COATING OF NANOPARTICLES USING A SUPERCRITICAL ANTI SOLVENT (SAS) PROCESS

Marilyn CALDERONE[1], Elisabeth RODIER*[1], Bernard FREISS[2], Jean Jacques LETOURNEAU[1] and Jacques FAGES[1]

[1]EMAC Ecole des Mines d'Albi-Carmaux Campus Jarlard 81013 Albi Cedex 09 France
[2]Institut de Recherche Pierre Fabre, BP 92, 81603 Gaillac France
*E-mail: Elisabeth.Rodier@enstimac.fr - Fax : 05 63 49 30 25

Nanoparticles represent a new field of interest especially for pharmaceutical applications such as controlled release or specific target delivery. Because of their high specific surface area, they are not easy to encapsulate. This paper deals with nanoencapsulation of silica particles using the SAS process. The co-injection of the silica particles dispersed in an organic polymeric solution and of supercritical CO_2 induces the solidification of the coating agent onto the silica nanoparticles, then forming nanocapsules. Two common polymers used in the pharmaceutical industry were chosen as coating agents. Hydrophilic nanoparticles were investigated so as to evaluate polymer/model particle interactions. We have worked with hypromellose phthalate HPMCP and ethylcellulose EC. The organic solvents used were acetone and ethanol. The coating experiments using supercritical CO_2 were performed in a semi continuous process. Before injecting, the mixture of silica particles and dissolved polymer into organic solution was dispersed by sonication. Once pressure and temperature conditions in the vessel are established, the injection started. Then the last stage was an extraction of the residual solvent in the coated nanoparticles. The CO_2/solvent mixture was continuously separated by adjusting pressure and temperature conditions in the cyclonic separators. Different parameters were adjusted to obtain a successful coating of nanoparticles. Both polymer/silica and CO_2/organic solution ratios, pressure and the way to bring into contact the polymeric organic suspension with the silica particles have been tested. Perkin Elmer Fourier Transform Infrared Spectrophotometer (FT-IR) and BET specific surface area were used to evaluate encapsulation efficiency. ESEM was used for morphological visualisations.

INTRODUCTION

Because 100 μm is about the size limit for coating particles with a fluidised bed, coating of particles in the nanometer range is one of the new challenges in the pharmaceutical industry. Since they reduce particle attraction, supercritical fluids are one of the conceivable possibilities to avoid agglomeration during the coating process. This paper deals with hydrophilic silica nanoparticles coated with classical pharmaceutical polymers using a SAS process. The main variables tested are the capillary size, the pressure in the vessel during the polymer solidification, the way to bring into contact the polymeric organic suspension with the silica particles and finally both the flow rate of supercritical CO_2 and organic suspension during injection.

The coating efficiency was evaluated with BET specific surface area and FT-IR spectra. ESEM was used for morphological investigations of the coated particles.

I - MATERIALS AND METHODS

Two polymers were tested for silica coating experiments : HP50 (ShinEtsu, Japan), an hypromellose phthalate (MW = 84 000 g.mol^{-1}) and ethylcellulose EC N7 (MW = 57 500

g.mol^{-1}) (Hercules, USA). Some previous experiments on these materials done with a RESS (Rapid Expansion of Supercritical Solution) process showed that they were insoluble in supercritical CO_2. All polymers are also totally insoluble in water and they present total or partial solubility in the organic solvents used in this work.

The solvents used were acetone (Fluka, Switzerland, 99.8 % pure) and ethanol (Aldrich, Switzerland, 99.8 % pure). Acetone and ethanol were chosen because of their high miscibility with CO_2 under supercritical conditions [1]. Some previous solubility measurements proved that the saturation of HPMCP in a mixture acetone/ethanol (50/50 % wt) was about 5 % wt and the solubility of EC in pure acetone was about 6 % wt.

As a model for nanopowders we used silica hydrophilic nanoparticles (Aerosil® 90, Degussa, Germany). The mean primary particle size is about 20 nm. Previous size analysis on a dry sample powder in a counter particle size analyser (Aerosizer, TSI) based on aerodynamic measurement showed that Aerosil® 90 always existed as clusters. The mean number diameter of the clusters is about 1.45 µm. Consequently, a risk of coating the agglomerates and not the primary particles exists. These agglomerates might be broken by shearing in HPLC pump during injection although we can not quantify this.

