Large Unilamellar and Giant Hybrid Polymer/Lipid Vesicles: the influence of lipid fluidity, architecture and molar mass of copolymer on membrane structuration

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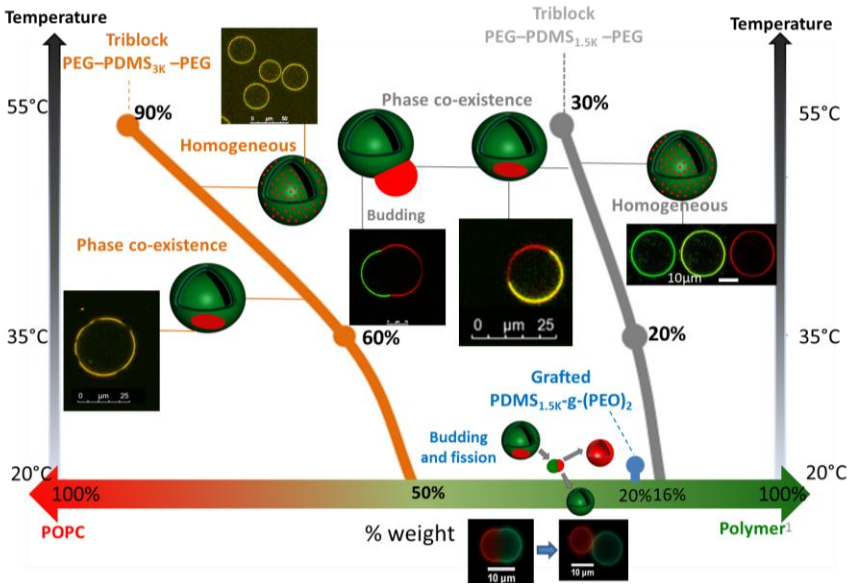
Compared to liposomes, hybrid vesicles resulting from the combined self-assembly of amphiphilic copolymers (P) and phospholipids (L) integrate the best from the two different systems (bio-functionality of lipids, improved stability and various coupling chemistries of polymers) in a single hybrid vesicular structure.[1, 2] Promising properties have been evidenced recently in literature in term of drug targeting, bio-recognition or modulation of membrane stability and permeability.[3-6] However, little knowledge has been acquired on the molecular and external parameters governing the membrane structuration. At the nanoscale (Large Unilamellar Vesicles), the organization of lipids and polymer chains in the membrane is unknown. From previous studies performed on Giant Unilamellar Vesicles (GUV) by epifluorescence and confocal microscopy it seems that hydrophobic mismatch between polymer and lipid phase as well as lipid fluidity are important parameters.[1]

In this work we have studied the phase diagram (membrane structure) of GUV hybrid vesicles by confocal microscopy, lipid and polymer phase being respectively tagged by rhodamine and fluorescein fluorophores. LUV have been also studied by Small Angle Neutron Scattering, and time-resolved Förster Resonance Energy Transfer (TR-FRET) which offers the possibility to study nanostructural changes at the membrane level, and cryo-TEM. The phase diagram has been explored by playing on the composition (polymer/lipid ratio), polymer architecture (graft copolymer or triblock) and molar mass of the copolymer hydrophobic block to tune the thickness mismatch between lipid and polymer membranes and play with the conformational constraints of the polymer chains at the L/P boundary. We used a grafted copolymer with a flexible poly-(dimethylsiloxane) backbone and two poly(ethylene oxide) pendant moieties (PDMS-*g*-$(PEO)_2$), with a PDMS molar mass of 1500 g/mol, and several triblock copolymer PEO-b-PDMS-*b*-PEO with a molar mass of 1500, 3000 and 5000 g/mol for PDMS and 400, 600 or 750 g/mol for PEO. All these copolymers form vesicles with a membrane thickness of 5, 5, 8, and 12 nm respectively, allowing a fine tuning of thickness mismatch between lipid and polymer phases in the hybrid membranes.

In the figure 1 are summarized the different structures obtained on giant hybrid vesicles obtained from mixture of POPC and different copolymers at different compositions and temperatures.



We have clearly shown that the architecture and molar mass of the hydrophobic block have a strong influence on the phase diagram and membrane structuration. When hydrophobic mismatch is expected to be weak, (e.g PEO_{400}-*b*-$PDMS_{1500}$-*b*-PEO_{400}) heterogeneous hybrid vesicles can be observed once the lipid content is above 16% in weight, whereas 50% at least, are necessary with thicker block (PEO_{600}-b-$PDMS_{3000}$-b-PEO_{600}).

Another part of the study has been focused on LUV. At first, SANS studies were performed on vesicular suspensions made from the grafted copolymer and deuterated 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (d_{62}-DPPC) at ~20% weight ratio of lipid. D_2O/H_2O mixtures were used to separate the respective L/P contributions. The fitting of the data by different form factors in lipid and polymer matching conditions tends to prove that phase separation leading to the existence of lipid domains can also occurs in LUV. TR-FRET results on these systems show also heterogeneous distribution of the components in the membrane.[7] New results will be presented on the hybrid vesicles made from triblock PEO-*b*-PDMS-*b*-PEO described previously.

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