a 600 µm full cone nozzle (Spraying Systems), by opening valve *V3* (Parker 4M4Z-B2LJ). The powder was collected in a 10 L vessel (*Ve2*). The used operating conditions were chosen accordingly to preliminary experiments performed to establish the lipids melting point curves under scCO$_2$ conditions.
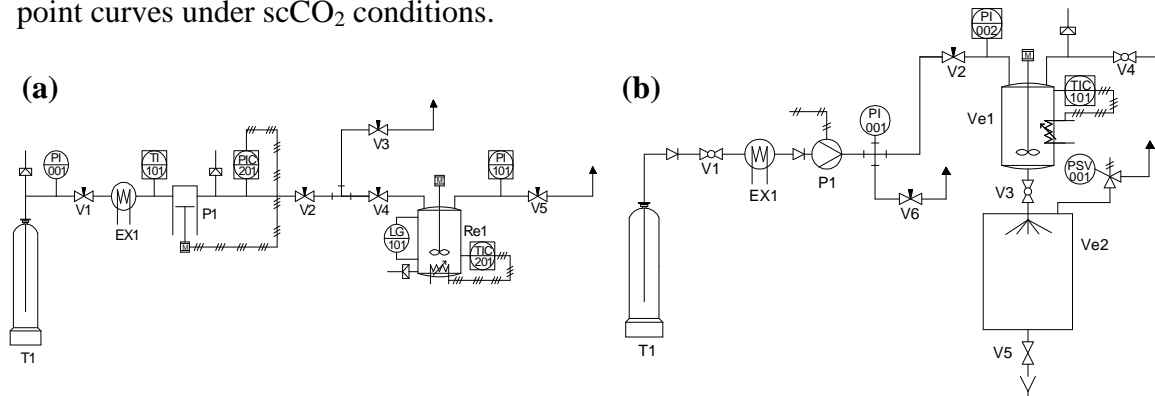

(a) **(b)**

Figure 1: Process flow diagrams of the equipments used for: (a) scCO$_2$ silanization, and (b) PGSS processing. *T1*: CO$_2$ reservoir, *EX1*: cooling unit, *P1*: pump, *V1-V6*: valves, *Re1*: high pressure reactor, *Ve1*: high pressure vessel, *Ve2*: collector.

2.3. Characterization techniques

ATR-IR spectra of TiO$_2$ samples were recorded using a Perkin Elmer Spectrum One spectrometer equipped with a Universal ATR sampling accessory. The thermal stability of obtained lipidic samples was studied under Ar atmosphere using thermogravimetric analysis (TGA, Perkin Elmer 7). Particles were analyzed by X-ray diffraction (XRD) with a Rigaku Rotaflex RU200 B using CuKα$_1$ radiation. The amount of caffeine inside the particles was determined by HPLC (Elite Lachrom equipment) using a L-2435 UV–Vis detector. Caffeine was extracted from the lipid matrix according to the method described in literature [3]. Scanning electron microscope (SEM) images were taken using a JEOL JSM 6300 equipment.

3. RESULTS

3.1 TiO$_2$ silanization

ATR-IR spectroscopy was used to determine the presence of deposited silane on the TiO$_2$ surface (Fig. 2). The spectra of the scCO$_2$ silanized TiO$_2$ sample presented the characteristic bands of the octyl chain in the silane molecules at 2957 and 2870 cm^{-1} assigned to CH$_3$ group and 2920 and 2853 cm^{-1} assigned to CH$_2$ group. The presence of two broad bands at 1106 and 1035 cm^{-1} corresponding to Si-O stretching vibration indicated Si-O-Si cross-linking or Si-O-Ti bonds with TiO$_2$ surface [6].
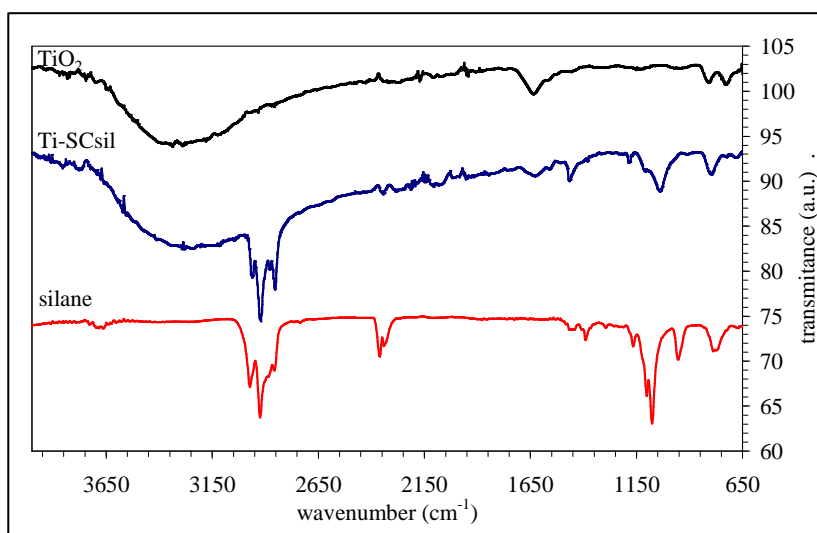

Figure 2: ATR-IR spectra of pure silane and raw (TiO$_2$) and silanized powder (Ti-SCsil sample)

3.2. TiO$_2$ encapsulation in solid lipids

TiO$_2$ silanized nanoparticles were further encapsulated in a mixture of HCO and GMS lipids. In order to evaluate the most feasible operating conditions to produce lipid-based particles by PGSS, the effect of scCO$_2$ on the melting point of the used lipids was first analyzed. The melting point of the lipids under pressurized CO$_2$ was determined according to a previously described procedure [7]. The melting temperature of both lipids decreased significantly as the pressure was increased up to a value of ~11.0-12.0 MPa (Fig. 3). Use of higher pressures than the mentioned values led to negligible melting point variations. For 1:1 mixtures of HCO and GMS, the melting point decreased 14 K by increasing the pressure from atmospheric to 13.0 MPa. A temperature of 345 K was chosen to process the lipid mixtures by PGSS.
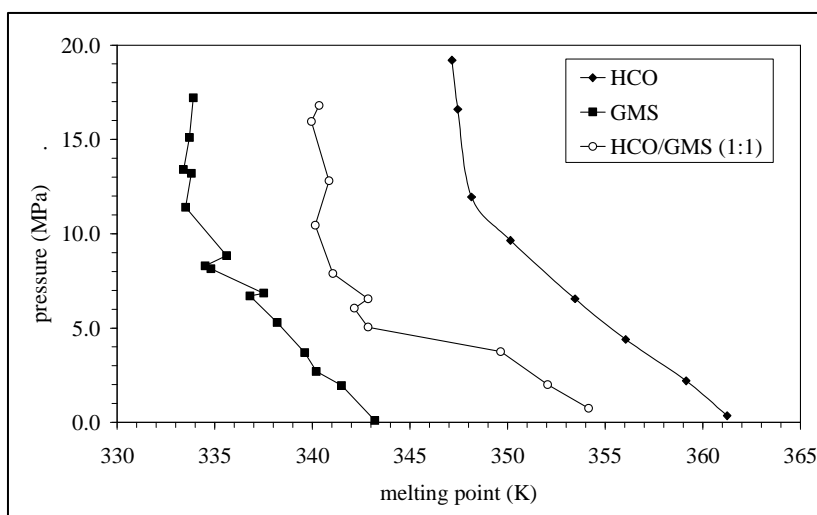

Figure 3: Melting points of HCO, GMS [3], and HCO:GMS (1:1) in the presence of scCO$_2$.

Mixtures of lipids (L), lipids + silanized TiO$_2$ (L+Ti), lipids + caffeine (L+Cf), lipids + silanized TiO$_2$ + caffeine (L+Ti+Df), lipids + caffeine + water (L+Cf+W) and lipids + silanized TiO$_2$ + caffeine + water (L+Ti+Cf+W) were processed by PGSS. The composition of the mixtures is depicted in Table 1. Water was added to some of the combinations containing caffeine in order to attain a proper mixture of the active agent with the lipids and, thus, avoid nozzle blockage. Without water addition, the maximum content of caffeine accepted by the mixture of lipids without segregation was 10 wt%.

Table 1: Composition of the initial mixtures added to the PGSS vessel and HPLC estimated caffeine content in recovered lipid particles

Sample	Initial weight content (wt%)					Recovered samples	
	HCO	GMS	Ti-SCsil	Caffeine	Water	Caffeine content (wt%)	Process yield (%)
L	50	50	-	-	-	-	-
L+Ti	47	47	5	-	-	-	-
L+Cf	45	45	-	9	-	3.8	42
L+Ti+Cf	43	43	4	9	-	4.2	48
L+Cf+W	25	25	-	10	40	10.1	61
L+Ti+Cf+W	24	24	2	10	40	12.5	78

