Abstract

The present PhD thesis, which is entitled “Design of new bio-gated nanodevices for advanced communication processes and targeted controlled release of therapeutic agents” is focused on the development of new functional hybrid organic-inorganic materials for applications in the field of the controlled delivery of target molecules.

The first chapter of the present thesis gives an introduction to the organic-inorganic hybrid materials functionalized with “molecular gates" and its application in controlled release processes.

The second chapter of this thesis is focused on the development of a new nanodevice able to deliver its cargo as a function of the glucose concentration. The nanodevice is based on mesoporous silica nanoparticles loaded with a suitable fluorophore and functionalized with propylbenzymidazole moieties on the pore outlets. The mesopores are then capped with an active cyclodextrin modified glucose oxidase enzyme (through the formation of an inclusion complex between the cyclodextrins and the propylbenzymidazole group anchored to the solid support). When glucose is added its enzymatic oxidation produced gluconic acid. This acid induced a decrease in the pH of the medium and the protonation of the benzymidazole group that might result in the inclusion complex dethreading and the subsequent cargo release.

The third chapter of the thesis is focused on the development of a new redox-responsive material for the controlled delivery of cytotoxic drugs in cancer cells.
The system is based on mesoporous silica nanoparticles loaded with a reporter (safranin O) and functionalized with two different sized polyethylene glycol chains in the pore outlets using a disulfide linkage. In presence of glutathione, the disulfide bonds are cleaved allowing the release of the entrapped cargo. Once confirmed the aperture protocol, the uptake of the gated nanoparticles and their ability to deliver the cargo (fluorophore or cytotoxic agent) in HeLa cells were tested. Moreover, cell viability assays were also performed.

The fourth chapter of the thesis is focused on the preparation and the study of a nanodevice for the controlled delivery in senescent cells in a murine model of pulmonary fibrosis. The material is prepared using mesoporous silica nanoparticles (as an inorganic support) and galactoligosaccharide (molecular gate) moieties anchored on the external surface. In presence of senescent cells, which overexpress β-galactosidase enzyme, the hydrolysis of the galactooligosaccharide capping molecules take place and the cargo release from the inner of the pores is produced (rhodamine B). After the *in vitro* studies, the ability of nanoparticles to accumulate and release their payload in tissues with abundance of senescent cells was evaluated *in vivo*. For that purpose, mice with induced pulmonary fibrosis, pathogenesis with associated increased alveolar senescence, were treated with the synthesized material and subsequently examined to assess its ability to accumulate and release its payload (fluorophore) in lung's damaged areas.

In the fifth chapter of the thesis it has been explored the concept of cascade chemical communication using different types of nanodevices, each of them loaded with a certain messenger and externally functionalized with a gate-like entity that controls the release of the payload. When the enzyme able to hydrolyze the molecular gate that blocks the pores of the first type of nanoparticles (**S1**), is added to an aqueous suspension containing the three nanoparticles, the delivery of the chemical messenger 1 is produced. This messenger is able to open the second type of nanoparticles (**S2**) which delivers the messenger 2. Finally, the messenger 2 triggers the aperture of the third group of gated system (**S3**), which ultimately delivers its load (a dye) as a final response.