Polymeric micro and nanoparticles are a versatile kind of nanocarrier to improve the stability and bioavailability of active compounds [1, 2]. The Supercritical Fluid Extraction of Emulsions is an innovative process capable of producing such particles with controlled particle size [3, 4, 5].

The advantage of the application of the supercritical extraction in contrast to the conventional methods to prepare micro and nanoparticles is that the product no longer is exposed to high temperatures for a long time. Furthermore, the supercritical extraction offers the possibility to reduce the content of the residual organic solvent in the final product because of the high solubility of organic solvents in supercritical fluids. This high solubility is due to the fact that the density of a supercritical fluid is nearly the same than the density of a liquid. In contrast to a liquid solvent which is used for the conventional extraction of emulsions, a supercritical fluid exhibits a diffusion coefficient in the same range than the one of a gas which leads to a very fast mass transfer. Because of this the mass transfer no longer is the limiting factor of a supercritical fluid extraction of emulsions. [4,5,6]

Current study highlights the potential of SFEE as an alternative, attractive and scalable process used in manufacturing of microparticles for pharmaceutical applications.

The process consists of extracting the organic solvent of the drops in the disperse phase of the emulsion with supercritical carbon dioxide, in the way the drug can be encapsulated inside of polymeric microparticles [7,8,9].

MATERIALS AND METHODS

Ethyl acetate and dicloromethane with a purity of 99.5 %, which were provided by Panreac, were used as the organic solvent. The used two different types of the block copolymer Pluronic® were provided by BASF as the surfactant. These were a solid (F127: EO100-PO65-EO100) and a liquid one (L64: EO13-PO30-EO13) which differ in their HLB values. Ibuprofen, obtained by Sigma Aldrich, was used as model drug.

The supercritical extraction was operated with CO2 with a purity of 99.95 % which was received from Carburos Metálicos S.A. (Spain).

The size of the particles was determined by dynamic light scattering. The used DLS instrument (Autosizer Lo-C, Malvern Instruments Ltd.) which measures the size of particles by laser diffraction technology is equipped with a 4 mW diode laser (λ = 670 nm) and it is suitable to measure particle sizes ranging from 0.003 to 3 µm.
The amount of residual organic solvent in the final product was determined by gas chromatography. Before the measurement 10 ml of each outlet of the extractions were filled into vessels closed by a septum. These were stored at a temperature of 35 °C and after 15 minutes 100 µl of the formed gas phase were taken by a syringe and inserted into the chromatograph (HP 6890 Series, GC System). The results of the chromatography were then compared to a calibration to determine the content of the residual organic solvent.

Changes in the interfacial tension between water and ethyl acetate by adding the polymer were determined by the Wilhelmy plate method with a Krüss EasyDyne Tensiometer [10].

The equipment used for the process consists of a container in which the emulsion is loaded, with a temperature control system (in this case, an oven). Supercritical CO₂ is introduced through the extraction vessel to remove the organic solvent. A schematic representation of the equipment is shown in Figure 1.

![Schematic representation of the extraction equipment](image)

**Figure 1. Schematic representation of the extraction equipment**

**RESULTS**

**Critical micelle concentration**

A lower interfacial tension leads to a higher stability of the emulsion because of the lower tendency of separating into two phases.

Both the surface tension against air and the interfacial tension against ethyl acetate reach a minimum value which cannot be lowered by adding more polymer. Measurements were made with Pluronic® L64 in a concentration range between 0 and 0.4 wt%. Diagrams 2 and 3 show that both the surface tension of water against air and the interfacial tension between water and ethyl acetate exhibit a minimum by adding L64 as well. The surface tension can be lowered until a value of 41.5 mN/m by adding Pluronic® L64. The minimum of the interfacial tension is 2.3 mN/m. Hence, the critical micelle concentration of L64 is about 0.3 wt%.
Figures 2 and 3. Surface tension of water against air lowered and Interfacial tension of water against ethyl acetate lowered by Pluronic® L64

Stability of the emulsions

Emulsions were prepared with both types of Pluronic®. During the preparations the concentration of Pluronic® and the amount of ethyl acetate had to be optimized.

The emulsions of 1 wt% Pluronic® L64 with a concentration range of ethyl acetate between 25-50 ml were the most stable because the separation of the phases did not start until two days of storage.

Elimination of the organic solvent

In the experiments carried out operating with discontinuous equipment and dicloromethane as organic solvent, 97% of elimination was archived.

There is no visible dependency of the concentration of Pluronic and the content of residual organic solvent.

Figure 4. Organic solvent concentration and particle size vs operating time
CONCLUSION

Stable aqueous suspensions of composite micro and nanoparticles, having sizes ranging between 0.25 and 0.3 µm were consistently obtained. Other parameters investigated included surfactant and drug concentrations in solvent and emulsion solvent fraction. The surfactant Pluronic ® L-64 is the most suitable for the ethyl acetate-water system. The partial solubility of ethyl acetate in water complicates the work with it as an organic solvent.

REFERENCES:


