In-situ drug release monitoring using quantitative 3D mass spectrometry imaging for a drug delivery stent formulation optimization

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Introduction

Drug eluting stents (DES) development for the treatment of coronary artery diseases involves studying the accurate local release of the drug into the tissue microenvironment. Currently, the common *in vitro* drug release profiles in liquid solvent do not reflect exactly what could happen *in vivo*. Therefore, personalized DES development could be adopted by studying their diffusion profiles that could be optimized following several selected polymers for nanofibers stents embedding. In this proof of concept study, *in-situ* diffusion profile of simvastatin contained in the nanofibers and released by the stent in the different pathological artery layers was analyzed by QMSI. 2D and 3D pharmacokinetics and pharmacodynamics studies were applied to evaluate the pathological aspect of the artery and the treatment efficacy.

Methods

Stents covered by nanofibers sheath loaded with simvastatin (33%-wt) were deposited by electrospinning and implanted into pork iliac arteries. After 45min, pork was euthanized and arteries containing stents were harvested and frozen at -80°C until use. 2,5-dihydroxybenzoic acid (2,5-DHB) matrix was sprayed onto arteries sections of 10 µm thickness with the automatic TM Sprayer (HTX Technologies, LLC) prior analysis. Data acquisition was performed using High Resolution Mass Spectrometer and analyses were set at 50 µm spatial resolution in full scan positive mode. Acquired data were treated with Multimaging™ software (ImaBiotech). Diffusion profiling was established using Multimaging™ software. Histological staining was applied on adjacent and imaged sections.

Results

Using QMSI analysis, simvastatin level was evaluated in the three histological layers of the artery. It allowed establishing the diffusion profile of the drug in the tissue of interest. First, a gradient of concentration was observed between the layer in contact with the stent and the periphery of the artery. The concentration in this intima layer reached 100 µg/g of tissue after 45 min of iliac stenting with simvastatin-loaded stent. In the media layer, the concentration was between 30 and 100 µg/g of tissue. In the adventitia layer, the concentration was homogeneous, reaching an average at 15 µg/g of tissue. The diffusion was not homogenous on the whole artery surface that was in contact with the stent. This could be due to the inhomogeneity of the nanofibers (shown by *in vitro* analysis of nanofibers alone by MSI), or to the diffusion itself. Regarding the pharmacodynamics aspect, a large number of metabolites and lipids that are implicated in coronary artery diseases were also highlighted and differences between the control and treated arteries were also observed, like lysophosphatidic acid or phosphatidic acid modulation in atheroma plates.

The combination of all these data, in addition to the impact of 3D MSI, allowed to better visualize the drug and its release around the stent and to extend our understanding on the relative contribution of simvastatin in reducing the risk of developing coronary artery diseases. With the development of personalized medicine, such as eluting stents, it requires a deep understanding of the interplay between the drug concentration and efficacy in the artery microenvironment. Overall, drugs, metabolites and lipids can now be highlighted by QMSI as biomarkers of response to treatment towards enhancing stent's efficacy.

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Novel aspect

Highlighting and quantifying *in situ* stent drug diffusion in the tissue microenvironment using QMSI