Impregnation of core-shell submicronic polymer particles using supercritical fluids for biomedical applications

Anne-Claire Le Meur[1,2], Thierry Tassaing[3], Valérie Héroguez[1], Cyril Aymonier[2], Marie Mourgues[4] and François Mourgues[4].

Université de Bordeaux, [1]Laboratoire de Chimie des Polymères Organiques, [2]Institut de Chimie de la Matière Condensée de Bordeaux, [3]Institut des Sciences Moléculaires, ENSCPB, 16 avenue Pey-Berland, 33607 PESSAC Cedex, France

[4]Institut de Développement de Produits pour la Santé, Zone Industrielle d'Artigues, Avenue Gay Lussac, 33370 ARTIGUES PRES BORDEAUX, France

INTRODUCTION

Controlled drug delivery devices using biocompatible polymers have received considerable attention in the last years. These substances provide in general a more controlled release rate and consequently assumption of the drug by the body improving its therapeutic action[1]. The drug diffusion rate depends on the polymers used, the morphology of the system and the molecular state of the active principle within the matrix. The conventional methods to prepare solid dispersions of polymer/ drug formulations are microencapsulation by solvent extraction/ evaporation technique or the co-precipitation of polymer and drugs[2]. Solvents used are usually removed from the product by a final evaporation step but are rarely completely purified.

Supercritical fluid technology has already proved its applicability to the area of pharmaceutical formulations. This includes particles formation via antisolvent precipitation, aerosolisation and rapid expansion of supercritical solutions. Another possible approach is to use supercritical fluid as a solvent for impregnation. Duarte et al. has synthesized and impregnated with drugs Poly(diethylene glycol dimethacrylate) particles under supercritical carbon dioxide ($scCO_2$)[1]. CO_2 is the preferred supercritical solvent because of its non-toxicity, non-inflammability, cheapness and high diffusivity in the polymers. Indeed, it has been demonstrated that the effect of $scCO_2$ on glassy polymers mimics the effect of heat inducing mobility of polymer chains and segments leading to the swelling of the matrix[2]. An additional advantage is that the process with $scCO_2$ does not leave any residual solvent in the processed polymer/ drug formulation since CO_2 is a gas under ambient conditions and once the process is complete CO_2 leaves the sample.

This work describes the original impregnation of core-shell submicronic polymer particles with Salicylic Acid (SA) as a model drug using $scCO_2$. Particles of spherical morphology have been developed with an inner part composed of a hydrophobic polyolefin (core), and a shell of a hydrophilic polymer (shell), enabling to avoid recognition of the particle by the immune system. Those particles are synthesized by ROMP. Their impregnation is realized under $scCO_2$ with salicylic acid. Impregnating a polymer with a supercritical fluid supposes three main steps: first dissolving the solute in the $scCO_2$, then swelling the polymer with a solute saturated flow of $scCO_2$ and finally, depressurizing the system. In this paper we will first see the solubility measurement of the different components in $scCO_2$. In a second part, we will see the impregnation of salicylic acid in the core polymer, than the shell polymer and finally, in the particles. The swelling, the impregnation of the constitutive polymers and the molecular state of salicylic acid in the different matrixes have been studied using FTIR spectroscopies inspired from Vitoux et al works[3]. The results of particle impregnation have been determined by Thermal Gravimetric Analysis and have been compared to those obtained with the core and the shell alone.

EXPERIMENTAL

Synthesis of core-shell particles. Core-shell (30/70% vs weigh) particles latexes have been prepared by ROMP dispersion[4]. Size of particles can be controlled from 300 nm up to 500 nm. Figure 1 shows an example of TEM image of such particles.

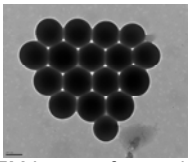

Figure 1: TEM Image of core-shell particles.

Polymer swelling and impregnation. Polymer swelling and impregnation were studied by Infra Red in situ measurements. Those measurements were performed with a Biorad interferometer and a home made stainless steel cell equipped with two cylindrical silicium windows. The cell conditions are determined with an accuracy of about 2K for the temperature and 1 bar for the pressure. For the analysis of polymer swelling or impregnation, one of the two silicium windows is covered with a film of core or shell. The film was directly formed on the window by spin coating of a solution of the polymer diluted in dichloromethane. The thickness of each film was measured with a profilometer. For the impregnation experiments, salicylic acid was directly placed at the bottom of the cell. Once the set-up of the cell is complete, CO_2 was added to the desired pressure and temperature. The system was kept under isobaric and isothermal conditions for at least few hours. Due to polymers properties, all the experiments were performed at 33°C. Spectras have been recorded every 20 minutes.