Using TGA analysis, the content of encapsulated TiO$_2$ was calculated as the weight fraction remaining at temperatures higher than 750 K (Fig. 4). The weight loss due to the silane deposited on TiO$_2$ surface was considered negligible. For all the samples, the amount of TiO$_2$ encapsulated inside the lipidic particles was *ca.* 6-7 wt%, which corresponded to a slight enrichment of TiO$_2$ in the lipidic phase with respect to the initial quantity added to the precipitation vessel (4 wt%).
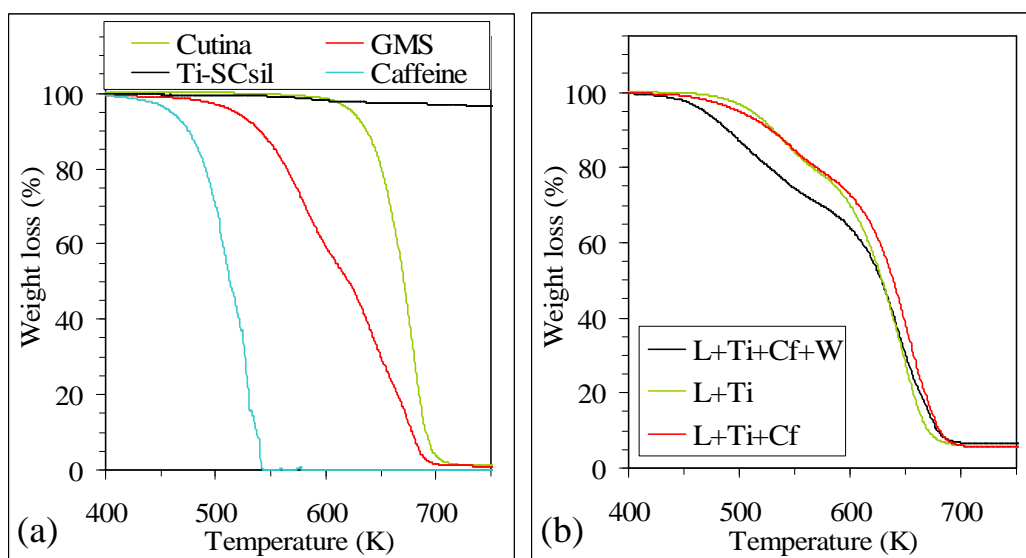

Figure 4: Thermogravimetric analysis of lipid particles: (a) raw materials, (b) PGSS-processed particles

For the lipids loaded with caffeine in the anhydrous conditions, HPLC analysis indicated a caffeine content of ~4 wt% (Table 1). The addition of water resulted in increased caffeine loadings, up to values of ~10 wt%. Moreover, the process yield, i.e., the caffeine content in the lipid particles recovered in the collector (Ve2 in Fig. 1b) with respect to the initially added in vessel (Ve1 in Fig. 1b), also increased by adding water to the mixture (Table 1). Caffeine losses with respect to the initial amount added to the reactor were due to partial solubilization in $scCO_2$ during the mixing and further precipitation inside the reaction vessel (Ve1) during decompression [3].

The crystalline structure of the raw materials (Fig. 5a) and precipitated mixtures (Fig. 5b) was studied by XRD. Major peaks of HCO (2θ= 5.3, 19.7, 22.0º) were also observed in PGSS processed samples. The peak broadening observed for peaks at 19.7 and 22.0º suggested the formation of a less ordered structure. Peaks corresponding to GMS (2θ= 5.5, 19.6, 20.8, 22.0, 23.4, 23.7º) were not observed in the precipitated particles, because of either the formation of an amorphous phase or the overlapping by HCO peaks. The presence of an incipient broad peak at low contact angles supported the first option. The presence of TiO_2 in the mixture was confirmed by the peak appearing at 25.3º that corresponded to anatase TiO_2 phase.

