PEG conjugated with drug through covalent bond using click chemistry in $scCO_2$

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Polyethylene glycol (PEG) is a polyether and have an indispensable role as packaging in drug delivery systems (DDS) in pharmaceutical, because of its high structure flexibility, biocompatibility, amphiphilicity and hydration capacity. It is the most used protective coating material for drug delivery liposomes, nanoparticles, and has also provided the same protection as a covalently bound conjugate to proteins and other drug molecules. However, PEG only has two functional groups, what limits the possibilities of further derivation with targeting ligands. Subsequently, in this research the mPEG-alkyne with allyl group was used to covalently link with different drugs.

The understanding of the phase behavior of the mixture mPEG-alkyne and $scCO_2$ and the variation of the polymer melting point are essential prerequisites in order to determine appropriate conditions and develop high pressure processes that allow the obtention of a conjugate mPEG-alkyne with a drug or protein. In this research, the equilibrium sorption of CO_2 into mPEG-alkyne was determined with a variable-volume view cell employing a static method. These experiments were carried out in the temperature range 308 and 318 K, and at 8-17 MPa of pressure. It was observed a progressive decrease of melting point temperature of mPEG-alkyne induced by the adsorption of CO_2, what was determined with a high-pressure differential scanning calorimetry in a pressure range of 0-17 MPa. In addition, the synthesis and characterization of click conjugated was successfully reported using FTIR, ^{1}H NMR and MALDI TOF. Subsequently, a preliminary study was carried out, using response surface methodology to examine the variables that most affect the use of $scCO_2$ as a reaction medium, such as pressure, temperature and molar ratio of catalyst.

The purification of click conjugate was carried out due to this type of reaction requires copper as a catalyst, being the most discussed disadvantages of click chemistry because the associated potential toxicity. A new catalysis strategy is currently being developed and studied, in the green chemistry context, heterogeneous catalysis in click chemistry. One the purpose of this contribution is to employ the latest the most significant methodological advances of the CuAAC.

The development of a technology for covalent attachment of gemcitabine, doxorubicin and coumarin to a polymer will allow a controlled slow release. The use of click chemistry techniques, combined with the environmentally friendly of $scCO_2$ to obtain these vectors, makes the study of great interest to the pharmaceutical industry.