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Piezoelectric patch and strategies to release drugs for the regeneration of infarcted heart tissue

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Introduction

Myocardial infarction (MI) is one of the principal causes of mortality worldwide. Due to the scarce regenerative capacity of the cardiac tissue, a severe risk for patients surviving MI is represented by heart failure, because of the replacement of ischemic cardiomyocytes with fibrous tissue which critically compromises the structural and functional properties of the heart. To respond to this issue, the Horizon Europe REBORN project (https://www.rebornproject.eu/) proposes the development of a novel acellular implantable patch for functional heart tissue remodelling. The developed multifunctional patch aims to provide, after the occurrence of myocardial infarction, the release of anti-fibrotic and anti-inflammatory drugs to the epicardium preventing the formation of non-functional fibrotic tissue and the consequent heart dysfunction. Specifically, the project involves the design of a piezoelectric patch enriched with nanocarriers for the controlled delivery of therapeutics with spatiotemporal resolution.

With this aim, ultrasound (US) responsive nanocarriers based on mesoporous silica nanoparticles (MSN) loaded with anti-inflammatory drug as well as poly(lactic-co-glycolic acid) nanoparticles (nPLGA) for the long-term release of anti-fibrotic were developed. The drug-loaded nanocarriers have been incorporated into a polymer solution that has been subsequently electrospun to produce a piezoelectric patch with aligned nanofibers to enable the electromechanical coupling to the myocardium and the biomimicry of the extracellular matrix to support the colonisation and orientation of cardiomyocytes. The possibility to further control the drug release kinetics has been explored by developing nanofibers with core-shell morphology, enabling the incorporation of nPLGA into the fiber's core for the prolonged release of anti-fibrotic molecules.

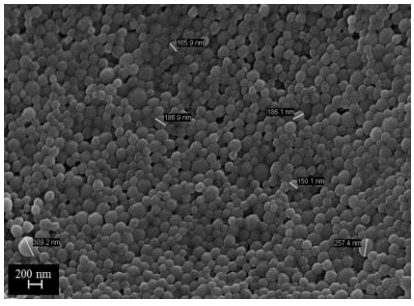
Results and Discussion

An oil-in-water single-emulsion protocol, followed by solvent evaporation [1], was optimized to prepare nPLGA containing anti-fibrotic drug. The oil phase was prepared dissolving PLGA and the anti-fibrotic drug (2:1 ratio) into dichloromethane (DCM), while the aqueous phase was added with a surfactant (2%wt. polyvinyl alcohol) to increase the emulsion stability. The emulsion process was performed using a probe sonicator homogenizer for 2 minutes at 80% amplitude. Drug encapsulation around 35% wt. of the particle weight was achieved. Drug release tests showed that less than 20% wt. of the total loaded cargo was released by the nanoparticles after 3 days of immersion in a 0.1 M Tris HCl aqueous solution.

US responsive carriers based on MSN loaded with ibuprofen and grafted with crosslinked sodium alginate (SA) were prepared. Amino groups, needed for the covalent grafting of SA, were introduced on silica surface by post functionalization of MSN with 3-aminopropyl triethoxysilane (APST) in N_2 atmosphere [2]. The amino-functionalized nanoparticles (MSN-NH_2) were loaded with ibuprofen (IBU) by incipient wetness (360 mg IBU/g MSN-NH_2) and then grafted with a SA solution; different SA concentrations were tested, and successful functionalization was confirmed by FT-IR analysis. To reduce drug release in absence of US stimulation, the resulting IBU@MSN-SA nanoparticles were added to a 3% wt. $CaCl_2$ solution to crosslink the alginate coating (referred as IBU@MSN-SA-Ca).

Complete characterization of both nPLGA and MSN-based nanocarriers was performed. DLS was employed to evaluate particles size and zeta potential, while drug loading was confirmed by TGA analysis. FESEM analysis assessed that PLGA nanospheres with homogeneous size around 200 nm were obtained (**Figure 1a**) and that well-dispersed IBU@MSN-SA-Ca (average size 120 nm) with spherical morphology were produced (**Figure 1b)**.

a)



b)

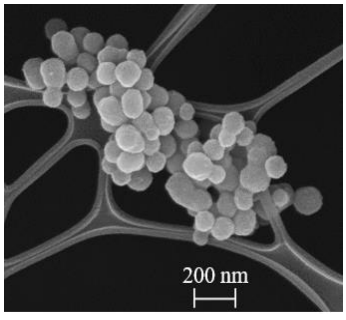


Figure 1: FESEM analyses on **a)** PLGA nanoparticles; **b)** IBU@MSN-SA-Ca nanoparticles

