Abstract

This PhD thesis entitled “Nanotechnology and supramolecular chemistry in controlled release and molecular recognition processes for biomedical applications”, is focused on two important subjects: molecular recognition and controlled delivery processes.

This PhD thesis is structured in four chapters.

The first chapter introduces the concept of organic-inorganic hybrid materials containing switchable “gate-like” ensembles and their biomedical applications as nanomaterials for targeting and control drug delivery. Furthermore is introduced a short review about chromo-fluorogenic chemosensors based on basic principles of supramolecular chemistry, particulary in molecular recognition processes.

In particular, in chapter 2 is focus on the development of enzymatic-driven nanodevices. These hybrid materials are composed of two main units: an inorganic silica based mesoporous scaffold, able to store organic molecules and an organic compound anchored on the external surface of the inorganic mesoporous support than acts as molecular gate. All the systems proposed use peptidic gates that respond to temperature or enzimatic stimulis. A short review about peptides in nanomedicine and their multiple applications as targeting ligands, proteases substrates and molecular gates is reported.

The first example was based on the design , synthesis and characterization of mesoporous silica nanoparticles using peptides as molecular gates in which the release of the cargo entrapped inside the pores was achieved by a progressive α-helix-to-disordered transformation when temperature increased.

A second example was focused on the design, synthesis, characterizations and applications of a new protease-responsive nanodevice for intracelular-controlled release. The system consist of MCM-41 nanoparticulated mesoporous scaffold loaded and capped with a peptidic sequence designed to be selectively hydrolysed by cathepsin B enzyme overexpressed in several cancer cells. Viability and internalization studies in HeLa cells and controlled delivery studies of a chemotherapeutic agent have been carried out. In the same way, the fourth

example describes a system based on mesoporous silica support capped with a peptide with the objective of release a therapeutic for decreasing unwanted cell death. We have focused on caspase 3 enzyme and developed a peptide containing a target sequence for this enzyme. We report the preparation of gated MSNs capable of selectively deliver their cargo in the presence of activated caspase 3 enzyme in cells, once apoptosis has been induced. The next example describes a new targeted delivery systems using mesoporous silica nanoparticles (MSNs) capped with a peptide with great affinity to a receptor which is overexpressed in lymphoma cells. The results shows that peptide is able to gide the nanoparticles to lymphoma cells to facilitate MSNs uptake *via receptor*. The last example of this chapter is centered on the development of a protease-responsive nanodevice as carrier for peptide delivery inside cells. Herein, the material has been based on the use of MCM-41 mesoporous silica nanoparticles capped with the polymer ε-poly-L-lysine that could be degradated by lysosomal enzymes inside cells. It is known that peptide used (C9h) disrupt the interaction between caspase-9 and PP2Acα interaction with subsequent apoptosis induction. The nanoparticles provided peptide protection from degradation additionally allowing a dose reduction of up to ten times to observe an apoptotic effect when compared with the peptide alone or in combination with a cell-penetrating peptide.

The second part of this PhD thesis is focused on the design and development of a new chemical compound capable of detecting carbon monoxide in vivo. The probe is based on a ruthenium(II) vinyl complex suitable for use in aqueous systems bearing a 5-(3-thienyl)-2,1,3-benzothiadiazole (TBTD) ligand as a signalling unit. It is a coloured complex and in presence of CO, the TBTD is displaced and a concomitant colour change is observed. The results has shown that the probe is capable of selectively detecting carbon monoxide in cells (treated with CORM-3 or hemin) and *in vivo* using mice with a subcutaneous air pouch as a model for inflammation.

In summary, for all the results above mentioned we can say that this PhD thesis constitutes an original scientific contribution to the development of supramolecular chemistry. Its results derived from the studies presented leaves

open routes to continue the study and development of new hybrid materials and more efficient chemical sensors with biomedical and therapeutic applications.