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Microencapsulation by a Solvent-Free Supercritical Fluid Process: Use of Density, Calorimetric, and Size Analysis to Quantify and Qualify the Coating

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Coating of microparticles or microencapsulation is a widely used operation in which a thin layer of a coating agent is deposited onto a solid particle. Currently, the technique faces two challenges: being solvent-free and being applicable for coating particles smaller than 80 microns. In this work, several techniques are used to test the feasibility of a new solvent-free coating process using supercritical fluid technology. Some model microparticles, glass beads, and an active compound (AC) are coated with Precirol®, which is a mixture of fats. The process involves two steps: first supercritical CO_2 is dissolved in molten Precirol®, then the melt solution is sprayed onto the host particles by a rapid expansion. The particles coated in this way are examined by particle size analysis, environmental scanning electron microscopy (ESEM), and IR spectrophotometry. Also mass ratios of host particle to coating are evaluated using both helium pycnometry to determine sample density and calorimetry to measure the heat of fusion of the coating agent. The results show that these analytical techniques can be used for qualitative analysis as well as quantification of the coating. Thus they give relevant information on reproducibility and feasibility of the new process.

Keywords coating, particle characterization, particle size analysis, supercritical fluids

Introduction

Supercritical fluids (SFs) are fluids at a pressure and a temperature above their critical point. CO_2 is the most widely used supercritical fluid because it is abundant, safe, and inexpensive and its critical properties are easy to reach at laboratory scale. The critical temperature of CO_2 is 304.1 K and its critical pressure 73.8 MPa. Over the past 20 years, SFs have found many applications in various fields such as extraction, reaction, and powder generation (Fages et al., 2004). They have been used to prepare micro-composite particles, especially for pharmaceutical purposes: protection of an active compound from deterioration, taste masking, formation of controlled-released systems, and enhancement of the dissolution rate of poorly soluble active ingredients (Perrut et al., 2005). The present work is included in this research domain.

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A review of coating processes based on supercritical technology shows that the characterization of microparticles is a delicate but essential point in order to validate the process. This implies the quantification of the coating agent deposited onto particles and qualification of this coating. Qualification herein implies characterizing the way the coating is deposited (homogeneous deposition, agglomeration phenomena) and the coating efficiency. Usually, particle size measurements are performed together with other techniques. Thus, each new process faces analytical challenges. A few illustrations follow.

Kröber and Teipel (2005) encapsulated monodispersed glass beads (between 7 and 80 microns) by stearyl alcohol solubilized into supercritical CO_2 using a fluidized bed. The ratio of coating agent to coated particles was determined both by thermal gravimetric analysis (TGA) and density measurements to calculate the thickness of the deposited shell. However, no indication was given of the homogeneity of the coated samples or of the reproducibility of the process. Ribeiro Dos Santos et al. (2002) developed a process to coat bovine serum albumin, BSA (0–500 μm), with fatty compounds. The raw materials were introduced into a vessel fitted with an impeller. Supercritical (SC) CO_2 solubilized the coating agent while BSA was maintained in suspension in the supercritical media. By adjusting both pressure and temperature, the solvent power of SC CO_2 was reduced and the lipid precipitated onto BSA to form core/shell-designed particles. Morphology, surface appearance, and particle diameters were investigated by scanning electron microscopy (SEM). The mass ratio was determined by melting the coating and analyzing the remaining BSA by spectrophotometry. The coating efficiency was determined by the in-vitro release kinetics. Here the overall aggregation phenomenon was not investigated and optical microscopy did not allow a general overview of the whole sample. Perrut (2002) reported a technique where a coating agent was saturated with the super- or subcritical fluid and mixed with the solid particles in an agitated autoclave. The depressurization of the mixture induced solidification of the fat onto the particles. The final composition was determined by dissolving the microparticles. However, no additional indication of the coating efficiency was given.

A new microencapsulation process developed in our laboratory has the specificity of processing separately the coating agent and the particles. This gives both protection of the particles from any deterioration and the opportunity to control the coating agent/particle ratio. The present article focuses on the analytical methods used on the microcapsules formed to quantify or qualify the coating obtained and on the corresponding information given in terms of reproducibility and feasibility of the process. Micrometric glass beads and an active compound have been coated with a fatty component, Precirol®. Results for particle size analysis, environmental scanning electron microscopy (ESEM) observation, solids density, and calorimetric measurements are discussed.

Experiments and Characterization Methods

Materials

Two types of particles were used in the experiments: glass beads and an active compound (AC). Several sieve cuts of glass beads from 0 to 80 microns (Sovitec, France) were used as ''model'' particles to be coated. They are considered as a ''model'' because of their spherical shape, smooth surface, and well-defined size distribution.