An *ad hoc* LIPUS (Low Intensity Pulsed Ultrasound) setup was employed to investigate the possibility to trigger drug release from MSN-based nanocarriers. Appropriate US stimulation is expected to reversibly weaken the coordination bonds between Ca^{2+} and the carboxyl groups (COO^-) of SA, allowing drug release; when stimulation stops, the reformed bonds prevent undesired cargo loss [3]. As reported in **Figure 2a**, 3 minutes US stimulations at different frequencies (1 MHz and 2 MHz) and intensities (250 mW/cm^2 and 500 mW/cm^2) were proved to be effective in enhancing the release of ibuprofen from IBU@MSN-SA-Ca at different time points.
In parallel, the process for the fabrication of a polyvinylidene fluoride (PVDF) piezoelectric membrane by ESP was optimized: the effects of different formulations (i.e. polymer concentration, solvent type) and the ESP process parameters (voltage, flow rate, distance, drum speed) were investigated [4]. The MSN-based nanocarriers were then incorporated into the optimized PVDF solution (18% wt./vol in acetone/DMSO) to obtain a suspension with a concentration of 5% wt./vol. The suspension was processed by ESP coupled with a rotating drum, resulting in aligned nanofibers containing nanoparticles (**Figure 2b**). Ibuprofen release from the patch containing the nanocarriers was confirmed and slower kinetics were obtained. The piezoelectric properties of the patch were not affected by the incorporation of the nanoparticles.

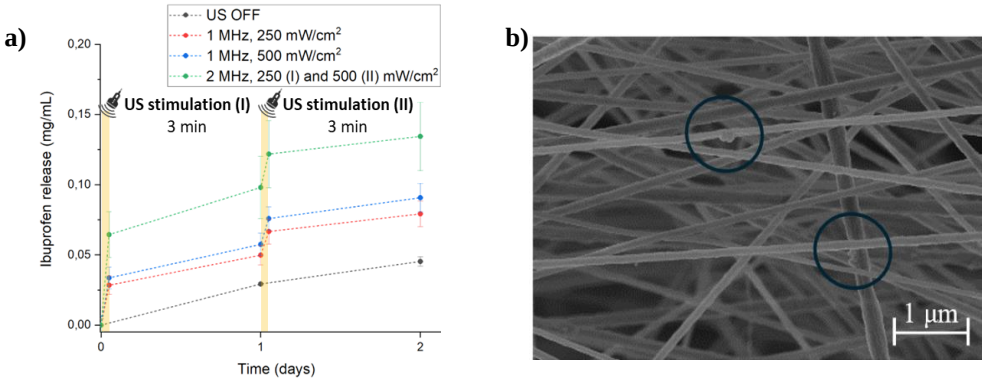


Figure 2: a) US-stimulated drug release from IBU@MSN-SA-Ca (carrier concentration 10 mg/mL in Tris HCl 0.1 M) **b)** FESEM analysis on PVDF electrospun patch enriched with 5% wt/vol IBU@MSN-SA-Ca

Preliminary tests for the incorporation of nPLGA into the core of a core-shell electrospun structure were carried out. Since the polymeric nanoparticles dissolve in most of the organic solvents, an aqueous-based core formulation has been optimised and allowed to produce core-shell nanofibers enriched with nPLGA. The characterization of the electromechanical behaviour and the drug release properties of the patch are in progress.

Conclusions and/or Outlook

In the present work, the development of nPLGA was successfully performed by adopting single-emulsion technique. High drug loading (35% wt.) and good cargo retention were provided by the polymeric carriers (release < 20% wt. of the total loaded drug in 3 days). Hybrid inorganic-organic nanoparticles, obtained by amino-functionalized MSN grafted with SA and crosslinked with $CaCl_2$, were responsive to US when stimulated at different frequencies and intensities: the 2 MHz stimulation provided the highest effect on ibuprofen release rate. A PVDF solution enriched with 5% wt./vol of MSN-based nanocarriers was successfully electrospun into aligned nanofibers and the piezoelectric properties of the polymeric matrix were retained; the possibility to incorporate higher amounts of IBU@MSN-SA-Ca into the fibres is under investigation.

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