$SCCO_2$-Based Process for Encapsulation of Target Compounds

*Garay, I., Bilbao, A., Angulo, I., Aranberri, I., Guijarro, J. & Salas, O.
GAIKER Technology Centre. Parque Tecnológico, Edif. 202. 48170 Zamudio (Bizkaia) SPAIN.
Phone: 34 94 6002323, Fax: 34 94 600 23 24; contact e-mail: garay@gaiker.es

This work has as main objective the development of a model process to encapsulate target compounds with an acrylate-methacrylate copolymer (Eudragit L100® and Eudragit EPO®), as coating agent, using supercritical carbon dioxide as antisolvent (SAS). Molecular alloys are the target products on which this SCCO2-mediated encapsulation has been evaluated. After studying the behaviour of the molecular alloy and copolymers in SC-CO2 at different operation conditions (pressure, temperature and presence of EtOH), efforts were invested in the optimization of Eudragit EPO® precipitation from an organic solution using carbon dioxide as antisolvent in batch mode. After loading the precipitation vessel with a fixed quantity of the copolymer dissolution, the SC-CO2 has been added until the pressure of operation has been reached. Three process parameters, namely solution nature, presence of surfactants and organic solvent removal step, have been evaluated. The precipitation trials were carried out using a supercritical fluid plant (Iberfluid Instruments) fitted with a 1000ml autoclave, equipment that it is been used for new trials regarding to molecular alloy encapsulation with Eudragit EPO®. Preliminary results of these last studies will be presented as well.

Keywords: Supercritical carbon dioxide; Supercritical antisolvent; Encapsulation, Acrylate-methacrylate copolymer; Molecular alloy

1. Introduction

The encapsulation of compounds has been found of particular interest in the pharmaceutical industry for the controlled release of drugs, genes and other bioactive agents. Nevertheless, there are more an more the industrial sectors that are interested in applying it on the development of new products, case of packaging, food and new material processing sectors, among others.

Many techniques for encapsulation have been described in literature. Most of them, such as organic phase separation, spray drying, solvent separation and the widely studied emulsification/solvent evaporation method and its modified versions, involve the use of organic solvents to mix the polymer and the additive to be encapsulated [1, 2]. Therefore, there has been a continuing growth of interest in replacing conventional organic solvents with environmentally friendly supercritical solvents in encapsulation processes.

The encapsulation of target products using a supercritical fluid as antisolvent offers several advantages over other encapsulation methods such as uniform encapsulation, controlled coating thickness and morphology of final particles and particle size distribution control with changes in the operation conditions, including the coating to particle weight ratio and reactor pressure and temperature [3]. Moreover, the mixing between the supercritical antisolvent and the liquid is much faster than in conventional liquid antisolvent processes, thus leading to higher supersaturations and smaller particle diameters. The supercritical antisolvent can be easily removed from the final product by reducing pressure, in contrast with the complex purification processes often required when organic anti solvents are used. And it is possible to carry out the process at low temperatures, avoiding the thermal degradation of the product [4].

The aim of the research presented here was to implement this supercritical antisolvent technology to encapsulate target compounds with an acrylate-methacrylate copolymer. Molecular alloys were chosen

as model target compound for this study. These compounds are excellent materials for thermal protection and for thermal energy storage because they combine a relatively high heat of melting with a suitable melting temperature, properties that make them to have an enormous potential for heating and cooling of buildings as alternative of solar energy, which availability is often intermittent, variable and unpredictable.

Molecular alloys as phase change materials are used for thermal protection and energy storage in many industrial sectors offering opportunities, specially, where the classics phase change materials (PCM) can not be used. In order to be part of the building's construction material, the molecular alloys will be encapsulated to be retained when they became liquid.

2. Experimental

2.1. Set-up.
SCF analysis, to study the behaviour of acrylate-methacrylate copolymers and molecular alloy in SC-CO2 at different operation conditions of pressure and temperature, with and without the presence of organic solvents, were performed using a Lab Scale Supercritical fluid, (Suprex-Prepmaster), equipped with a cell of extraction of 50ml of capacity, Figure 1.