The coating experiments using supercritical CO_2 were performed on a pilot-scale apparatus (Separex, France) which is shown on figure 1. Liquid CO_2 (purity 99.8 %, Air Liquide, France) is admitted from a cylinder (1), then cooled through an heat exchanger (2) and circulated by a membrane pump (Lewa, Germany) (3). Compressed CO_2 flows through a heater (4) and becomes supercritical. In SAS configuration, the Aerosil® suspension containing the solvent and the dissolved polymer (5) is co-injected with the CO_2 stream at the top of the vessel and reach the nozzle (Topindustrie, France) by an HPLC pump (6) (Gilson, 307 piston pump). It is then sprayed into the 500 cm^3 heated vessel. The powder formed is collected in a collector (8) inside the extraction vessel (7). CO_2-solvent mixture is depressurised by a back pressure regulator (9) and separated in two cyclonic separators (10). After purification through an active carbon bed (12), the condensed CO_2 runs back to the heat exchanger (2) or goes in the vent line (13).

1: CO_2 supply
2: cooler
3: membrane pump
4: heater
5: polymeric / Aerosil® 90 suspension
6: liquid pump

7: nozzle
8: high pressure vessel
9: back pressure regulator
10: cyclonic separators
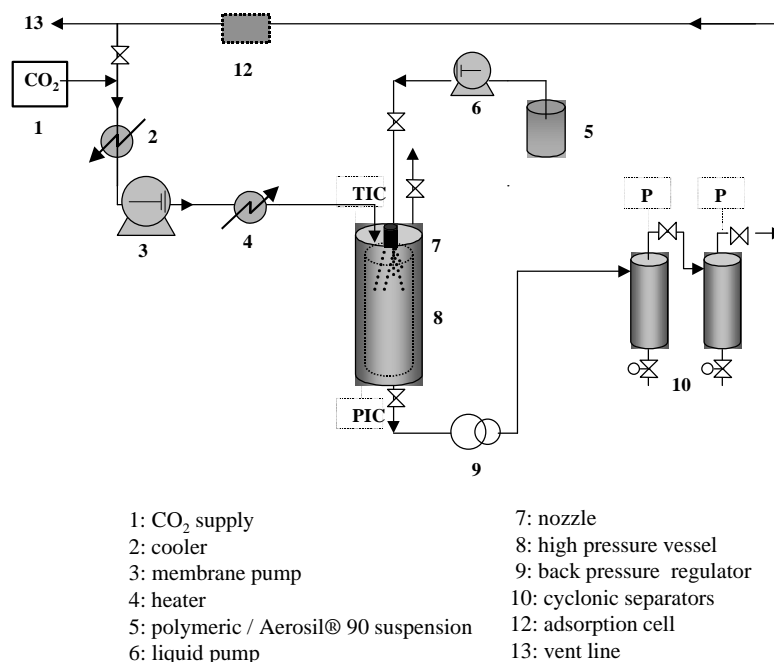12: adsorption cell
13: vent line

Figure 1: Experimental set-up for SAS coating of nanoparticles

The mass ratio polymer/Aerosil® 90 was 1:1. The suspension was sonicated before being pumped to be injected. After 20 minutes, the flow of the suspension was stopped and pure CO_2 continued to be run through the vessel for 40 min in order to remove the residual solvent from the powder. The pressure and temperature conditions inside the vessel during injection and flushing were chosen according to the required solvent density. A low density was preferred to improve polymer solidification by enhancing anti-solvent effect [2]. The experimental conditions are given in table 1 and table 2. In previous studies we have adjusted experimental conditions to solidify the polymers without nanoparticles.

Powders obtained were analysed using an ESEM Philips XL 30 FEG for morphological analysis. The resolution conditions were 40 mA and 1,2 kV. Fourier Transform-Infrared (FT-IR) Spectroscopy using a PerkinElmer infrared spectrophotometer was used to evaluate coating efficiency. The spectra were acquired in the range 400-4000 cm^{-1} and were measured on tablets. They were obtained by mixing the component (0.5 % wt) with ground KBr and then mix in a mortar. Then the mixture was pressed under vacuum for 10 minutes using a press kit. The spectrum was immediately acquired and KBr reference was subtracted from the obtained spectrum. The specific surface area of the solute particles was measured using the BET method (ASAP, 2010 Micromeritics) with nitrogen. The samples were all degassed before N_2 adsorption during one night at 373 K.

