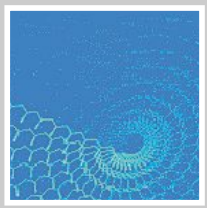
doi:10.2533/chimia.2012.715



Polymer and Colloid Highlights

Division of Polymers and Colloids
A Division of the Swiss Chemical Society

Shear Stress as Drug Delivery Trigger

Margaret N. Holme[abc], Bert Müller*[a], Till Saxer*[b], and Andreas Zumbuehl*[c]

*Correspondence: Prof. B. Müller[a], Dr. T. Saxer[b], Prof. A. Zumbuehl[c], [a]Biomaterials Science Center (BMC), University of Basel, c/o Universitätsspital Basel, CH-4031 Basel; [b]University Hospitals of Geneva, Cardiology Division, Department of Medicine, Rue Gabrielle-Perret-Gentil 4, CH-1211 Geneva; [c]Departement für Chemie, Universität Freiburg, Chemin du Musée 9, CH-1700 Freiburg. E-mail: bert.mueller@unibas.ch; till.saxer@unige.ch; andreas.zumbuehl@unifr.ch

Keywords: Cardiovascular disease · Drug delivery · Liposomes · Phospholipid synthesis · Shear stress

In Switzerland over 20,000 people die each year from an atherosclerosis-derived cardiovascular disease, accounting for 37% of all deaths. Mortality is highest in the first hour after a heart attack. It is therefore important to have efficient first-line treatments in the emergency vehicle. Currently, an injection of the vasodilator nitroglycerine acts on the entire vasculature, which can lead to a dangerous drop in blood pressure without treating the diseased stenosed vessel responsible for a heart attack or stroke. A preferential release of a vasodilator at the site of a stenosis would greatly improve both the acute treatment by a selective vasodilatation and the subsequent quality of life of the patient.

There is no specific biomarker overexpressed at the site of a stenosis in diseased arteries. Therefore, it is impossible to use a standard biological targeting factor. Under a grant of the Swiss National Science Foundation NRP 62 'Smart Materials', we asked ourselves if it was possible to use the tenfold increase in shear stress between a healthy and a diseased artery as a purely physics-based trigger for targeted drug delivery (Fig. 1).[1]

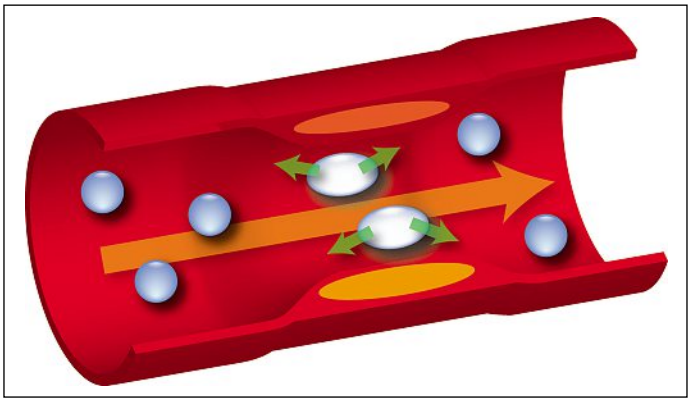


Fig. 1. Concept of using changes in local shear stress as a purely physical trigger for targeted drug delivery to stenosed arteries.

A new type of phospholipid vesicle was introduced: Natural liposomes made from eggPC leak their content spontaneously and will do so even more if they are shaken. Other liposomes made from 16:0 SM or DPPC do not leak spontaneously or when shaken. However, vesicles from the artificial synthetic 1,3-diamidophospholipid Pad-PC-Pad[2] with a lentil-shaped morphology show no spontaneous leaking but can release their content under mechanical stress. This observation qualifies these vesicles as drug delivery vehicles.

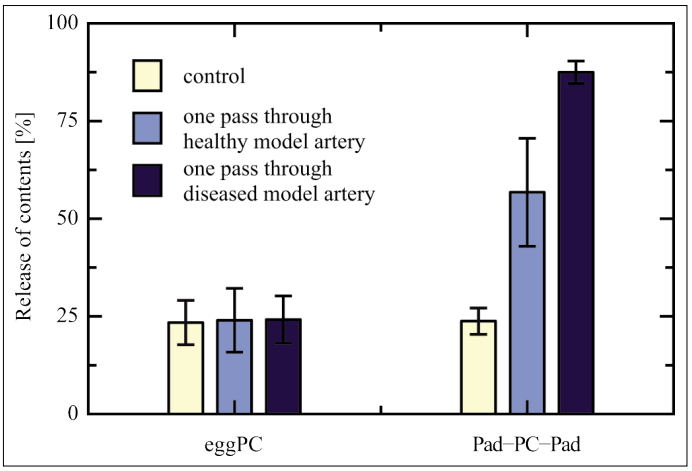


Fig. 2. Proof-of-concept that it is possible to use a mechanosensitive phospholipid vesicle as shear-sensitive drug delivery vehicle. 5(6)-Carboxyfluorescein release from designed artificial phospholipid Pad-PC-Pad vesicles is compared to release from natural eggPC vesicles.

The Pad-PC-Pad vesicles were loaded with the self-quenching fluorescent dye 5(6)-carboxyfluorescein and passed through an artificial cardiovascular system. An extracorporeal heart pump provided appropriate hemodynamic flow and temperature conditions. It was linked to a model of healthy and diseased artery morphology. After one passage through this system, the released carboxyfluorescein was measured and a significant difference between the two systems was found. No effect was measurable with natural phospholipids such as eggPC.

Using the human body's own physics as a drug delivery trigger is a highly attractive concept and might find a wide field of applications. Indeed, recently Korin *et al.* used the same concept in order to target stenosed vasculature with a shear-responsive nanoconstruct.[3] The time seems ripe for mechanosensitive drug delivery.

Received: July 27, 2012

[1] M. Holme, I. A. Fedotenko, D. Abegg, J. Althaus, L. Babel, F. Favarger, R. Reiter, R. Tanasescu, P.-L. Zaffalon, A. Ziegler, B. Müller, T. Saxer, A. Zumbuehl, *Nature Nanotechnol.* **2012**, *7*, 536.
[2] I. A. Fedotenko, P.-L. Zaffalon, F. Favarger, A. Zumbuehl, *Tetrahedron Lett.* **2010**, *51*, 5382.
[3] N. Korin, M. Kanapathipillai, B. D. Matthews, M. Crescente, A. Brill, T. Mammoto, K. Ghosh, S. Jurek, S. A. Bencherif, D. Bhatta, A. U. Coskun, C. L. Feldman, D. D. Wagner, D. E. Ingber, *Science* **2012**, *337*, 738.

If you are interested in submitting a new highlight, please contact:
Prof. A. Dieter Schlüter, Institut für Polymere, ETH Zürich
E-mail: dieter.schluter@mat.ethz.ch, Tel.: +41 44 633 63 80