Synthesis in $ScCO_2$ of Nano-hydrogels for proteins delivery

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Recently, nanohydrogels were largely developed as very efficient carriers for hydrophilic drugs like proteins. One of the most common way to obtain such small size hydrogels is based on the heterogeneous polymerization of a hydrophilic monomers in an hydrophobic medium. However, when biomedical applications are considered, the use of potentially toxic organic solvents should be avoided as hydrophobic medium should be avoided. Due to its unique physico-chemical properties, supercritical CO_2 represents an alternative of choice to the use of organic solvents. The main objective of this research project focuses on the synthesis of nanohydrogels by dispersion polymerization in supercritical CO_2. In order to achieve this goal, a series of novel fluorinated amphiphilic stabilizers of different architecture (diblock, grafted, or palm tree copolymers) were successfully prepared by reversible addition-fragmentation chain transfer and used as surface active agents for stabilizing poly(hydroxyethyl methacrylate) (PHEMA) growing particles in $scCO_2$, providing small sized particles which can encapsulate proteins like insulin for diabetics applications. The surfactant properties of these fluorinated stabilizers were investigated by interfacial tension measurements at water/trifluorotoluene (TFT), water/CO_2 and water/air interfaces and the results were correlated to stabilizing efficiency of each surface active agent in the case of dispersion polymerization of HEMA in $scCO_2$. However, as a result of the marked hydrophobic character of the fluorinated chains, the use of fluorinated stabilizers for preparing hydrogels induces a major limitation for their application in the biomedical field for which aqueous dispersions are required. In order to avoid this problem, a new fluorinated stabilizer bearing an o-nitrobenzyl (ONB) photocleavable junction between the hydrophilic and the hydrophobic sequence was designed for efficiently stabilizing PHEMA growing particles in $scCO_2$. By simple UV irradiation, the ONB junction was cleaved and the fluorinated part of the stabilizer was easily extracted form the hydrogel. Following this approach, water dispersable nanohydrogel were successfully prepared in $scCO_2$.