Doctoral Dissertation
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Mesoporous Silica Spheres as drug carrier for wound treatment

By

Sara Saber Younes Mohamed
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Supervisor(s):
Prof. Barbara Onida, Supervisor
Prof. Mauro Banchero, Co-Supervisor

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Summary

Wound healing is a natural physiological process that aims at restoring skin integrity. Although skin possesses optimal regenerative ability, in some cases different underlying pathologies, such as diabetes, could impair the healing process so resulting in non-healed wounds, which can lead to severe consequences such as amputations or even death. Various strategies including both traditional therapies and modern approaches have been employed in wound treatment. However, most of them results inadequate or expensive. Therefore, various drug delivery systems based on lipids, polymers and inorganic particles have emerged as an alternative approach to enhance skin regeneration. In particular, mesoporous silica (MS)-based materials have gained much attention due to their unique properties and biocompatibility. In fact, owing to their unique physicochemical properties and high loading capacity, MS can be loaded with different bioactive molecules, aiming at obtaining a device with improved wound healing properties. Moreover, in an aqueous environment, MS reacts with water and forms orthosilicic acid, a small molecule that promotes wound closure. In addition, MS-based materials have shown great ability in promoting blood clotting and in achieving hemostasis without inducing dangerous side-effect. In this context, the present PhD thesis aims at studying the use of MS spheres as a material to develop drug delivery systems that combine the beneficial intrinsic effects of the MS spheres with the therapeutic effects of the supported drug in the prospect of future wound healing applications.

The first part of this research project focused on the development of a novel hemostatic material based on MS loaded with tranexamic acid (TXA), an antifibrinolytic drug. The purpose is to exploit the hemostatic ability of the carrier (i.e. MS) and prevent any possible dissolution of the clot by releasing the TXA. To this purpose, two different materials, Mesoporous Silica Microspheres (MSM and Spherical Mesoporous Silica Particles (SMSP), were synthesized and their hemostatic ability was investigated. Then, the material with the best hemostatic performance was loaded with TXA.

MSM (with particle size ranging from 1 to 5 μm and an average pore diameter of 25 nm) were synthesized under acidic conditions using Pluronic P123 as a template agent, TEOS as a silica precursor and mesitylene as a swelling agent. The final product was calcined at 500 °C for 6 h with two different heating rates (1 °C/min and 15 °C/min). SMSP (with particle sizes ranging from 0.15 to 0.80 μm and an average pore diameter of 2.4 nm) were synthesized through a base-catalyzed reaction by a sol–gel process involving the use of hexadecyltrimethylammonium bromide (CTAB) as the surfactant and tetraethyl orthosilicate (TEOS) as the silica precursor.

A clotting blood time test was performed to evaluate the hemostatic efficiency of the samples and the results revealed that all samples were able to promote blood

clotting, in accordance with the literature. In particular, the MSM-15°C/min sample exhibited the best hemostatic ability.

TXA was loaded into the MSM-15°C/min sample through the incipient wetness impregnation method using water as a solvent. A Preliminary *in vitro* release test of TXA was performed to verify the possibility of a fast release of the drug from the microspheres since a fast release represents an important factor in bleeding control. The result of the test showed that the material was able to deliver TXA to the release medium within one hour.

The second part of the project dealt with the study of the impregnation of MS with arginine (ARG), with the goal to develop a multifunctional material for wound treatment, which combines the beneficial action of both MS and ARG. ARG, in fact, is an amino acid that may have a beneficial role in tissue repair of acute and chronic wounds. In particular, the research work focused on the effect of the pH of the impregnating solution on the stability of the MS spheres as it is known that MS-based materials may dissolve under basic pH conditions and ARG solutions are alkaline (pH about 11).

SMSP were loaded with ARG through the wet impregnation technique using water as a solvent at different pHs (i.e., 5, 9, 10 and 11). From the analysis of the results, it emerged that the impregnation performed at pH ≈ 11 induced a significant change in the porosity and in the surface of the particles, probably due to the degradation ascribed to partial silica dissolution and reprecipitation. On the other hand, the impregnation performed adjusting the pH of the ARG solution to acidic conditions (about 5) did not affect the carrier. To overcome this degradation issue, MSM, which should present higher stability with respect to SMSP, was considered for the impregnation with ARG solution (at pH 5 and 11). The results revealed that the impregnation process performed at acidic (i.e., pH ≈ 5) and basic pH (i.e., pH ≈ 11) seemed not to induce any significant modification of the porosity and of the surface of the particles.

Finally, the release of ARG was studied from both carries (i.e. SMSP and MSM) impregnated at acidic (i.e., pH ≈ 5) and basic pH (i.e., pH ≈ 11). The desorption tests carried out in water evidenced that ARG could be desorbed in water by all systems. A complete desorption was observed from both samples (SMSP and MSM) impregnated at pH 5, whereas the desorption appeared to be less extensive from the samples impregnated at the original basic pH of the ARG impregnating solution.