Table 1: Experimental conditions for SAS coating with HPMCP - Polymeric concentration 4.4 % wt.

Trials	1	2	3
Aerosil ® 90 introduction	Suspended in organic polymeric solution	Suspended in organic polymeric solution	Suspended in organic polymeric solution
Injection organ	Capillary 100 μm	Capillary 100 μm	Capillary 100 μm
P during suspension injection (MPa)	8.5	8.5	8.5
T during suspension injection (K)	323	323	323
Q CO_2 during suspension injection (kg.h^{-1})	4	5	4
Q suspension during injection (mL.min^{-1})	0.7	0.7	1.4

Table 2: Experimental SAS conditions for nanoencapsulation with ECN7 - Polymeric concentration 5.4% wt.

Trials	4	5	6	7 and 7.1	8
Injection organ	Capillary 100 μm L=1,5 cm	Nozzle 200 μm	Capillary 100 μm L=1,5 cm	Capillary 100 μm L=1,5 cm	Capillary 100 μm L=7,5 cm
Aerosil ® 90 introduction	Suspended in organic polymeric solution	Suspended in organic polymeric solution	Suspended in organic polymeric solution	Initially in the vessel	Suspended in organic polymeric solution
P (MPa) during suspension injection	8.5	8.5	17.0	8.5	8.5
T (K) during suspension injection	323	323	323	323	323
Q CO_2 during suspension injection (kg.h^{-1})	4	4	4	4	4
Q suspension during injection (mL.min^{-1})	0.7	0.7	0.7	0.7	0.7

II - RESULTS AND DISCUSSION

In the experiments of coating hydrophilic silica nanoparticles with ECN7, we obtained a very fine powder, easier to handle than the pure Aerosil® 90 nanoparticles. Figure 3 compares ESEM images of the coated and uncoated particles. It appears that the coated

nanoparticles are larger than uncoated nanoparticles. Notice that the coated Aerosil® 90 is always in form of agglomerates which confirms the previous particle size analysis.

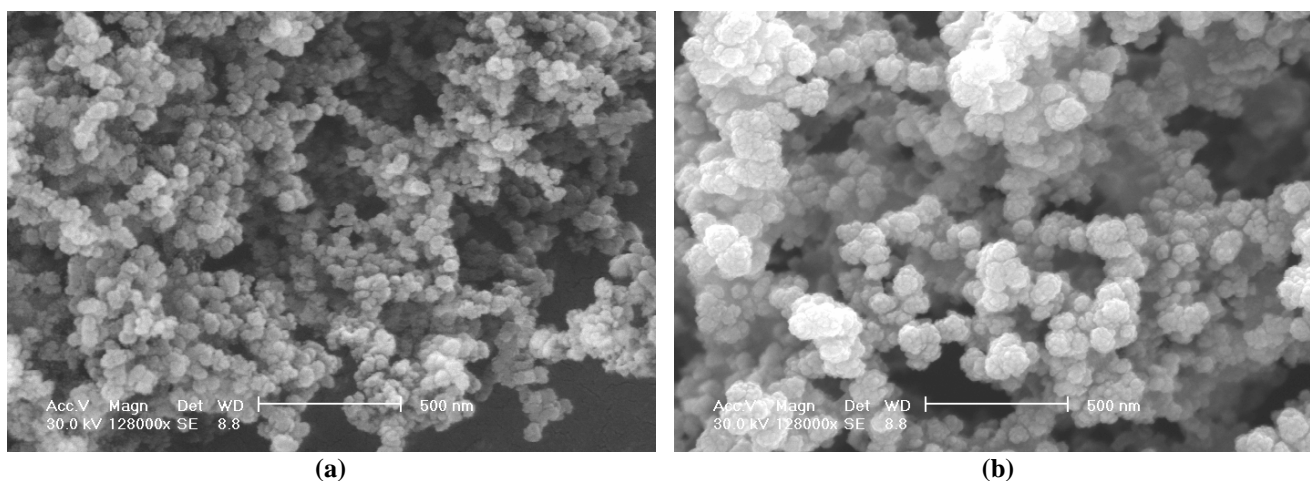(a)   (b)