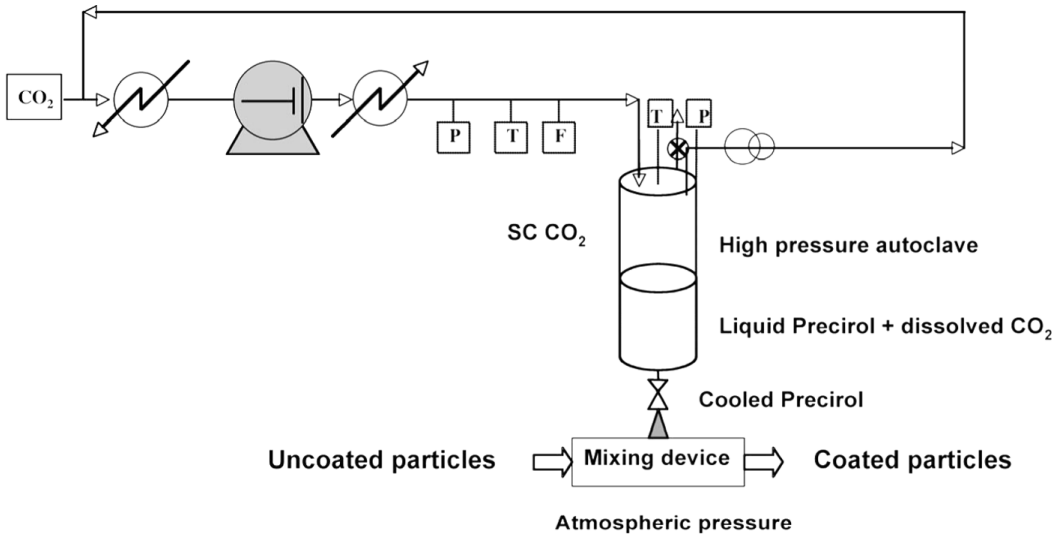


Figure 1. Experimental setup of the supercritical fluid coating process.

The pharmaceutical active compound (AC) has a mean volume diameter of about 15 microns and the size distribution is very dispersed. The coating agent used was Precirol ATO5® powder (Gattefossé, France), which is a commercial mixture of mono-, di-, and triglycerides, the main component being a mixed diglyceride with a C_{16} and a C_{18} saturated carbon chain. Its melting point at atmospheric pressure measured by differential scanning calorimetry (DSC) (Perkin Elmer, UK) is 56.9°C. Precirol® is widely used as an excipient in the pharmaceutical industry.

Operating Procedure

The coating experiments using supercritical CO_2 were performed on a lab-scale apparatus (Separex, France) modified for coating purposes (Figure 1). The procedure was the following: solid Precirol® was first introduced into a 500 cm^3 heated vessel. Liquid CO_2 (purity 99.8%, Air Liquide, France) was admitted from a bottle, then cooled through a heat exchanger and pressurized to 11 MPa using a membrane pump (Lewa, Germany). The compressed CO_2 then flowed through a heater to reach supercritical conditions. This SC CO_2 was then introduced into the vessel and dissolved into the coating agent until equilibrium was reached. The vessel temperature had to be high enough to maintain the CO_2 under supercritical conditions but was held below the normal melting point of the Precirol®. The operating temperature was then around 323 K. This molten phase was expanded and Precirol® solidified as a fine powder and deposited onto the uncoated particles. The mass ratio of Precirol® to uncoated particles was 2:3. The resulting mixture was collected in a gas solid separator. The coated particles were then characterized.

Characterization Methods

Size Measurement

The particle diameter was measured using a time-of-flight particle size analyzer (PSD 3603, TSI, USA) (Figure 2). Using the measured time and a fixed reference

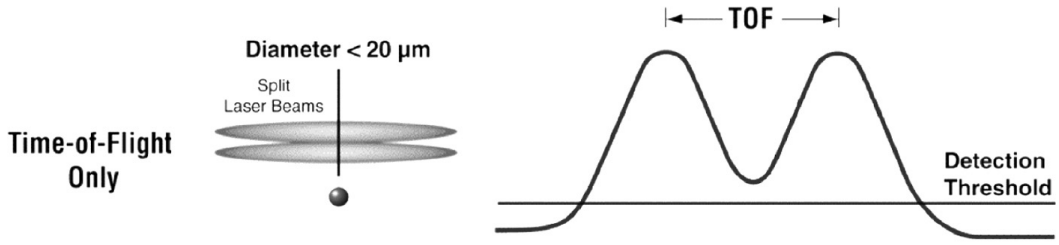


Figure 2. Time of flight detected by Aerosizer® (TSI, USA).

