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Nanocontainers for the Targeted Delivery of Nitroglycerin During Myocardial Infarction

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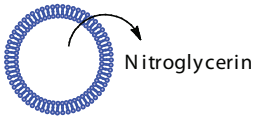
INTRODUCTION

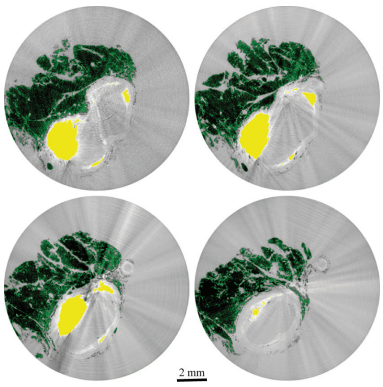


Atherosclerosis is the leading cause of death in today's world. Characterised by the hardening of the arteries with age, the disease begins naturally at the age of around 25. It is accelerated by so called "risk factors" including smoking, drinking alcohol, obesity and a family history of heart disease. In its later stages it leads to the build up of plaques in the arteries that cause heart disease and in extreme cases, heart attack [1]. Nitroglycerin is a vasodilator drug that widens stenosed arteries during heart attack to alleviate symptoms and restore blood flow [2]. This is of crucial importance, since if starved of blood for a prolonged period of time necrosis develops in the heart muscle leading to permanently diminished myocardial function. However, nitroglycerin is not target-specific and leads to systemic vasodilation, the indiscriminate widening every vessel in the body, leading to a potentially dangerous drop in blood pressure. By development of nanocontainers that specifically deliver nitroglycerin to the site of atherosclerotic constriction, we aim to overcome the problem of systemic vasodilation and allow the localised dilation of stenosed arteries without the negative side effects of systemic vasodilation.

SRμCT

Synchrotron radiation micro-tomography (SRμCT) at the DESY synchrotron in Hamburg has been carried out on human coronary arteries with varying degrees of stenosis.

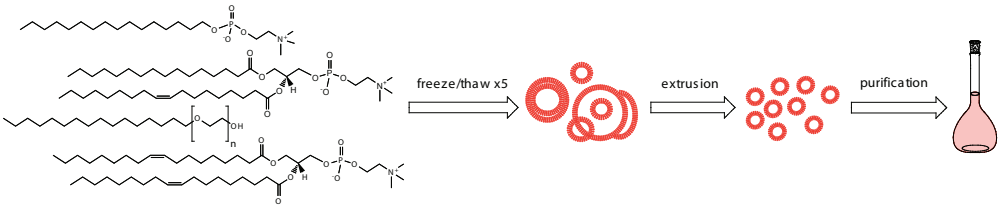
The data acquisition took place at the beamline BW2, where the GKSS-research team operates the SRμCT. The scan was performed at 23 keV photon energy, yielding a dataset with 4.9 μm isotropic voxel size. The images obtained allow the visualisation of cross-sections of the lumen including the morphology of the plaque containing parts.



The figure above shows four virtual slices of the SRμCT. One clearly recognises the vessel bifurcation because of the slightly different absorption of the vessel wall with respect to the surrounding liquid. The open lumen can be quantified from the tomography data. However, this artery exhibits a plaque-induced occlusion that is much smaller than that observed in symptomatic late stage coronary heart disease, where 70% occlusions are typical [3].

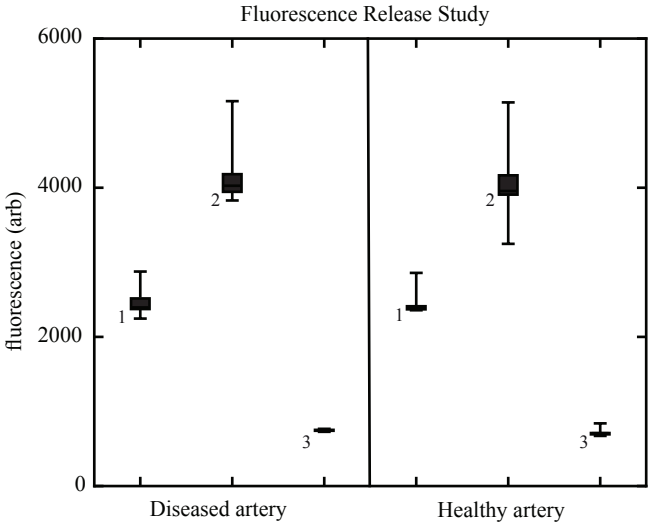
LIPOSOMAL FORMULATIONS

Liposomes were prepared from phospholipid/surfactant/rigidifier formulations by the thin film method. A lipid film was saturated with a fluorescent dye, subjected to 5 freeze-thaw cycles, extruded through a 100nm polycarbonate membrane (Whatman Nucleopore) and purified by size exclusion chromatography. Extent of fluorescence release induced by disease specific triggers was analysed using a 96-well plate reader. Below, a general scheme illustrating liposome formulation from lipid/surfactant/rigidifier formulations.



FLUORESCENCE RELEASE STUDIES

A fluorescence assay has been optimised to simulate the drug release from different liposomal formulations after having been subjected to disease specific release triggers. Fluorescence assay results have found formulations with up to 50% fluorescence release after exposure to disease specific triggers The figure on the rigth shows the fluorescence release after subjecting liposomes to diseased and healthy artery conditions (1. subject to trigger, 2. after 100% release of fluorophore, 3. control). However, this extent of release was also observed for liposome samples subjected to heathly artery conditions. We have shown that release under disease specific triggers is possible, but that the liposomal formulation needs to be tailored to prevent release in healthy artery models.



CONCLUSION AND ACKNOWLEDGEMENT

Fluorescence release studies have shown that formulations exist whereby the release of a fluorescent dye in a disease specific triggered model is possible. However, the current formulations investigated are too sensitive to these triggers and exhibit release in healthy models too. New formulations that are less sensitive to the small amounts of this trigger found in healthy arteries should be found. Imaging of human coronary arteries using SRμCT provides information about morphology and relative ratios of different tissue types that make up the blood vessel wall in cases of atherosclerosis. Further imaging studies using critically stenosed vessels are planned, which will shed further light on their physical and biological characteristics.

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[1] E. Ritz, *The American Journal of Cardiology,* 2007, **100**, 53J-60J. [2] L. J. Ignarro, *Journal of Physiology and Pharmacology*, 2002, **3**, 503-514.
[3] N. H. J. Pijls, *The American Journal of Cardiology*, 2009, **103**, 1204-1205.