Figure 3 : ESEM images of Aerosil® 90 coated with ECN7 x 128 000 - Working conditions P = 8.5 MPa, T = 323 K - capillary size 100 mm - (a) uncoated Aerosil® 90 (b) coated nanoparticles

FT-IR spectra of both the coated silica and the physical mixture Aerosil® / EC 50:50 were acquired. Ethylcellulose is an ethyl ether of cellulose, a long polymer chain consisting of glucopyranose units joined together by acetal linkages. Each glucose unit has three replaceable hydroxyl groups which are substituted to the extent of 2.25-2.60 ethoxy groups (OC_2H_5) per unit, equivalent to an ethoxy content of 44-51% [Figure 4a]. Silica has siloxan and silanol groups onto the surface [Figure 4b].

(a)   (b)

Figure 4: Structural formula of silica (a) and ethylcellulose (b)

Figure 5 shows the spectra of pure ethylcellulose, Aerosil®, physical mixture of Aerosil® with ethylcellulose and coated particles. Then table 3 summarizes the main resolved peaks [3].

Table 3: FT-IR spectra main peaks of pure Aerosil® 90, pure ethylcellulose, physical mixture of both compounds and coated nanoparticles

Compounds/Function	Si-OSi	Si-OH	SiO-H	C-OH	C_2H_5	C-O
Aerosil® 90 (cm^{-1})	1130.4	818.9	3409.1	-	-	-
ECN7 (cm^{-1})	-	-	-	3454.5	2863.6	1128.2
Physical mixture (cm^{-1})	1130.4	818.9	3409.1	Not visible	2863.6	Not visible
Coated particles (cm^{-1})	1130.4	818.9	-	3454.5	2863.6	Not visible

The spectrum of the physical mixture ethylcellulose / Aerosil® is the addition of the one of pure Aerosil® and of the one of ethylcellulose, whereas the spectrum of the coated particles shows some differences. The intensity of Si-OH at 818.9 cm^{-1} is weaker in the case of coated particles than in the physical mixture. The spectrum of coated particles does not seem to have

the SiO-H bond but the CO-H bond instead, on the contrary of the physical mixture. The intensity of the C_2H_5 bond is stronger in the case of coated particles. From these remarks we conclude, at least in a qualitative way, that the coating of silica nanoparticles with ethylcellulose seems to be effective.
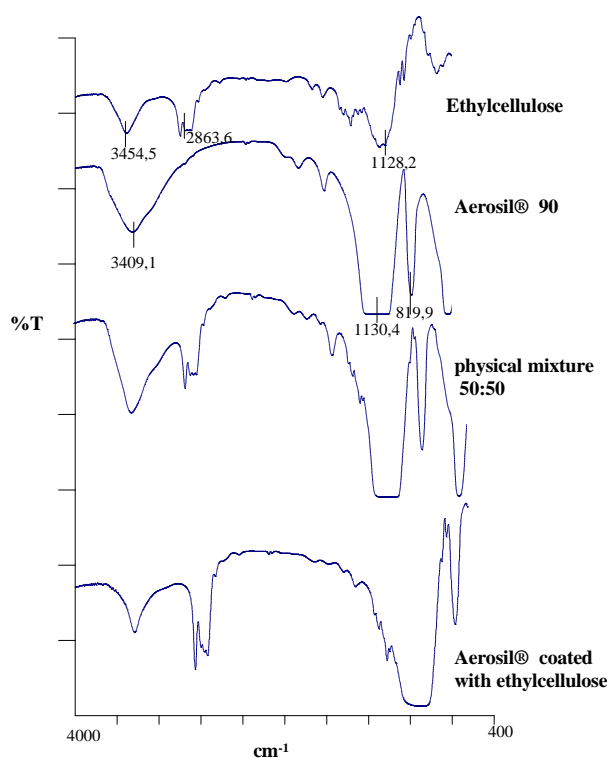

Figure 5 : FT-IR spectra for ethylcellulose (a); Aerosil ®90 (b); Physical mixture of Aerosil ® 90 with ethylcellulose (c) and for the coated silica with ethylcellulose (d)

Then the specific surface area of the samples was measured. The points 2, 4 and 7 and bare Aerosil® were done three times with different samples so as to evaluate the homogeneity of the powder obtained [Table 4].