curve, the equivalent aerodynamic diameter (EAD) is determined as:

$$EAD = KU^{1/2} \tag{1}$$

K is a constant depending on the configuration of the apparatus, and U the velocity of the particle. This gives a number distribution of particle size. To take into account the true particle density, the Particle Instrument Manager® (TSI, USA) software converts the EAD into an equivalent geometric diameter (EGD) according to relation (2):

$$EGD = EAD^{*}\sqrt{TrueDensity} \tag{2}$$

In this work, the number size distribution was numerically converted into volume size distribution to have a higher sensitivity to small changes in diameter, which should be the case in coating phenomena. In addition, the Aerosizer® is more accurate for the lower part of the size distribution. In the higher part, a big single particle may significantly diffract the incident light beam, thus perturbing the measure. As a consequence, the average volume diameter D[4,3] can be in error, and we have chosen to consider the median diameter D_{50} (Allen, 1997). The results are presented together with the cumulated volume size distributions. Each sample was measured twice so as to determine the homogeneity of the sample.

True Density Measurement

The true density was measured on the whole sample using a helium pycnometer (Accupyc 1330, Micromeritics, USA). These density measurements give an evaluation of the mass ratio of coating agent, $f_{\text{coating agent}}$, which is the mass of coating agent divided by the total mass through relation (3):

$$\frac{1}{d_{coated\ particle}} = \frac{f_{coating\ agent}}{d_{coating\ agent}} + \frac{1 - f_{coating\ agent}}{d_{uncoated\ particle}} \tag{3}$$

where d_i are the densities. However, the overall density measurements do not give any information on the coating quality.

Calorimetric Measurement

The mass ratio of the coating agent deposited onto the particles was determined by thermal analysis performed with a DSC 7 (Perkin Elmer, UK) apparatus. The weight

of the analyzed samples was about the thousandth part of the coated sample mass, around 5 mg. Heating curves were recorded from 20° to 90°C at the scan rate of 5°C/min, under nitrogen flow. The amount of Precirol® was then determined from relation (4):

$$x = \frac{\Delta H_{melting}^{coating\ agent\ onto\ the\ sample}}{\Delta H_{melting}^{pure\ coating\ agent}} \tag{4}$$

where x represents the mass ratio of the coating agent in the coated particles, $\Delta H_{melting}^{coating\ agent\ onto\ the\ sample}$ is the heat of fusion of Precirol® in the coated particles samples, and $\Delta H_{melting}^{pure\ coating\ agent}$ is the heat of fusion of Precirol® solidified via the supercritical fluid process.

In addition, the coated particles were observed using an ESEM XL 30 FEG (Philips, Netherlands).

Results and Discussion

Coating of the Sieved Glass Beads

The glass bead coating experiment was repeated three times under identical experimental conditions to quantify a standard deviation, thus obtaining information in terms of process repeatability. Due to time constraints and application requirements, further repeatability experiments could not be performed. The sieved fraction studied here is less than 20 microns. The true densities, the corresponding coating agent/glass bead mass ratio, and the same ratio determined by DSC are shown in Table 1. Table 2 gives the absolute and relative deviations; the relative deviation is defined as the absolute deviation divided by the mean value. The mass ratios obtained according to both methods are rather different (Table 2). True density measurements were performed on the whole sample, whereas DSC analysis was done on a sample representing only a thousandth of the whole sample mass without taking the excess Precirol® crystallized alone, which spontaneously segregates. Thus, true density gives information on the whole Precirol® sample but DSC better quantifies the Precirol® deposited onto the particles. As for the relative deviations, that for the DSC results is greater than that for the density measurements. In DSC analysis, the error arising from the inhomogeneity of the sample is taken into account, which is not the case for density measurement. In any case, if we consider only the mass ratio quantification, the reproducibility of the process is rather poor. Considering the particle size measurements, the three trials done on the coated 20–30 microns sieve fraction are shown in Figure 3(a). Accumulating the errors due to the analysis method and the three trials, a relative deviation of 5.3% ($0.6\%_{\text{trials}} + 4.6\%_{\text{analysis}}$) was found for the mean volume diameter and 3.4% ($1.0\%_{\text{trials}} + 2.4\%_{\text{analysis}}$) for the median diameter. Here the reproducibility of the process is reasonable, although it could be improved.

