

Polymer and Colloid Highlights

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Understanding Vesicle Origami

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Phospholipid vesicles are self-assembled bilayer structures surrounding an aqueous inner cavity. This cavity can take up drug molecules and such liposomes represent a well-advanced field of nanomedicine with several formulations translated into the clinics.^[1] The field, however, seems stuck and particularly in tumor targeting no significant advances have been made in the past decade.^[2] This is a clear sign that we do not understand the tools we are using and it is therefore vital to take a step back and study the fundamental biophysical properties of phospholipid vesicles. We decided to do this by probing the forces at play in liposome self-assembly using artificial phospholipids.

A typical drug delivery vesicle is in a liquid crystalline phase which leads to a spherical shape.^[3] Compared to this, a vesicle in a gel phase possesses a much stiffer membrane and because of strain energy minimization, the membrane moves out-of-plane and forms facets, akin to the icosahedra of some viruses. Playing with the attractive and repulsive forces in a membrane, we can actively change the shape of a vesicle, leading to vesicle origami.

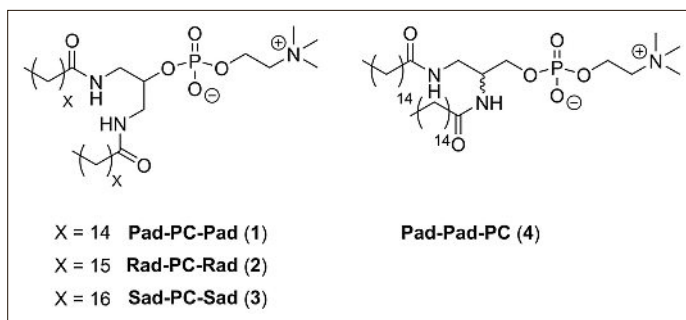
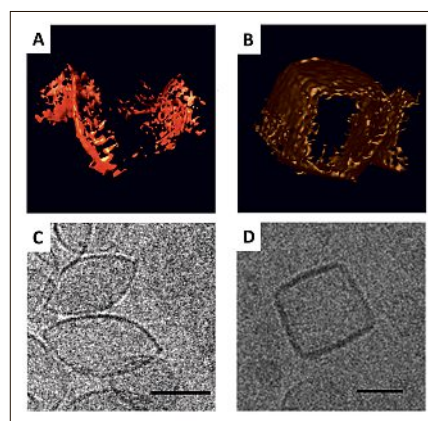


Fig. 1. Molecular structures of the class of 1,3-diamido phospholipids (**1**, **2** and **3**) and the 1,2-diamido phospholipid Pad-Pad-PC (**4**).

In the past years, we investigated different approaches to alter membrane properties, combining organic synthesis with monolayer and bilayer studies. A first motive leading to faceted vesicles are 1,3-diamido phospholipids (Fig. 1: **1–3**). Compared to natural *sn*-1,2 phospholipids, the acyl chains are spaced further apart, which leads to bilayer membrane leaflet interdigitation.^[4,5] Cryogenic transmission electron tomograms reveal non-spherical vesicles of a developable form with overall zero Gaussian curvature (Fig. 2: A,C). The defect line at the intersection of the membrane faces renders the vesicle mechanoresponsive leading to a new concept in nanomedicine: targeting of atherosclerotic blood vessels through a physically triggered release mechanism.^[6]

A second way to induce extreme vesicle faceting is to increase the attractive intermolecular forces with large hydrogen bond networks. Here, an optimized geometry is achieved with 1,2-diamido phospholipids (Fig. 1: **4**), forming stiff membranes in a subgel herringbone packing that cannot be bent in any direction. Forcing **4** to self-assemble into a closed 3D structure leads to a minimization of membrane intersections (edges) and a maximization of flat membrane faces, resolved in a cuboid structure (Fig. 2: B,D).^[7]



Our approach to synthesize artificial phospholipids gives us the flexibility to optimize our existing drug delivery system for pharmaceutical applications. Combining the fundamental knowledge on membrane self-assembly from our diamido phospholipid studies^[4] and research on the phospholipid substitution patterns^[7] prompted us to synthesize the odd-numbered 1,3-diamido phospholipid Rad-PC-Rad (**2**).^[5] Compared to Pad-PC-Pad (**1**) ($T_m = 37^\circ\text{C}$),^[6] Rad-PC-Rad (**2**) shows an elevated main phase transition temperature of 45°C and a processability that is lacking in Sad-PC-Sad (**3**).^[5] These properties make Rad-PC-Rad (**2**) suitable for shear stress-triggered release of drug molecules in stenosed arteries, as a first-line treatment of myocardial infarction.

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