Solid lipid microparticles processed without water presented a peak at 2θ=12.0º corresponding to the major peak from anhydrous caffeine ($C_8H_{10}N_4O_2$). The presence of water during the precipitation of the caffeine-loaded lipid particles led to the formation of a non-stoichiometric caffeine hydrate ($C_8H_{10}N_4O_2 \cdot 0.8H_2O$), revealed by the presence of the peaks at 2θ= 8.1, 10.6, 12.2, 13.2º [8].
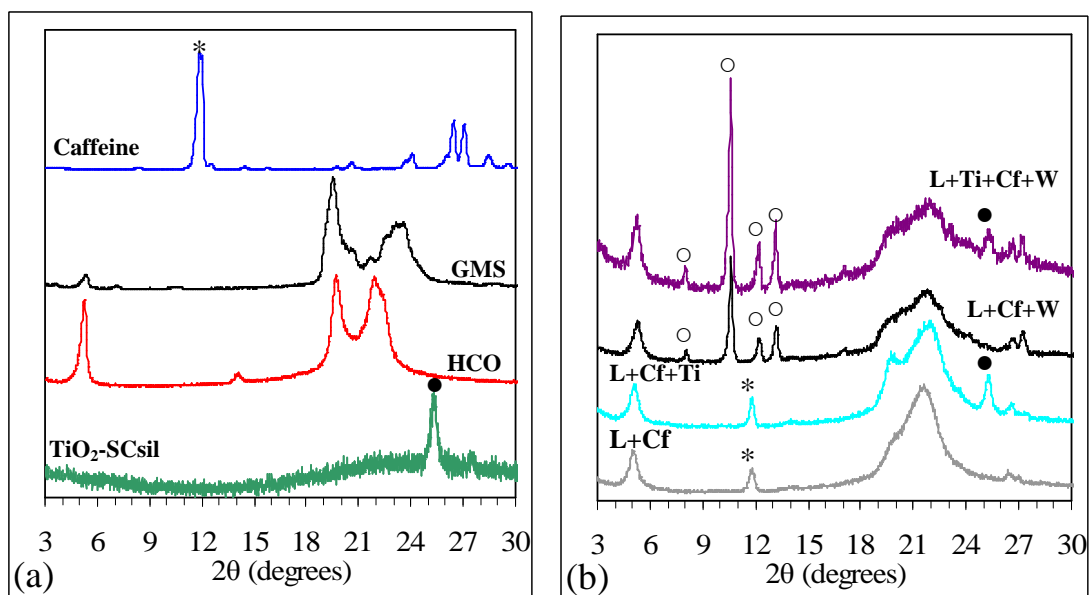

Figure 5: Normalized X-ray diffraction patterns of: (a) raw materials, and (b) lipid-based particles containing caffeine. Symbols: * caffeine; ● TiO_2; ○ caffeine hydrate.

SEM images of the precipitated mixtures with caffeine (with and without water addition) indicated the presence of a significant amount of needle-like crystals of caffeine on the surface of the particles (Fig. 6).
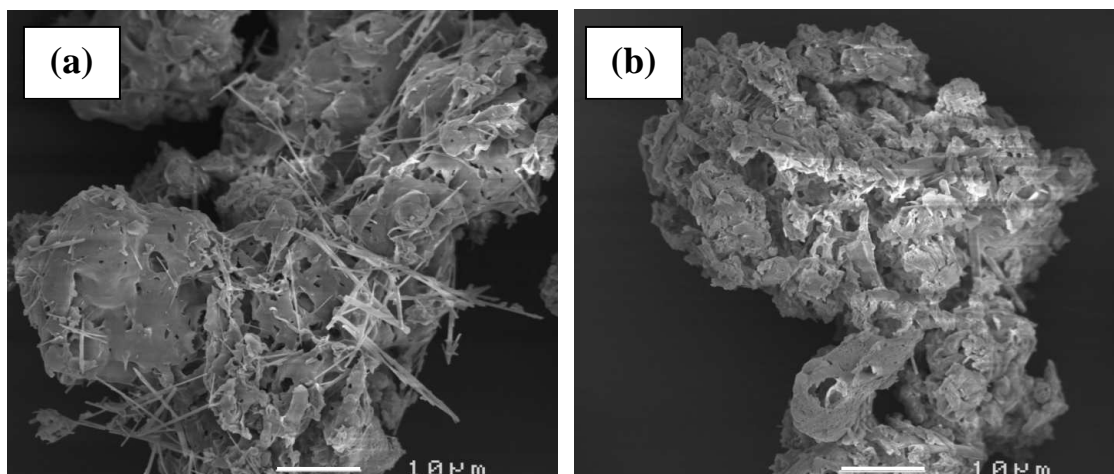
Figure 6: SEM images of caffeine-loaded particles prcipitated by PGSS: (a) without, and (b) with water addition.

4. CONCLUSIONS

Hydrophobization of TiO_2 nanoparticles was successfully performed by silanization in a $scCO_2$ medium. Silanized TiO_2 particles were embedded in micrometric lipid-based particles by using the PGSS process, which could facilitate the incorporation of the nanoparticles in cosmetic formulations. Visual examination of obtained composite mixtures with TiO_2 and caffeine indicated caffeine precipitation outside the matrix. Hence, caffeine release tests are being performed in order to elucidate if either the caffeine was only present in the form of crystals outside the lipidic matrix or also partially encapsulated.

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