In order to analyze the coating of the different particle size distributions, the particle size analysis results are shown in Figures 3(a)–(d). The volume median diameters D_{50} and the spans are in Table 3. The span is defined by the relation $(D_{90}\text{-}D_{10})/D_{50}$ and characterizes the width of the distribution (Allen, 1997). The spans remain unchanged for the coated particles above 20 microns compared to the uncoated particles; the span variation is less than 20%. This would mean that the particles are individually coated. In contrast, if one considers the distribution

Table 1. True densities and mass percent of coating agent measured for the raw materials used and the coated samples

Sample	Uncoated glass beads	Precirol® solidified via supercritical process	Coated glass beads, trial 1 $ø_{beads} < 20\,\mu m$	Coated glass beads, trial 2 $ø_{beads} < 20\,\mu m$	Coated glass beads, trial 3 $ø_{beads} < 20\,\mu m$
True density (g/cm^3)	2.45	0.99	1.78	1.78	1.89
Precirol® determined by true density (% w/w)	0	100	29.9	29.9	23.4
ΔHfus (J/g)	—	114.3	22.8	13.8	27.4
Precirol® determined by DSC (% w/w)	—	100	19.9	13.8	23.9

Table 2. Reproducibility of the process

Sample	Coated glass beads, trial 1 $\varnothing_{beads} < 20\,\mu m$	Coated glass beads, trial 2 $\varnothing_{beads} < 20\,\mu m$	Coated glass beads, trial 3 $\varnothing_{beads} < 20\,\mu m$
Average Precirol® determined by true density (% w/w)		27.7 ± 3.0	
Relative deviation on true density measurements		10.9	
Average Precirol® determined by DSC (% w/w)		19.2 ± 4.1	
Relative deviation on DSC measurements		21.6	

under 20 microns, the span is modified with a variation of more than 40%. It will be shown later that this can reasonably be attributed to agglomeration effects. In all cases, after coating the median diameter is shifted towards higher values.

The mass ratios of Precirol® contained onto the samples and evaluated by calorimetry are listed in Table 4. Assuming that the mean surface diameter was close to the mean volume diameter, which is normally the case for spherical particles, the specific surface area of the uncoated glass beads was calculated by the following relation:

$$S_0 = \frac{6}{D[3;2]} * \frac{1}{density_{beads}} \tag{5}$$

Knowing the specific surface area of each size class of beads and the mass ratio of Precirol® deposited onto the particles, it is then possible to determine the volume of coating agent deposited onto particles versus the available surface area. The resulting calculations are presented in Table 4 and Figure 4.

The results show a good linear correlation between the calculated surface area and the quantities of Precirol® deposited onto the different bead sizes, except for the smallest particles. This implies coating of individual particles. In contrast, the correlation is not valid for the highest specific surface area, which may be due to an agglomeration effect simultaneous with the coating. The results are in agreement with the span values before and after coating.

Table 3. Granulometric parameters of the uncoated and coated glass beads

	Uncoated glass beads			Coated glass beads		
Sieved class (μm)	D[4,3] (μm)	D50 (μm)	Uncoated glass beads span	D[4,3] (μm)	D50 (μm)	Coated glass beads span
20	17.1	13.4	1.9	17.0 ± 1.3	16 ± 1	1.06 ± 0.08
20–30	27.5	27.2	0.53	28.9 ± 0.1	29.3 ± 0.3	0.51 ± 0.12
30–40	32.3	31.9	0.43	39.4 ± 1.3	36.9 ± 3.6	0.46 ± 0.02
40–55	45.9	45.9	0.36	50.4 ± 0.8	51.2 ± 1.1	0.43 ± 0.02
55–80	59.5	59.3	0.37	64.7 ± 1.7	65.4 ± 1.5	0.41 ± 0