RESULTS AND DISCUSSION

The determination of the solubility of salicylic acid in $scCO_2$ has been first studied as a function of the $scCO_2$ density in order to control the amount of drug component that can be carried out for impregnation. Then, the extent of polymer matrix swelling with $scCO_2$ has been determined in order to evaluate the ease of impregnation in the different polymers. Finally, the impregnation of each polymer and of core-shell particles has been studied.

Determination of SA solubility in $scCO_2$. Loading of impregnated polymer can be controlled by the salicylic acid solubility in the $scCO_2$ as a function of pressure and temperature. To determine salicylic acid concentration solubilized in $scCO_2$ in the experiment cell at specific conditions, an excess of salicylic acid was charged and the IR absorbance was determined for temperature that goes from 35°C to 55°C and pressures from 10 MPa to 20 MPa. According to the Beer-Lambert law, knowing the absorbance of SA, we can have the solubilized concentration: $A = \varepsilon . l . s$ where A is the SA absorbance, s the solubilized SA concentration, ε the SA molar absorption coefficient and l the path length. A theoretical equation based on the Chrastil model has been determined[5]:

$$\ln s = k . \ln d + \frac{a}{T} + b$$

Where d is the CO_2 density in g/L, T the temperature in K and k, a, b, the Chrastil coefficients. Experimental results are needed to determine k, a and b as presented in Table 1.

Table 1: Chrastil coefficients of SA-$scCO_2$.

k	*a*	*b*
4,00	-4953,58	-11,03

Swelling of polymers. Once the $scCO_2$ is injected in contact with the polymer, it swells. For the IR beam, it means that the concentration of the polymer decreases when the concentration of $scCO_2$ inside increases (Figure 2). The study of the polymer swelling is very important because it is directly linked to the possibility of SA impregnation.

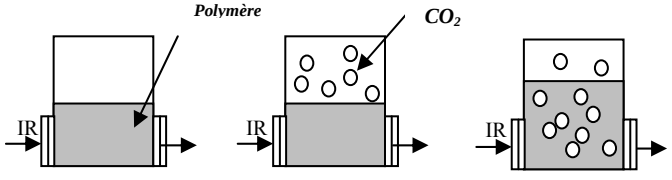

Figure 2: Schematic presentation of the in-situ experiment using a transmission optical cell to study swelling and impregnation of polymer by $scCO_2$.

According to Beer-Lambert law, the swelling of a polymer can be determined knowing its initial and final states:

$$A_0 = \varepsilon.l.c_0 \quad [1] \qquad A = \varepsilon.l.c \quad [2]$$

with A_0 and A the polymer absorbance before and after $scCO_2$ injection respectively, c_0 and c polymer concentrations seen by the IR beam before and after adding $scCO_2$ respectively and ε, the molar absorption coefficient of the considered specie. If we consider that the polymer sample occupies a volume (V) before exposure and $(V+\Delta V)$ during exposure to CO_2, the following equation defines the swelling S:

$$\frac{c_0}{c} = \frac{V + \Delta V}{V} = 1 + \frac{\Delta V}{V} = 1 + S \quad [3]$$

Thus, combining [1], [2] and [3] equations, the swelling degree of the polymer is obtained directly from A_0 and A:

$$S = \frac{A_0}{A} - 1 \quad [4]$$

Polyolefine core: Swelling of the core has been evaluated using the height of the bending mode of C-H bonds band. Figure 3 shows an evaluation of the core swelling as a function of time at different pressures at 33°C.

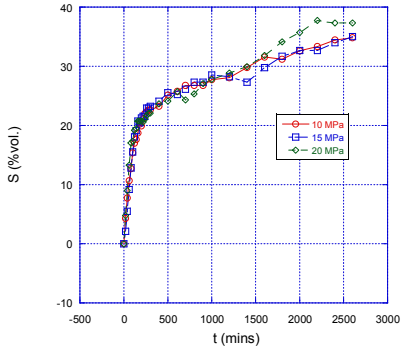

Figure 3: Swelling of core during its impregnation with SA.

These results show that $scCO_2$ can swell the polyolefine core until 35% vol., what doesn't depend on the pressure. Same results will be observed with pressure during core impregnation. Therefore it has been decided to work at one pressure, 15 MPa to study the shell and the particles.

