Understanding shear-stress sensitive nano-containers for targeted drug delivery

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INTRODUCTION: A shear-sensitive nano-container formulation for the treatment of myocardial infarction through the release of vasodilatatory drugs has recently been discovered [1]. The mechanical properties of the phospholipid nanometer-sized vesicles should be tailored to ensure a local drug release in constricted human coronary arteries. Dynamic Light Scattering (DLS) technique provides the required size control while Small Angle X-ray Scattering (SAXS) combined with microfluidic devices is a promising tool for the investigation of vesicles behavior in terms of membrane deformation as well as rupture under selected shear stresses. Complementary studies on human coronary diseased arteries have been performed by means of micro-CT experiments [2, 3] as a basis for flow simulations used to determine the shear stress range in healthy and constricted regions.

METHODS: Two phospholipid formulations have been tested: the mechano-sensitive 1,3-diamide Pad-PC-Pad synthetized as described [1] and the 1,2-diester DPPC (Lipoid, Zug, Switzerland) used as a control, both prepared in aqueous solution. After several cycles of freeze thawing, extrusion by means of polycarbonate filters is performed to obtain unilamellar vesicles. The vesicle preparation is followed by light scattering analysis using a Delsa Nano C (Beckman Coulter, USA) to check vesicles size distribution essential for SAXS measurements. Micro-channels pattern mimicking healthy and diseased regions of blood vessels are molded from Kapton films and NOA81 glue [4]. Preliminary SAXS measurements in microfluidic devices were carried out at Paul Scherrer Institute (SLS, Villigen, Switzerland) scanning the micro-channel through an energy of 12.4 keV, using a focused spot size of 40 μm^2 and a sample-detector distance of 2.2 m.

RESULTS: Extruding through 50 nm diameter filter leads to a solution containing unilamellar vesicles with a diameter distribution centered on 75.3 nm with a FWHM of 70.6 nm (Fig.1). SAXS measurements of DPPC vesicles solution have already shown a reasonable scattering signal.

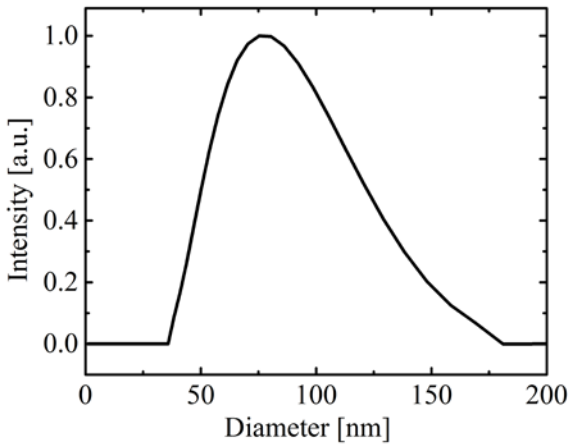

Fig. 1: DPPC vesicles size distribution determined by light scattering

DISCUSSION & CONCLUSIONS: 100 nm phospholipid vesicles sensitive to shear variation have already shown promising results. Here, we pointed out how important is to control the sample size after the preparation to set accurately the parameters in further experiments. Microfluidics combined with SAXS technique will be the main technique used to determine the range where the drug carriers locally release their cargo avoiding not desired side effects.

REFERENCES: [1]M. N. Holme et al (2012) *Nat. Nanotech* **7**(8):536-43. [2]M. N. Holme et al (2014) *Nat. Protoc.* **9**(6), 1401-15. [3]M. Buscema et al (2014) *Proc of SPIE* 9212. [4]B. Weinhausen et al (2012) *Lab Chip*, **13**:212-15.

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