Hybrid polymer/lipid vesicles: state of the art and future perspectives

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Hybrid vesicles resulting from the combined self-assembly of both amphiphilic copolymers and lipids have attracted particular interest from chemists and (bio)physicists over the last five years. Such assemblies may be viewed as an advanced vesicular structure compared to their liposome and polymersome forerunners as the best characteristics from the two different systems can be integrated in a new, single vesicle. To afford such a design, the different parameters controlling both self-assembly and membrane structure must be tuned. This highlight aims to present a comprehensive overview of the fundamental aspects related to these structures, and discuss emerging developments and future applications in this field of research.

Introduction

Liposomes are the archetype of synthetic vesicular structures obtained through a self-assembly mechanism, where amphiphilic molecules such as lipids, *e.g.* phospholipids are simply transferred into water. Liposomes have been extensively studied and used since the 1970s as nano- and microreactors, cell membrane models or drug delivery systems [1]. It was demonstrated in the late 1990s that amphiphilic block copolymers were also able to self-assemble into vesicular morphologies, and were therefore named polymersomes in reference to their lipid analogs [2,3]. This discovery had a great scientific impact on the self-assembly research field and polymersomes rapidly appeared as an interesting alternative to liposomes which possess a poor modular chemical functionality and in some cases (*e.g.* osmotic shocks) suffer from relatively weak stability. The larger molar masses of polymer chains over lipid tails and the versatility of chemical functions that can be integrated in polymer structures make polymersomes attractive to significantly improve and modulate membrane bulk properties (toughness, permeability) and surface functionality of vesicles [4]. In particular, polymersomes can be used as model tools to better understand biological events where the physical properties of membrane are of prime importance (bending elasticity, spontaneous curvature...) like the cell plasmic membrane adhesion, fusion or fission [5]. However, the cell biomimetic character of polymer vesicles is

rather limited compared to liposomes as block copolymers are generally synthetically made, while phospholipids are mostly natural components of the cell membrane. In addition, the high mechanical stability and low permeability of polymersomes can be viewed as both positive factors and as limiting features in some applications where a controlled diffusion of species through the membrane is required. To tackle this challenge, stimuli-responsive polymersomes have been designed, where the membrane destabilization and the concomitant release of molecules are obtained in defined conditions [6–9]. However, this approach requires a careful synthetic design of the block copolymer structure and is often limited to usage in specific conditions. While different approaches were proposed to modulate the membrane properties of polymersomes [4], a very promising method has recently emerged to overcome intrinsic limitations of both polymersomes and liposomes. The proposed methodology consists of designing mixed vesicles from both copolymers and lipids (Fig. 1). The main expected benefit of such hybrid structures is the fine tuning of the membrane physical properties. Besides, depending on how lipid and polymer chains are distributed within the membrane, one can expect an improved control of (bio)functionalization of the vesicles' surface, which is of interest in many applications such as drug delivery at a specific target (*e.g.* a site of inflammation or tumor environment). Beyond the challenging aspects of formulation, the development of such hybrid vesicles allows addressing many questions about the formation of a stable membrane:

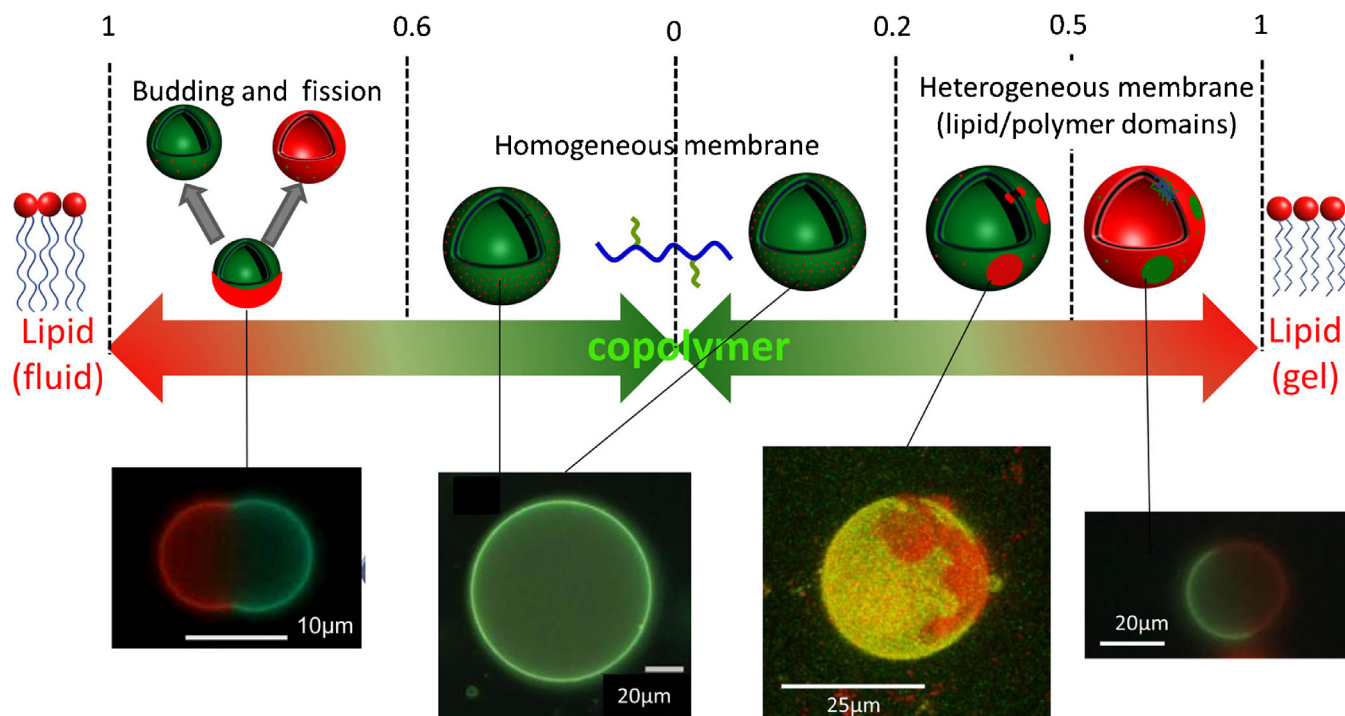*Corresponding author:. Le Meins, J-F. (lemeins@enscbp.fr)

FIGURE 1

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. Sketches on the top lines illustrate the different cases obtained by study of the epi- or confocal fluorescence microscopy images. All these hybrid vesicles were formulated with polydimethylsiloxane-graft-poly(ethylene oxide) and dipalmitoylphosphatidylcholine (DPPC) in the gel state or 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) in the fluid state at room temperature [10].

- How intimately the molecular components need to be mixed, and what is the influence of variations of polymer structure and size (molecular weight)?
- Is it possible to get control over membrane structure and composition, meaning a homogeneous distribution of both components or the formation of heterogeneous domains?
- What is the long-term stability of such hybrid vesicular assemblies?

Condition of formation of hybrid vesicles

A crucial parameter controlling the formation of stable hybrid vesicles is the discrepancy of chemical composition and size of hydrophobic segments between polymers and lipids. In addition, the thermodynamic incompatibility, due to both entropic and enthalpic differences between the hydrophobic blocks, may also drive a phase separation and the subsequent formation of liposomes and polymersomes separately. In order to compare these fundamental expectations with real systems, we will first review the hybrid vesicles reported so far in the literature. On the polymer side, amphiphilic block copolymers studied to elaborate hybrid vesicles were based on poly(dimethyl siloxane) (PDMS) [10,11], poly(isobutylene) (PIB) [12,13] or poly(butadiene) (PBut) [14–17] as hydrophobic blocks, and poly(ethylene oxide) (PEO) or poly(2-methyloxazoline) (PMOXA) as hydrophilic blocks. All these polymer blocks exhibit a low glass transition temperature (T_g), allowing dynamic exchange of the chains and leading to the equilibrium structure of the membrane when it forms. Concerning the choice of lipids, most studies were performed with phosphatidylethanolamine [11,15] or phosphatidylcholine [10,12–14, 16,17] head-groups with either saturated or unsaturated tails,