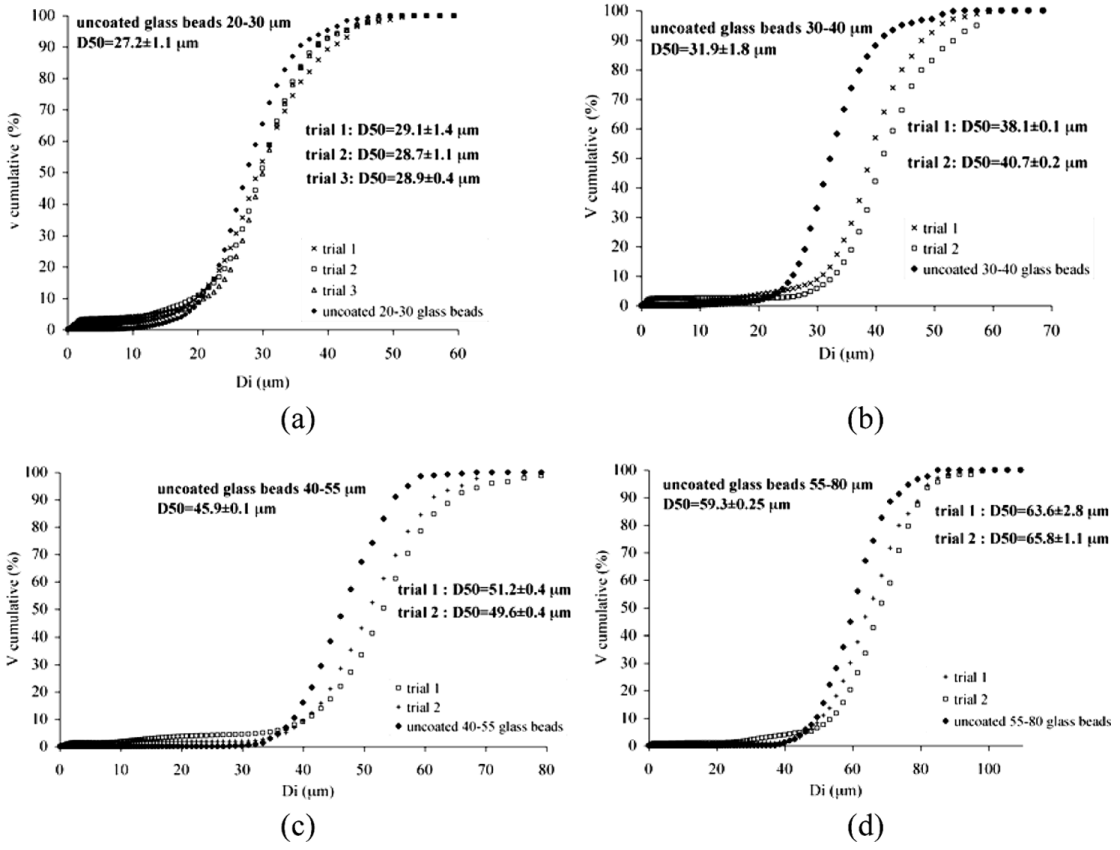


Figure 3. Cumulative percent volume versus mean diameter of the coated particles of the sieved cut glass beads by a supercritical process (a) 20–30 µm; (b) 30–40 µm; (c) 40–55 µm; (d) 55–80 µm.

As for the obtained mass ratios, they vary between 0.26 for the largest glass beads to 0.37 for the smallest ones. These values may be compared to initial ratio of 0.66. Hence, a significant amount of excess coating agent is found.

However, these size measurements do not give any information on the homogeneity of the coating layer on the particles. The ESEM pictures presented in Figure 5 provide insight into the deposition of Precirol® onto the surfaces of the glass beads. A representative coating of the beads displaying the linear correlation is shown in Figures 3(b) and 3(d). It seems to be relatively homogeneous and differs completely from a physical mixture of both components (Figure 5(c)). This means that the

Table 4. Quantification of the Precirol® deposited onto the glass beads

Coated glass beads			Coating quantification		
Sieved class II (µm)	D[4,3] (µm)	$S_{calculated}$ (m^2/g)	Precirol® (% wt)	R (m Precirol®/ m glass beads)	cm^3Precirol®/ m^2 glass beads
20	17.5 ± 0.8	0.14	22.9 ± 4.8	0.369	2.60
20–30	28.8 ± 0.1	0.09	23.4 ± 10.1	0.305	3.47
30–40	39.4 ± 1.3	0.07	24.1 ± 2.4	0.317	4.23
40–55	50.4 ± 0.8	0.06	22.3 ± 1.8	0.287	5.22
55–80	62.9 ± 2.6	0.04	20.8 ± 0.9	0.263	6.40

