

Abstract

The present PhD thesis, which is entitled "Design of new hybrid nanomaterials with molecular gates as nanodevices for therapeutic applications", is focused on the development of new functional hybrid organic-inorganic materials for controlled delivery applications.

Both chapters of the present thesis that report the results obtained (second and third chapters) are directly related with the use of mesoporous silica nanoparticles as inorganic support to develop new hybrid organic-inorganic materials for controlled delivery applications. The results have been divided into two chapters depending on the stimuli applied for the on-command delivery of the entrapped guest moiety. In one chapter, the different developed materials are enzyme-driven nanodevices, whereas in the other chapter a change in the pH or in the electrostatic force (in both cases due to the presence of a pathogenic microorganism) causes the subsequent release of the cargo.

In the case of the enzymatic-driven nanodevices (see Chapter 2), three different solids have been developed. The first example was based on the design, synthesis and characterization of mesoporous silica nanoparticles capped with azopiridinium salts, which are hydrolyzed by esterases and reductases, both of which are present in the colon microflora. These salts, containing an azo bond, were selected for a possible selective delivery in the colon. Viability and internalization studies with HeLa cells and controlled delivery studies of the chemotherapeutic agent camptothecin have been carried out. A second example was focused on the design, synthesis, characterization and application of a new protease-responsive nanodevice for intracellular-controlled release using silica mesoporous nanoparticles capped in this case with the polymer ϵ -poly-L-lysine. In this case, it was intended to evaluate two different anchoring protocols of the polymer and both yield fine materials for controlled delivery applications, although a different release profile was obtained in each case. Cell viability and internalization of this new nanodevice was studied and also the camptothecin delivery in HeLa cells was tested. Finally, the last enzyme-responsive nanodevice included the design and application of a smart 3D "gated scaffold" which consisted of a combination of capped silica mesoporous nanoparticles and classical porous biomaterials. In this case mesoporous silica nanoparticles were capped with polyamines and ATP. These nanoparticles were incorporated in a gelatin macroporous scaffold during the synthesis, prepared by rapid prototyping (RP) techniques. In presence of acid phosphatase the delivery of the entrapped dye from the nanoparticles' pores was induced. Acid phosphatase was selected as trigger of this designed material because it is an enzyme whose concentration is used to assess osteoclast activity in bone remodelling processes, and as a marker for bone metastases. These features open up the possible use of this combination in the design of functional materials for the preparation of a number of advanced gated scaffolds, which could help in regenerative medicine and bone cancer therapy applications.

Regarding the other type of nanodevices (see Chapter 3), it was evaluated the possible use of mesoporous silica nanoparticles with molecular gates as carriers for drug delivery in the presence of a pathogen. Here, the design and development of new organic-inorganic hybrid materials has been based on the use of MCM-41 mesoporous silica nanoparticles as inorganic matrix, capped with organic moieties that could respond to a change in the pH of the environment or a change in the electrostatic force due to the presence of a pathogenic microorganism, such as fungi or bacteria. In one of these developed nanodevices, antifungal applications and properties were demonstrated using a tebuconazole loaded support capped with pH-driven gatekeeping moieties. The other material presented antibacterial properties against gram-positive and gram-negative bacteria and consisted of a vancomycin loaded nanodevice capped with ϵ -poly-L-lysine. In both cases, it has been demonstrated that the use of a nanoformulation setup can improve the drug effectiveness, enhancement and broadening of the action spectrum of the drug, thus opening a wide range of possible applications of these nanodispositives in the treatment of infections.

In summary, it can be concluded that new hybrid organic-inorganic solids have been developed and their application as controlled delivery systems have been described in this thesis. The obtained results could be useful in future design of advanced hybrid materials for biotechnology, biomedical and, particularly, therapeutic applications (i.e. cancer therapy, treatment of infections, regenerative medicine, etc.)