Development of particulate systems for the delivery of ursodeoxycholic acid (and conjugates): strategies to overcame the BBB.

Ursodeoxycholic acid (UDCA) and its conjugated species have antiapoptotic, antioxidant and anti-inflammatory effects in nerve cells indicating their therapeutic potential for central nervous system (CNS) disorders. However, although UDCA evidenced to reduce neurological injuries in animal models the concentrations achieved in brain tissue after its administration are much lower than those in serum. This fact is mainly due to the low permeability of the blood-brain barrier (BBB) to drugs, a challenging problem in drug delivery development.

Thus, in order to overcome this challenging, this project aims to develop unconjugated and conjugated UDCA delivery systems (UDS) able to circumvent obstacles presented by the BBB to these potential neuroprotective compounds, and therefore increasing their efficacy for CNS disorders. For this purpose, clean and mild supercritical fluid processes will be used which represent a viable option in particle engineering with relevant advantages, namely minimization of organic solvent, use of environmentally benign non toxic materials, and production of smaller particles with controllable morphology and narrow size distribution.

As first approach the candidate will carry out fundamental studies that will determine: i) solubility of UDCA species in the SCF phase (CO2); ii) solubility of the biomaterials selected as carriers systems in compressed CO2; and iii) melting temperature curves determined by a visual method.

Afterwards, the UDCA particulate delivery systems (UDS) will be produced from gas-saturated solutions (SCF as solute), or by supercritical anti-solvent precipitation processes (SCF as antisolvent). In both cases, rapid decompression will produce very high supersaturations leading to the formation of particles with a narrow size distribution.

The UDS will be physically characterized in terms of morphology, particle size (PS), particle size distribution (PSD) and solid state characterization.

Measurements of PS and PSD will be performed by photon correlation spectroscopy – PSC and morphology, such as shape and occurrence of aggregation phenomena, by scanning electron microscopy- SEM - and/or by transmission electron microscopy – TEM.

The evaluation of UDS solid-state as the degree of crystallinity (of polymers) and the evaluation of lipid modifications will be assessed by differential scanning calorimetry - DSC and by X-ray scattering, respectively. The coexistence of additional colloidal structures such as micelles and liposomes will be evaluated by nuclear magnetic resonance – NMR.