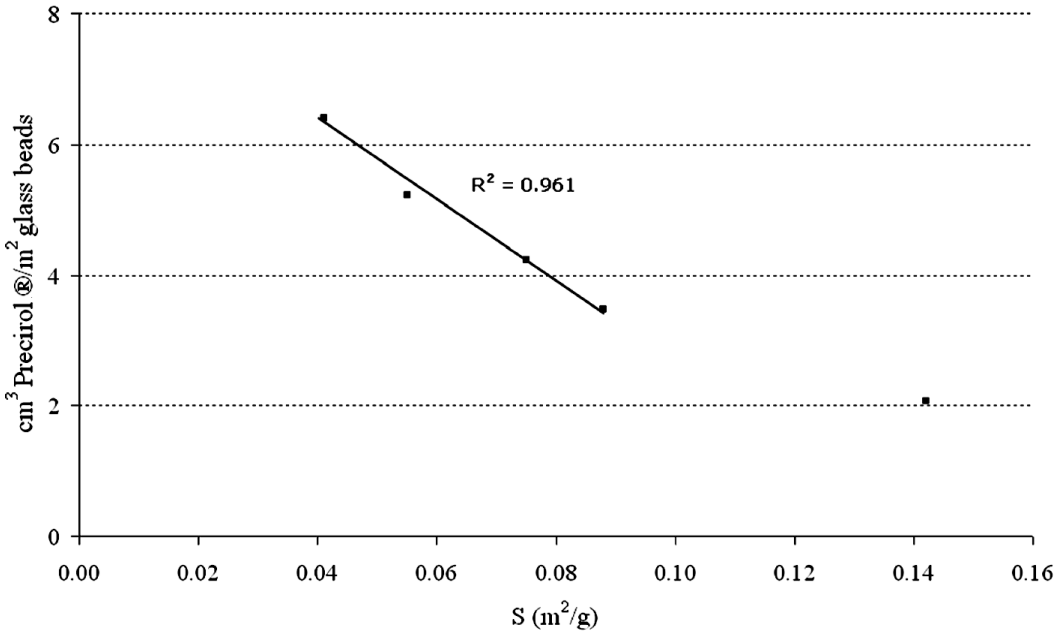


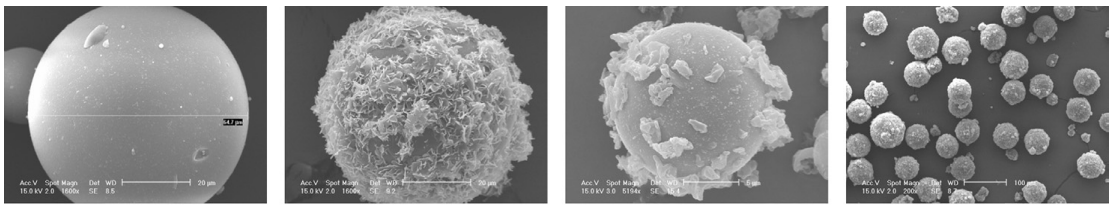
Figure 4. Volume of Precirol® deposited onto the particles vs. specific surface area of the coated particles.

coating is not just a deposit of solid Precirol® onto glass beads but implies a simultaneous solidification/deposition phenomenon onto the bead surfaces.

This statement is confirmed by Fourier transform-infrared (FT-IR) spectral analysis. The coated sample is compared to a physical mixture of Precirol®, solidified via SCF process, and glass beads. The corresponding spectra are shown in Figure 6. The spectrum of physical mixture is qualitatively different from that of the coated glass beads. The most relevant difference is located near 800–900 cm^{-1} region: the physical mixture presents the peak due to glass beads alone whereas the coated sample does not. The absence of this on the coated sample spectrum can be due to a deposit of Precirol® onto the glass beads surface.

Coating of the Active Compound

The experiment for coating the active compound (AC) was performed twice since we have already estimated the relative and absolute deviations on the process with the previous glass beads experiments. The measured true densities are shown in Table 5.



(a) (b) (c) (d)

Figure 5. ESEM pictures of (a) uncoated glass bead × 1600, (b) glass bead coated by supercritical fluids process × 1600, (c) physical mixture × 5194, (d) general view of coated glass beads × 200.

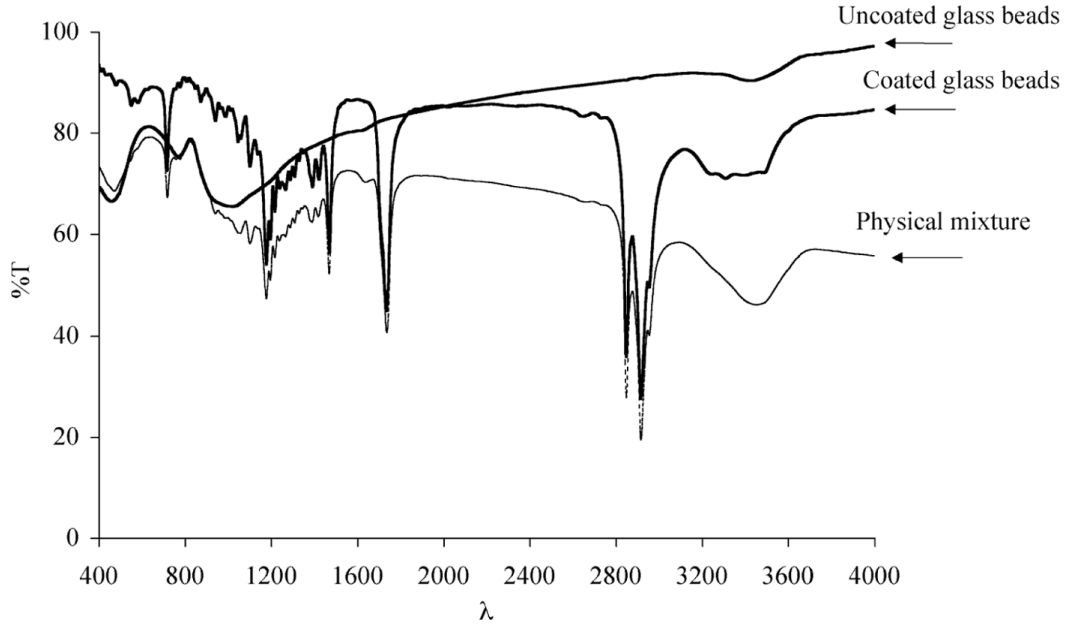


Figure 6. FT-IR spectra of the physical mixture and the coated particles.

Cumulative particle size distributions are shown in Figure 7. The D[4;3] and span results for the AC are given in Table 6.

The cumulative size curves show that, in this case, the width of the coated particle size distribution is slightly decreased compared to the uncoated particles. The ESEM pictures in Figure 8 confirm that the uncoated particles are very polydispersed. Furthermore, the coated particles tend to be agglomerated. In fact, there are more coated agglomerates than coated individual particles. In this case, agglomeration may occur before coating between the AC particles and during coating. The obtained mass ratio is here around 0.59, which is near the initial one, the excess coating agent contributing here to agglomeration.

If one measures the specific surface area of the AC alone using nitrogen adsorption-based apparatus and if we calculate the volumes of Precirol® deposited per surface area, one obtains, respectively, 0.71 m^2/g and 0.45 $cm^3_{Precirol}/m^2_{glass\ bead}$ for trial 1 and 2.11 $cm^3_{Precirol}/m^2_{glass\ bead}$. for trial 2. These latter results suggest a poor reproducibility of the experiments with this type of particle. Considering the relative deviation on the mass ratio determined by DSC measurement and given in Table 6, the poor reproducibility is confirmed. It may be mainly due to an uncontrolled agglomeration phenomenon, indicating that the more dispersed the size distribution, the more important the agglomeration. However, dissolution tests performed in distilled water at room temperature showed that the coating is effective since a sustained release is observed for the coated active compound (Figure 9).

Table 5. True densities measured for the coating of AC

Sample	Uncoated AC	Precirol® solidified via supercritical process	Coated AC, trial 1
True density (g/cm^3)	1.215	0.99	1.14

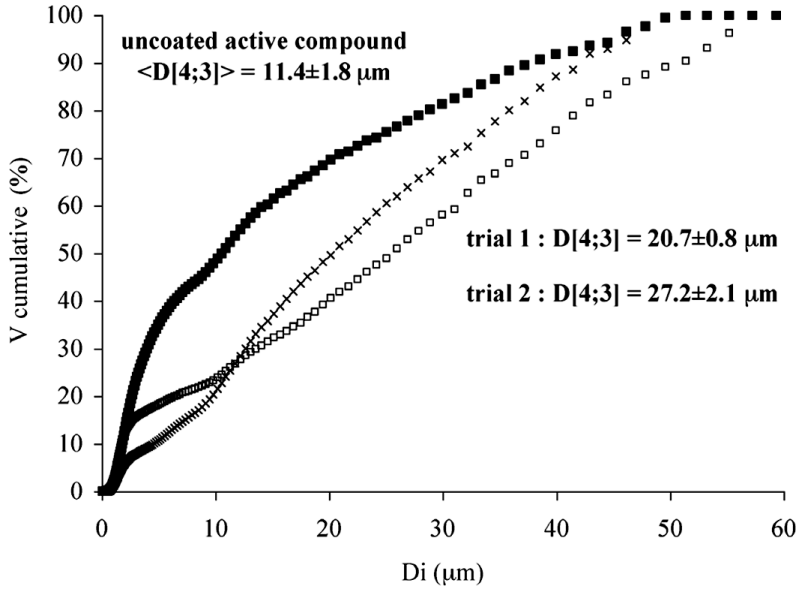


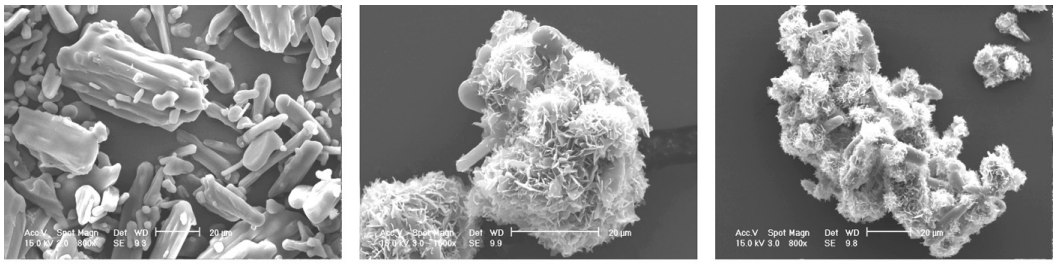
Figure 7. Cumulative volume size distribution of both uncoated and coated AC compounds vs. mean EAD.