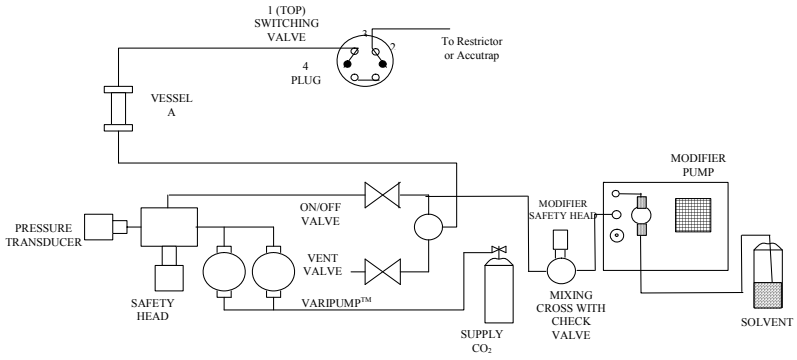


Figure1. Lab Scale Supercritical fluid, (Suprex-Prepmaster).

Encapsulation trials were achieved in a supercritical pilot plant connected to a 1000ml autoclave, Figure 2.

2.2. Materials.
As coating material two copolymers of acrylate and methacrylate were chosen, Eudragit L100® and Eudragit EPO® (Degussa). To evaluate the efficiency of the SC antisolvent encapsulation process, a molecular alloy designed for this project was chosen as target compound.

The chemicals used in this work were ethanol, acetone and dichloromethane grade HPLC supplied by Merck, carbon dioxide supercritical grade supplied by Air Liquid, SPAN 20 from Fluka and Sodium Dodecyl Sulphate from Prolabo. All materials were used as received without further treatment.

2.3. Methods.

2.3.1. Behaviour of the molecular alloy and copolymers in SC-CO2

First of all, it was studied the behaviour of Eudragit L100® and Eudragit EPO® in SC-CO2 at different operation conditions of pressure (10-20MPa), with and without the presence of organic solvents, specifically, EtOH, and a fixed temperature of 313K. The trials were carried out using the analytical-

scale SFE extractor (Suprex-Prepmaster), Figure1, in static and dynamic operation form, for assessment of cosolvent adding to the system. The aim of these experiments was to observe visual changes in Eudragit polymers after been exposed at different operation conditions and to study the solubility of the polymer in the supercritical fluid. A differential scanning calorimetry (DSC) of the obtained Eudragit was also done and compared with the DSC response obtained of the Eudragit commercial powder. Described experimentation was carried out again but using molecular alloy as tested compound, in order to determine its solubility in SC-CO2.

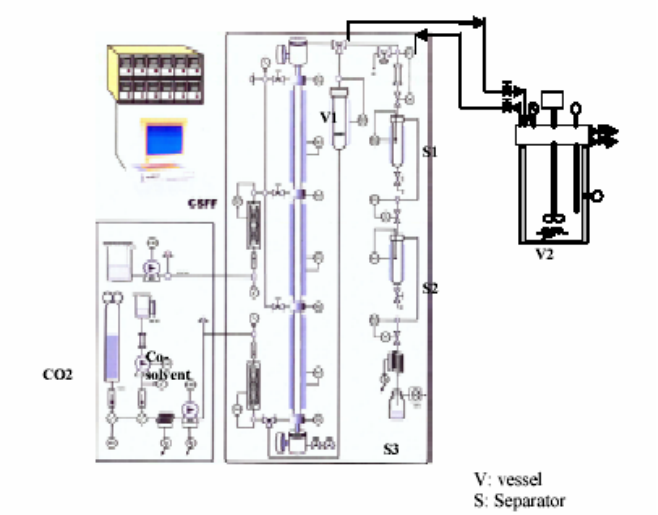


Figure2. Supercritical fluid plant. (Iberfluid Instruments S.A)

2.3.2. SCCO2-Based Process for Encapsulation

For first trials, to study the precipitation of Eudragit EPO® using antisolvent CO2, a polymer solution was prepared dissolving the polymer in an organic solvent. Ethanol, acetone, dichloromethane and an ethanol-water solution were used as solvents. The polymer solution was placed in the empty supercritical pilot plant's 1000ml autoclave, Figure2, and after being closed, CO2 was supplied to it up to pressure of operation was achieved. When steady state conditions of pressure (8-12,5MPa) and temperature (313K) were reached in the high-pressure vessel, the agitation was switched on and the high-pressure vessel was maintained in batch mode, at fixed operation conditions, for an hour. Thereafter CO2 was supplied again to the autoclave to remove all organic solvent until sample was completely dried. Finally, the high-pressure vessel was slowly depressurised and samples were collected for characterisation. In trials when the presence of surfactant (SPAN 20 and Sodium Dodecyl Sulphate) was study, it was directly added to the polymer solution (6%by weight).