Hydrophilic shell: Same analyses have been realized on the shell and show that it can be swells until 30% vol. at 15 MPa and 33°C.

Impregnation of polymers. Impregnation is narrowly linked to the polymer swelling. The salicylic acid concentration in the polymer is obtained from the Beer-Lambert law and then calculated in the units of gSA/cm^3. The final concentration is calculated in mass percentage by using the following equation:

$$\%massSA = \frac{c_{gSA/cm^3}}{c_{gSA/cm^3} + \frac{\rho}{1+S}} \quad [5]$$

where ρ is the polymer density and S the polymer swelling[6].

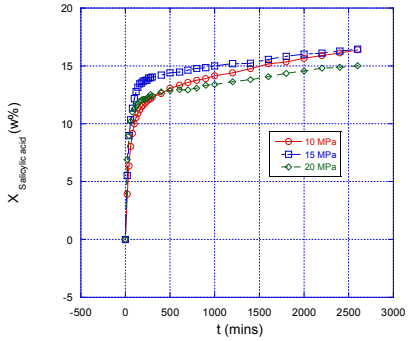

Figure 4: Mass percent of SA impregnated in the core matrix.

According to kinetics, it seems that impregnation of the matrix is directly linked to the swelling of the polymer. Figure 4 shows that the core can be impregnated with 15% w. of salicylic acid, mostly present in a dimeric form. This amount is obtained after 3 hours of impregnation and doesn't depend on pressure.

Shell: A similar study at 33°C and 15 MPa has been done with the shell showing that it can be impregnated with 35% w. of dimeric salicylic acid.

Impregnation of core-shell particles. Films of core-shell particles have been impregnated in the same conditions as polymer films (15 MPa, 33°C). The numerous informations on IR spectra prevented us to quantify swelling and impregnation of particles. The SA impregnated rates have been determined by TGA and show that particles can be impregnated with 15% of salicylic acid (Figure 5).

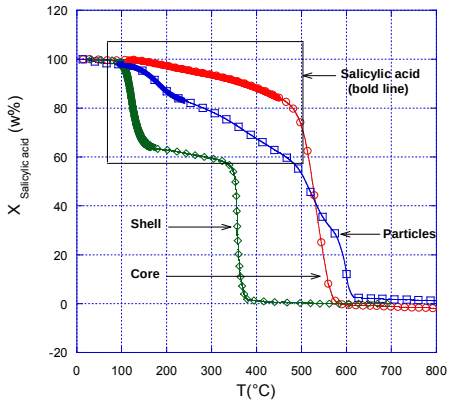

Figure 5: TGA of core film, shell film and core-shell particles film impregnated with salicylic acid.

According to the TGA of each single polymer impregnated film, we confirm that the SA concentration in the shell is higher than in the core. The core only represents 30% of the total weigh of one particle. This explains why particles impregnation results are closer to the core impregnation results rather than the shell ones.

Particles have also been impregnated directly from the latex form. Compared to the films impregnation, similar results have been obtained and don't show any effect on the colloidal structure of the core-shell particles.

CONCLUSIONS

Impregnation of core-shell particles by salicylic acid under $scCO_2$ has been successfully carried out. This process is governed by the solubility of the active principle and the swelling of macromolecules in $scCO_2$. Indeed FTIR spectroscopy has shown that in both polymers, swelling and impregnating the matrix have exactly the same kinetics. Identification of the exact location of the active principle within the core-shell structure is under investigation.

REFERENCES

(1) Duarte, A. R. C.; Casimiro, T.; Aguiar-Ricardo, A.; Simplício, A. L.; Duarte, C. M. M. *Journal of Supercritical Fluids* **2006**, *39*, 102-106.

(2) Kazarian, S. G.; Martirosyan, G. G. *International Journal of Pharmaceutics* **2002**, *232*, 81-90.

(3) Vitoux, P.; Tassaing, T.; F., C.; Marre, S.; Aymonier, C. *Journal of Physical Chemistry* **2009**, *113*, 897-905.

(4) Quémener, D.; Chemtob, A.; Héroguez, V.; Gnanou, Y. *Polymer* **2005**, *46*, 1067-1075.

(5) Chrastil, J. *Journal of Physical Chemistry* **1982**, *86*, 3016-3021.

(6) Guadagno, T.; Kazarian, S. G. *J. Phys. Chem. B* **2004**, *108*, 13995-13999.