Lipid-liquid crystalline cubic phase in drug diffusion studies

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Reverse cubic phase can be used to accommodate and controlled release of bioactive molecules ranging from the low molecular weight drugs to peptides or proteins. Efficiency of transport of the drug in the LCP (liquid-crystalline cubic phase) can be described e.g. by the diffusion coefficient. Diffusion of an incorporated drug from the LCP depends on the size and polarity of the molecules, the rate of transport can be tuned, e.g. by applying lipids with various acyl chains to modify the charge delineating the aqueous channels. To form the pH sensitive LCP a weak acid - linoleic acid (LA, pKa=5.6) was added to the neutral monolinolein (ML) [1]. Tunable interactions with the lipidic matrix led to the observed pH-dependent drug release from the phase. Here AQ2S, negatively charged neuroprotective drug was incorporated into monolinolein (ML) based LCP undoped or doped with linoleic acid. Structural parameters of the cubic phases formed with the incorporated lipids and AQ2S were characterized by small-angle X-ray scattering (SAXS). Because AQ2S is electroactive, its release profile was evaluated based on its electroreduction current. Release behavior of the drug was determined at pH 3 where phase was neutral because of the presence of protonated form of LA and at pH 7, where carboxyl groups were ionized. It was found that doping ML based LCP with linoleic acid have a major impact on the drug release at neutral pH, where electrostatic repulsion exists between negatively charged drugs and negatively charged lipidic domains [2]. Electrochemical methods - chronocoulometry and voltammetry at micro and normal size electrodes – were also applied to simultaneously determine the diffusion coefficients and effective concentrations of AQ2S in the LPCs. Using steady-state voltammetry on microelectrode and macroelectrode both diffusion coefficient (D) and concentration of the electroactive probe in the cubic phase were evaluated. It was shown that the concentration of AQ2S in the phase depends on the charge of the aqueous channel, and was found to be smaller than that introduced to the cubic phase, which reflects the contribution of drug interactions with the lipid bilayer.

Acknowledgements This work was supported by Sinergia project no. CRSII2 154451 financed by the Swiss National Science Foundation.

[1] R. Negrini and R. Mezzenga, *Langmuir*, 2011, **27**, 5296.

[2] R. Negrini, A.Sanchez-Ferrer and R. Mezzenga, *Langmuir*, 2014, **30**, 4280.