Conclusions

In this study, several complementary analytical measurements were performed to study the feasibility of a new solvent-free encapsulation process based on the use of supercritical CO_2. Sieved fractions of microparticles in 0–80 microns size range as well as an active compound were successfully coated. Particle size analysis showed that the larger glass bead particles seemed to be coated individually, whereas the ones having a size less than 20 microns tended to be simultaneously agglomerated. Comparing ESEM pictures of the physical mixture of both components and coated particles suggested that two phenomena occur simultaneously: solidification of the coating agent and its deposition onto the particle surface. In addition, the ESEM visualizations and FT-IR spectra of a simple physical mixture and of the coated particles turned out to be quite different. The coating of an active compound resulted mainly in agglomerates, which was confirmed by both ESEM visualization and size

Table 6. Mean volume diameter for the AC coating experiment

Materials	Uncoated AC	Coated AC, trial 1	Coated AC, trial 2
D[4;3] (μm)	14.9 ± 1.4	22.2 ± 1.8	26.9 ± 0.4
D50 (μm)	11.4 ± 1.8	20.7 ± 0.8	27.2 ± 2.1
Span	4.75	1.68 ± 1.9	1.75 ± 0.9
ΔHfus (J/g)	—	24.4	60.2
Precirol® determined by DSC (% w/w)	—	21.4	52.7
Precirol® determined by DSC (% w/w)	—	37.1 ± 15.7	
Relative deviation	—	42.3	



(a) (b) (c)

Figure 8. ESEM analysis of the (a) uncoated AC × 800 and (b) coated AC × 1600, (c) × 1900.

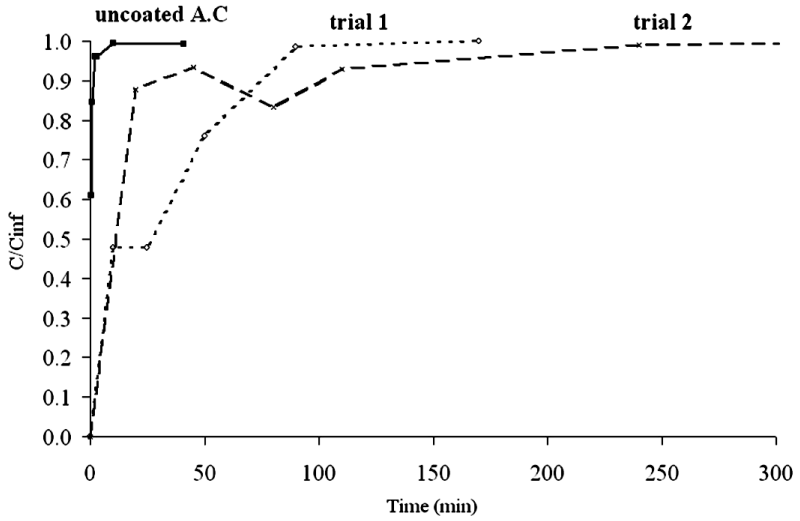


Figure 9. Test release of both coated and uncoated AC into distilled water.

distribution measurement. Yet, a dissolution test showed that the coating was effective in sustaining release. The reproducibility of the process turned out to be acceptable when no agglomeration of coated particles occurred, but it has to be improved in the case of highly dispersed particles less than 20 microns, mainly by limiting their agglomeration.

The characterization methods presented here show that the encapsulation process seems to be a promising route for solvent-free coating of pharmaceuticals in the micron range. Especially, as the present process treats the coating agent and particles separately, this permits processing of thermosensitive products and better controlling the coating agent/particle ratio.

Nomenclature

ø	diameter, m
ΔH_{fus}	heat of fusion, J/g
d_i	density of the compound i, kg/m^3
D[4,3]	mean volume diameter, m
D_{50}	median diameter, m
f_i	mass fraction of the compound i
S_0	specific surface area, m^2/g

Span	(D90-D10)/D50
U	velocity, m/s

References

Allen, T. 1997. Particle size measurement. In *Powder Sampling and Particle Size Measurement*, 5th ed. vol. 1. Londres: Chapman & Hall.

Fages, J., H. Lochard, J. J. Letourneau, M. Sauceau, & E. Rodier. 2004. Particle generation for pharmaceutical applications using supercritical fluid technology. *Powder Technol.* 141: 219–226.

Kröber, H. & U. Teipel. 2005. Microencapsulation of particles using supercritical carbon dioxide. *Chem. Eng. Process.* 44: 215–219.

Perrut, M. 2002. Method for encapsulating fine solid particles in the form of microcapsules. World Patent WO 02/05944 A1.

Perrut, M., J. Jung, & F. Leboeuf. 2005. Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes. Part II: Preparation of composite particles. *Int. J. Pharm.* 288: 11–16.

Ribeiro Dos Santos, I., J. Richard, B. Pech, C. Thies, & J. P. Benoit. 2002. Microencapsulation of protein particles within lipids using a novel supercritical process. *Int. J. Pharm.* 242: 69–78.