which are both major constituents of biological membranes. The copolymers and lipids used are summarized in Table 1. The solubility parameters (δ) of hydrocarbon moieties in phospholipids and hydrophobic polymer blocks are relatively close, that is, $\delta = 9.1$ cal$^{1/2}$/cm$^{3/2}$ for the fatty acid tail in lipids and $\delta = 7.3$ cal$^{1/2}$/cm$^{3/2}$, 7.7 cal$^{1/2}$/cm$^{3/2}$ and 8.32 cal$^{1/2}$/cm$^{3/2}$ respectively for PDMS, PIB and PBut blocks [18–20]. These relatively close values suggest that the chemical compatibility between the components is indeed a parameter of uppermost importance to enable the formation of hybrid vesicles even though the lateral phase separation of components inside the membrane still can occur for other reasons, as it will be commented in the following.

The effect of composition, namely the polymer/lipid molar ratio, on the formation of hybrid vesicles was rarely investigated in a systematic manner. Based on calorimetric measurements and fluorescence self-quenching analysis, Ruysschaert et al. suggested that Egg-Phosphatidylethanolamine (EPE) lipids distribute homogeneously in hybrid vesicles obtained with PMOXA$_{1.8k}$-b-PDMS$_{5.4k}$-b-PMOXA$_{1.8k}$ terpolymer whatever the molar composition [11]. In another study with vesicle-forming diblock copolymers, it was demonstrated that a minimum of 65 mol% of PBut$_{46}$-b-PEO$_{30}$ block copolymer was required to form hybrid vesicles with 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) [16]. Considering several other different results [11–13,15–17], it appears obvious that the parameter governing the production of such hybrid polymer/lipid vesicles are not trivial and that further investigations are needed to get both a better understanding and a certain predictability. Another difficulty arises from the fact that the molar composition of lipid and polymer in the final hybrid vesicles can be different from the starting composition, as evidenced by fluorescence microscopy

TABLE 1

The different copolymers and lipids used up to now to formulate hybrid vesicles and short comments about the membrane structure observed (homogeneous or heterogeneous distribution of the components, at the optical scale).

Authors	Copolymers	Lipids (state at room temperature)	Membrane structure/domains
Fournier et al. [11]	PMOXA$_{1.8k}$-b-PDMS$_{5.4k}$-b-PMOXA$_{1.8k}$ ($\overline{Mn}$ = 9000 g/mol)	Mixture of egg-phosphatidylethanolamine/egg-phosphatidylcholine (2/1 mol/mol) (fluid) Dipalmitoylphosphatidylcholine (DPPC) (gel, L'_β)	Homogeneous
Tsourkas et al. [14,15]	PBut$_{46}$-b-PEO$_{30}$ ($\overline{Mn}$ = 3800 g/mol) PBut$_{22}$-b-PEO$_{13}$ ($\overline{Mn}$ = 1800 g/mol)	1-Palmitoyl-2-oleoyl-sn-glycero phosphocholine (POPC) (fluid) Hydrogenated soy phosphatidylcholine (HSPC) (gel) 1,2-Distearoyl-sn-glycero phosphoethanolamine-N-poly(ethylene glycol) (DSPE-PEG) (fluid)	Homogeneous
Le Meins, Sandre et al. [10]	PEG$_{12}$-g-PDMS$_{22}$-g-PEG$_{12}$ $\overline{Mv}$ = 3000 g/mol	POPC (fluid), DPPC (gel, L'_β)	Homogeneous or heterogeneous depending on polymer/lipid ratio and lipid state (Fig. 1)
Vanderlick, Beales et al. [16,17]	A: PBut$_{46}$-b-PEO$_{30}$ ($\overline{Mn}$ = 3800 g/mol)	POPC (fluid), DPPC (gel, L'_β), cholesterol 1,2-Di-lauroyl-sn-glycerophosphocholine (DLPC) (fluid) 2-Ditridecanoyl-sn-glycerophosphocholine (DC13PC) (fluid)	A ≥ 70%: homogeneous 70 ≥ A ≥ 30: no vesicles obtained A ≤ 30% majority of liposomes Micrometric domains obtained via further crosslinking
Bacia, Binder et al. [12,13,21]	A: PIB$_{87}$-b-PEO$_{17}$ ($\overline{Mn}$ = 5350 g/mol) B: PIB$_{37}$-b-PEO$_{48}$ ($\overline{Mn}$ = 3970 g/mol)	DPPC (gel, L'_β)	A ≤ 28%: heterogeneous A > 28% homogeneous B < 40% vesicles with "holes"
Pispas et al. [22]	PEO$_{113}$-b-PCL$_{12}$ $\overline{Mw}$ = 7500 g/mol	DPPC (gel, L'_β)	No information available

experiments on giant vesicles [10,13]. Such an issue highlights the uppermost importance of controlling the formulation process and the need to find specific protocols.