Achieved Eudragit EPO® precipitation in form of microcapsules, only a few new trials have been carried out in order to evaluate the efficiency of the developed process for the encapsulation of molecular alloys.

2.3.3. Characterization of materials

In this study it was necessary the use of a Differential Scanning Calorimeter (DSC 30 Mettler Toledo) and a thermogravimetry (TG 50 Mettler Toledo), not only for thermal characterization of the raw materials but also for characterization of the obtained products after developed processes.

The mean size of particles was determined using optical microscopy (Nikon Optiphot AFX – II A) with a Buehler Omnimet image analyser system. For more detailed information about particles morphology an emission scanning electron microscope (SEM) will be used.

3. Results and discussion

3.1. Characterization of the raw materials.
Dealing with DSC, the glass transition temperature of the polymer was of 378K and for the molecular alloy 300,41K. Because of a large difference between compounds DSC analysis responses, DSC was considered an analysis of interest to detect Eudragit® and/or molecular alloy presence in obtained products during processes optimization.

Respect to thermogravimetric analysis, whereas Eudragit EPO® showed two maximum velocity of decomposition at 582K and 708,67K, the determined maximum velocity of decomposition for the molecular alloy was of 535,33K. This difference among compounds according to those characteristics temperatures, will be enough, not only to recognize each compound in final product, but also for the quantification of them. The thermogravimetric analysis will be of special interest in the study of the efficiency of the encapsulation process.

3.2. Behaviour of the molecular alloy and copolymers in SC-CO2
First of all, it was studied the behaviour of Eudragit L100® and Eudragit EPO® in SC-CO2 at a fixed pressure and temperature of operation, with and without the presence of EtOH as modifier. The trials regarding to this study are listed in Table 1. After experimentation, neither visual changes in Eudragit® copolymers nor changes in their thermal properties were observed.

Nevertheless, a relatively solubility of both copolymers in SCCO2 in presence of EtOH was detected. At 313K and 12,5 MPa, when a 12,5% of EtOH in dynamic form was added as modifier, Eudragit L100® showed a solubility of 35% weight, while the solubility of Eudragit EPO® was below 15% weight. Due to that, and knowing its better resistance to the thermal degradation and water contact, Eudragit EPO® was selected as copolymer of interest to work with it in the development of microencapsulation process using SC-CO2 as antisolvent.

Table1. Experimentation to study the behaviour of Eudragit® copolymers in SC-CO2.

Experiment	Sample	T (K)	P (MPa)	Modifier	Modifier EtOH (ml)
1	Eudragit L100	313	12,5	Static	0
2	Eudragit EP0	313	12,5	Static	0
3	Eudragit L100	313	12,5	Dynamic	12.5
4	Eudragit EP0	313	12,5	Dynamic	12.5
5	Eudragit L100	313	12,5	Static	13.5
6	Eudragit EP0	313	12,5	Static	13.5

Once the best polymer was chosen, a new series of experiments, in static operation form, were carried out so as to study the solubility of the polymer in SC-CO2 at 313K in the 10,0-20,0MPa range of pressures. As in the previous experimentation, EtOH was used as modifier. After samples analysis it was concluded that below 12,0MPa of pressure, the solubility of the Eudragit EPO® at studied operation conditions could be considered negligible, <0,01% weight.

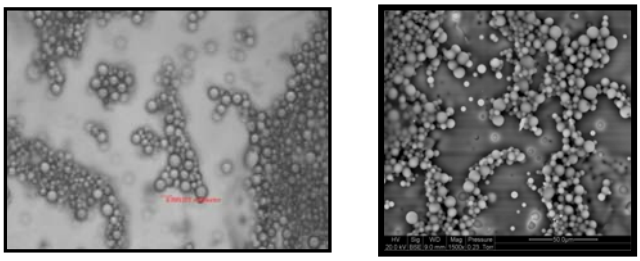
When same experiments were repeated using molecular alloy instead of Eudragit EPO®, it was found a clear solubility of this compound in the supercritical fluid, ≥90%weight, not only in presence of EtOH as cosolvent, but also when pure SC-CO2 is used.

