Shear Stress Sensitive Nanocontainers for Targeted Drug Delivery

M. N. Holme[1,2,3], A. Zumbuehl[1], T. Saxer[2], B. Müller[3]

[1] Department of Organic Chemistry, University of Geneva, Geneva, Switzerland.
[2] University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, Geneva, Switzerland.
[3] Biomaterials Science Center, University of Basel, c/o Universitätsspital, Basel, Switzerland.

INTRODUCTION: Heart attack is the leading global cause of disease and mortality [1]. Ambulatory treatment includes the intravenous administration of vasodilators such as nitroglycerin to restore coronary blood flow at critically constricted arteries and prevent further myocardial ischemia with ensuing arrhythmias and death. Unfortunately, systemic action of these drugs leads to complications such as vasodilation inducing severe hypotension and diminished blood perfusion of the suffering heart.

The lack of biomarkers in these critically constricted arteries demands the development of alternative methods for targeted drug delivery during heart attack. We propose using the body's own changes in shear stress as a purely physical trigger for the release of a vesicle payload. In *in vitro* fluorescence release studies, we investigated the properties of vesicles formulated from certain mixtures of Egg-PC and either the artificial phospholipid Pad-PC-Pad[2], or the surfactant Brij S10.

METHODS: In order to assess the feasibility of drug release from a vesicle through shearing, vesicles of varying formulations were subjected to *in vitro* shear stresses found in physiological hemodynamic flow conditions. 50 mM 5(6)-carboxyfluorescein encapsulated large uni-lamellar vesicles (LUVET100) were prepared by the thin film method [3] from lipid formulations of 30 µmol Egg-PC with Brij S10 added to the lipid mixture in varying concentrations of 0 to 1 mol% in increments of 0.1 mol%. Vesicles with varying compositions (10, 25, 50, 75 and 100 mol%) of Pad-PC-Pad and Egg-PC were prepared by the same thin film method.

To simulate the physical conditions in the heart a model cardiovascular system was used, with vesicles pumped through either a common (shear stress approx. 2 Pa) or constricted (shear stress approx. 10 Pa) model artery constructed from PMMA (Elastrat Sàrl, Switzerland). Both artery models were formed from tubes with an inlet diameter of 2.5 mm, one with constrictions of up to 95% cross sectional area along a 2.5 cm segment. An extracorporeal circulation (ECC) pump (Medtronic Bio-Pump, Bio Console 540, Medtronic, Switzerland) with low intrinsic shear stress simulated the heart [4, 5].

RESULTS: Vesicles formulated from mixtures of the natural phospholipid Egg-PC and 0-1 mol% of the surfactant Polyoxyethylene (10) Stearyl Ether (Brij S10) were found to release up to only an additional 14% of their payload after 40 passes through the constricted artery model, and 3% after 40 passes through a common artery model. This maximum effect was observed in Egg-PC vesicles incorporating 0.5 to 0.6 mol% of Brij S10. These findings build on studies performed by Bernard et al., who found that at shear rates of 10,000 s^{-1} there was a release of contents from Egg-PC vesicles containing 0.1% and 1% Brij S10 [6].

The shear stress-induced release from pure Pad-PC-Pad vesicles is an order of magnitude higher than formulations including Egg-PC. Formulations containing only Pad-PC-Pad were found to release an additional 51% of their payload after one pass through the constricted artery model, whereas in a common artery model only 27% additional release was observed. In both the Pad-PC-Pad and Egg-PC/Brij S10 formulations, background release was around 20%.

Vesicles formulated from mixtures of Pad-PC-Pad and Egg-PC become unstable, or leaky, with an increase in Pad-PC-Pad. Although a higher background release was observed with increased Pad-PC-Pad, they did not significantly increase their susceptibility to shear-induced release.

DISCUSSION & CONCLUSIONS: The results show that the shear-induced release properties of vesicles can be tuned by varying the lipid composition. The Pad-PC-Pad formulation shows great potential for preferential shear-induced release of heart attack drugs near arterial stenoses in the first pass through the blood stream. Investigations are ongoing for the suitability of these and similar non-natural lipid formulations for specificity in drug delivery at elevated shear stresses, for example for cardiac, neurologic or angiologic applications.

REFERENCES: [1] Lopez, A.D., et al., *Lancet*, 2006, **367**(9524), 1747. [2] Fedotenko, I.A., et al., *Tet. Lett.*, 2010, **51**(41), 5382. [3] Olson, F., et al., *BBA*, 1979. **557**(1), 9. [4] Curtis, J.J., et al., *Annal. Thoracic Surg.*, 1999, **68**(2), 666. [5] Paparella, D., et al., *ASAIO J.*, 2004, **50**(5), 473. [6] Bernard, A.L., et al., *J. Coll. & Interfac. Sci.*, 2005, **287**(1), 298.

ACKNOWLEDGEMENTS: The authors thank the Swiss National Science Foundation for financial support.