Table 4 : BET specific surface area analyses

BET (m^2/g) \ Trials	Aerosil® 90	1	2	3	4	5	6	7	7.1	8
Sample 1	179	28	31	54	47	62	57	76	60	26
Replicate 1	125	-	25	-	35	-	-	95	-	-
Replicate 2	89	-	24	-	-	-	-	-	-	-
Sample 2	105	-	23	-	42	78	-	-	-	-
Average BET	142 ± 37	-	25,7 ± 2,6	-	41,3 ± 4,2	70 ± 8	-	77 ± 12	-	-

Experiments 1 to 8, confirm that Aerosil® particles may be coated since specific surface areas are always significantly lower than that of the pure silica. In table 4 considering, experiments 2 or 4, it seems that the coated Aerosil® is stable with time, the BET specific surface area remaining unchanged when repeating the measurement on the same sample. On the contrary, the specific surface area of the bare Aerosil® changes between two measurements, considering both consecutive measurements on the same sample and measurements on two different samples. It may be due to the hydrophilicity of Aerosil®.

Comparing experiments with HPMCP and with EC the specific surface area of the coated silica is higher with EC than with HPMCP. It suggests two possibilities: the coating with HPMCP is more efficient or there is more agglomeration with HPMCP.

The coating in experiment 7 is not satisfactory since the samples are inhomogeneous : it can be seen in the sample obtained, on one hand polymer alone and on the other hand silica alone. Besides, the BET specific surface area is higher and varies more than in the other experiments. Two comments can be made. First, we did not control the mixing of Aerosil® particles with polymer and so the way they enter into contact. In addition, it seems that the polymer solidification happens just after the nozzle outlet and then silica particles initially in the vessel are not coated. Second, Aerosil® particles being put initially in the vessel in SC conditions, their degree of dispersion might be different. Indeed, interparticle interactions may be weaker and the resulting Aerosil® powder less agglomerated, leading to higher BET values for the specific surface area of the coated final powder.

Comparing experiments 4 and 5, surface area is higher using the nozzle rather than the capillary. The inlets of the antisolvent and of the dispersion in the vessel are nearer in the case of the nozzle. Hence, the solidification of the polymer is more rapid, inducing less agglomeration. This suggestion is reinforced by comparing experiments 4 and 8, that is when inlets are taken away using a longer capillary for the dispersion inlet, we observe more and more agglomeration. Comparing experiments 4 and 6, changing the pressure vessel seems to have no effect on the coating. We reach the same conclusion comparing 1 and 2 when the antisolvent flow rate is changed. Finally, comparing experiments 1 and 3, we see that the higher the suspension flow rate, the higher the specific surface area. Hence, the higher the suspension velocity at the capillary outlet, the lower the agglomeration.

CONCLUSIONS

The SAS experiments performed in this work and considering the FT-IR spectra, it seems that the coating of silica nanoparticles with EC or HPMCP is successful.

In addition, we can draw following conclusions. Firstly, when we inject separately a dispersion of nanoparticles in dissolved polymer solution and the CO_2 antisolvent, the way of introducing the dispersion is crucial to control the agglomeration of the coated particles. The proximity of both inlets seems to be a key-factor, as for the dispersion velocity at the nozzle or capillary outlet. Secondly, when we inject separately the dissolved polymer solution and the CO_2 antisolvent with nanoparticles previously put into the vessel, the coating efficiency may be not satisfactory because it is difficult to control the way particles and polymers are put into contact. However, these experiments suggest a possible effect of a supercritical environment on the dispersion of nanoparticles. Further work has to be done to improve the contact between nanoparticles and polymer, for instance, introducing an agitation in the vessel or pre-dispersing the nanoparticles before coating them. The problem of agglomeration of coated particles has to be investigated too, changing the mass ratio of particles and polymer depressurising in another fluid could be possibilities.

REFERENCES:

[1] JUPPO, A.M., BOISSIER, C., KHOO, C, Int. J. Pharm., Vol. 250, **2003**, p. 385.

[2] THIERING, R., DEHGHANI, R., FOSTER, N.R., J. Supercrit. Fluids, Vol. 21, **2001**, p. 159.

[3] SILVERSTEIN, R.M., BASLER, G.C., MORILL, T.C., Identification spectrophotométrique de composés organiques, DeBoeck Université publisher, **1998**, ISBN 2-8041-2462-0.