Structure of the vesicle membrane

The control of the membrane structure is a major feature brought about by hybrid vesicles. A large variety of levels of structure, ranging from a homogeneous distribution of both components to polymer- or lipid-rich micro-domains were obtained. A complete review on phase separation in model lipid bilayers whose reading can be helpful to get a general view of the parameters governing the formation of domains, has been published in 2003 by Binder and colleagues [23]. In the case of hybrid polymer/lipid vesicles, relevant parameters seem to be the physical state of lipids, which depends on their main chain transition temperature (from gel state at $T < T_m$ to fluid, liquid-crystalline state at $T > T_m$), and the composition of the polymer/lipid mixture. Hybrid vesicles can be compared to some extent to mixed liposomes made of lipids having different melting temperatures T_m [10,12,17]. For instance, the mixing of DPPC (T_m = 41 °C) with POPC (T_m = −2 °C) at room temperature gives rise to the formation of lipid domains within the membrane as a result of demixing of the two components. In case of polymer/lipid hybrid vesicles, similar results were observed provided that the initial amount of lipid was high enough. For example, the formation of lipid domains in a copolymer-rich membrane was described with lipids of high T_m such as hydro-genated soy phosphatidylcholine (HSPC) [15] or DPPC (1,2-dipal-mitoyl-sn-glycero-3-phosphocholine) [10] for a lipid content

higher than 20 mol%. Conversely, the formation of membranes presenting a homogeneous distribution of components, at least at the micrometric scale seemed to be favored when the lipid was used above its main chain transition temperature [11,12,16,17]. In addition to the gel or fluid state of the lipid used, the size mismatch between polymer and lipid chains also plays an important role on the membrane structure. The usual membrane (bilayer) thickness is indeed 3–5 nm for liposomes and varies from 5 to 50 nm for polymersomes (either bilayer for diblock or graft copolymers or monolayer for triblock). In case of a large size gap, the formation of a lipid domain would imply a high line tension at the lipid/polymer boundaries arising from the thickness mismatch between the domain and the surrounding polymer membrane with a concomitant exposure of hydrophobic polymer segments to water. To reduce this exposure and the resulting energetic cost of the boundary edges, the two opposite plausible scenarios are (i) conformational adaptation through elastic deformation of the polymer chains at the boundary (see Fig. 2a) at an entropic cost for the polymer chains (but globally reducing the line tension), or (ii) coalescence into domains of larger area. It is worth noticing that scenario (i) is analogous to elastic deformation of the membrane at the domain boundary in phase coexisting lipid membranes [24].