3.3. SCCO2-Based Process for Encapsulation.
3.3.1. Precipitation of Eudragit EPO®.

(a) Effect of organic solvent nature.
Eudragit EPO® is soluble at atmospheric conditions of pressure and temperature in ethanol, acetone and dichloromethane, so these organic solvents were selected for the dilution of the copolymer previous its precipitation with SC-CO2. For all trials a constant copolymer/organic solvent rate of 1/50(weigh/volume) was used. Once the polymer solution was placed in the empty 1000ml autoclave, and it was closed, carbon dioxide was continuously fed to the system up to pressure of operation was achieved. When steady state conditions of pressure (8-12,5MPa) and temperature (313K) were reached in the vessel, the agitation was switched on (300-1000rpm) and the high-pressure vessel was maintained in batch mode for an hour to ensure the maximum precipitation of the Eudragit EPO®.

Maintaining previous step's operation conditions but working in dynamic form, CO2 was supplied again to the autoclave until remove all organic solvent. When the drying step was completed, the vessel was depressurised at 0,1MPa/min. In all cases a compacted dry solid was obtained. The thermal characteristics of the Eudragit EPO® obtained particles were found to be no sensitive to pressure, agitation or solvent changes in the process, and they were identical to the obtained ones in the characterization of the copolymer. After optical microscope observation microcapsules were not found in the solid samples.

Looking for a new solvent to be assessment in the process, an EtOH/H2O solution was tested. The trials were carried out at 8MPa of pressure and 313K, maintaining the rest of variables constant respect to preceding process. As result of the experimentation an aqueous suspension of a very fine solid was obtained. This sample was observed with an optical microscope, and what is seems to be microcapsules of Eudragit EPO® of different size, Figure 4 (a), appeared. A differential scanning calorimetry (DSC) of the obtained sample showed exactly a same diagram response that the standard, so it was confirmed the precipitate's behaviour.



(a) (b)

Figure4. (a) Nikon Optiphot AFX – II A microscope made photographs of Eudragit EPO® precipitated from an EtOH/H2O solution using SC-CO2 as antisolvent.(b) SEM image of the precipitated particles.

An emission scanning electron microscopic analysis confirmed the presence of microcapsules in the obtained samples, Figure 4 (b).

(b) Effect of surfactant addition.
The goal of this study has been to analyze if the use of surfactant should avoid the formation of the large agglomerates that have been obtained in previous experimentation. Two surfactants, SPAN 20 (a no anionic surfactant) and Sodium Dodecyl Sulphate (a cationic surfactant) were directly added to the polymer solution (6%by weight) for this assessment. All trials were carried out at above described operation conditions of copolymer precipitation. Obtained final products showed similar morphological characteristics than obtained in absence of surfactants.

3.3.2. Molecular alloy encapsulation with Eudragit EPO®.

The final objective of this work is to entrap a designed molecular alloy within the Eudragit EPO® microcapsules. The molecular alloy encapsulation was carried out at same operation conditions optimized for developed Eudragit EPO® precipitation process, fixing the ratio of polymer to molecular alloy at 50% by weight. Preliminary analysis of obtained final product showed a great excess of molecular alloy, which was eliminated by heating the samples. The solid fraction was analysed by optical microscope and an emission scanning electron microscopic and microcapsules were not found.

4. Conclusions.

Precipitation of Eudragit EPO® in form of microcapsules using SC-CO2 as antisolvent has been the base of this study. The results revealed a great influence of the nature of the solvent used in the process for copolymer's dilution, as well as, of the drying step. However, the precipitation of Eudragit EPO® using SC-CO2 antisolvent process appears to be independent of the system pressure in the interval of 8-12,5MPa at 313K. The unique signs of Eudragit EPO® precipitation, in form of empty microcapsules, were achieved when an EtOH/H2O solution, without surfactants, was used. The research will be continued until achieve the best operation conditions for the encapsulation of molecular alloys with Eudragit EPO® using SC-CO2 technology.

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