Phase separation within hybrid polymer/lipid vesicles used as biomimetic membranes

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Hybrid vesicles resulting from the combined self-assembly of both amphiphilic copolymers and phospholipids may be viewed as an advanced vesicular structure compared to their liposome and polymersome forerunners, as the best from the two different systems can be integrated in a single hybrid vesicle and could be used in different fields such as: nano-reactors for enzymatic reactions, improved cell membrane mimics,[1], [2] etc… To afford such design, different parameters controlling both the self-assembly and membrane structure must be tuned. However, the exact mechanisms governing phase-separation of the membrane into domains analogous to lipid rafts in cells are not known so far. In this work, using different lipids and copolymers, we show that hydrophobic mismatch existing between polymer and lipid phase boundaries as well as the fluidity of the lipid phase are of prime importance on the membrane structuration, as schematically illustrated on Figure 1.

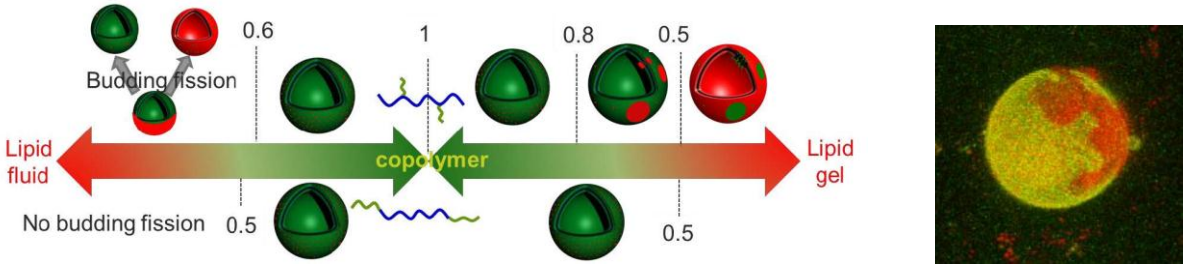

Figure 1: *Left:* Overview of the different hybrid vesicular structures that can be obtained according to the molar composition (polymer/lipid molar ratio) and thermodynamic phase of the phospholipid for a commercial graft copolymer $PDMS_{22}$-*g*-$(PEO_{12})_2$ and a triblock copolymer PEO_{17}-*b*-$PDMS_{68}$-*b*-PEO_{17} synthesized in the laboratory. *Right:* Confocal image

We have recently extended the study to small unilamellar Vesicles (SUV, D∼100nm) and obtained exciting preliminary results by SANS. Using deuteriated lipids and accurate D_2O/H_2O mixtures to match copolymer signal, we were able to detect only the lipid signal which can be fitted by a flat cylinder form factor giving a thickness $2H$=36 Å and a disc radius R_D=311 Å as shown on Figure 2. This strongly supports that phase separation occurs within the membrane, as observed for certain hybrid GUVs, and that the lipid phase probably adopts the shape of spherical cap(s) in the hybrid SUVs, which can be modeled with good approximation by flat disc shapes.

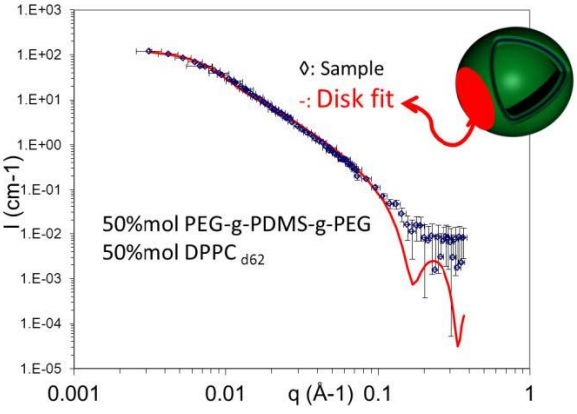

Figure 2: Intensity versus q fitted by cylinder form factor of 311Å radius and 36Å thickness (nano-disc)

Using lipids with different melting temperature and copolymers differing by their molecular weight, architecture (graft, di-block, triblock…) with similar hydrophobic and hydrophilic blokcs, we hope to establish a map of membrane structuration at micro and nanoscale and understand what are the molecular and macroscopic governing parameters of the phase separation. In that purpose, differential scanning calorimetry, Scattering techniques (light, Neutrons) as well as time resolved fluorescence spectroscopy (FRET) will be used for SUV in addition to Confocal microscopy for Giant vesicles. This study should clarify the elementary bricks necessary to modulate membrane properties of these new self assembled hybrid structures, in an optimized fashion regarding to different field of applications…

[1] J. F. Le Meins, et al., *Materials Today*, 2013, 16, 397-402
[2] M. Schulz, et al., *Soft Matter*, 2014, 10, 831-839