Figure 2a shows that conformational adaptation of the polymer implies a collapse of the hydrophobic polymer chains near the lipidic interface, opposing entropic elasticity of chains (reduction of the total number of conformations) and the natural stretching of polymer chains self-assembled as flat membrane [4]. Therefore it
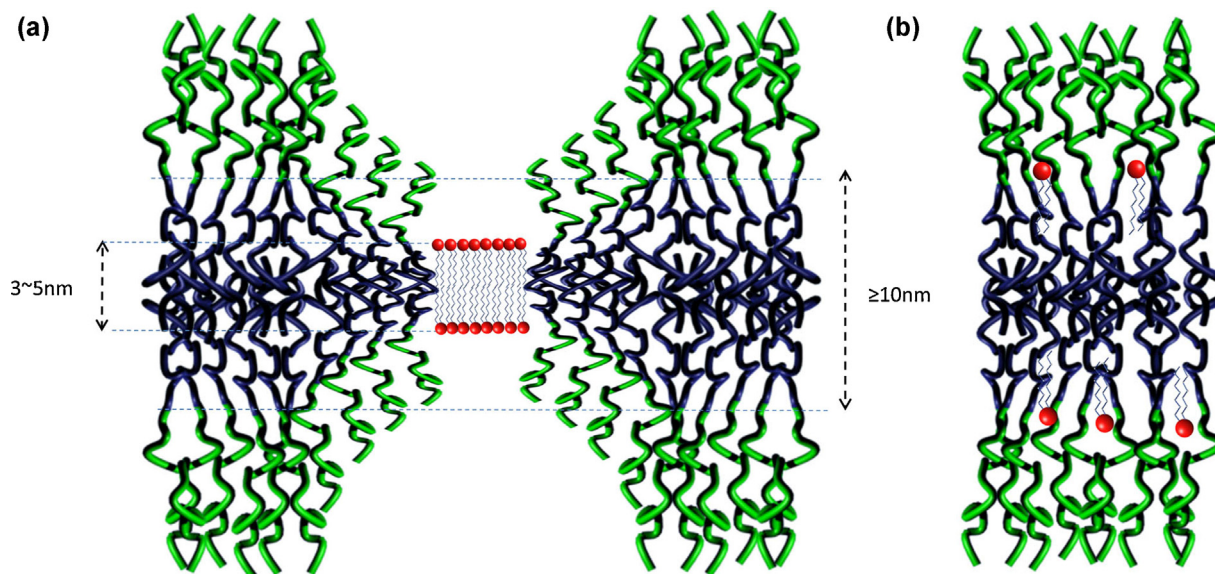
FIGURE 2

Impact of the cooling rate on the structure of the membrane of hybrid vesicles based on PBut-*b*-PEO/DPPC (60/40) adapted from [17]. The arrow indicates the increases of the cooling rate from to −0.1 °C/min to −0.4 °C/min.

is clear that the molar mass (or chain length) and rigidity of the hydrophobic polymer backbone plays a major role. If this adaptation cannot be achieved, then the domain formation is unlikely (spontaneously nucleated domains eventually collapse) and a homogeneous mixture of the components is expected (Fig. 2b).
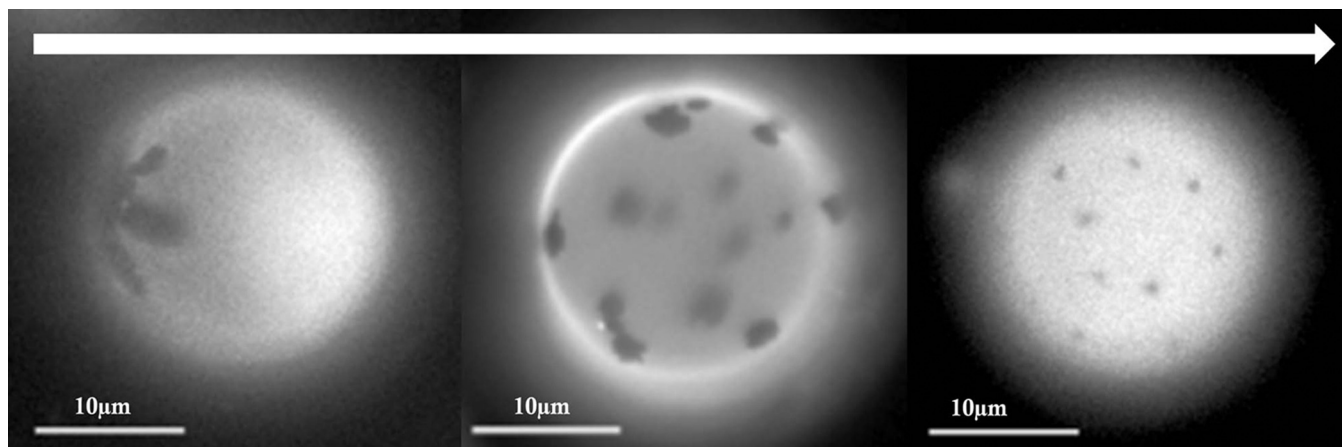
In a recent study [10], we evidenced that the use of PDMS-*g*-PEO copolymers, leading to vesicles with a membrane thickness close to that of liposomes (∼5 nm) [25], helps the spontaneous formation of micrometric lipid domains in hybrid vesicles in a large composition range (from 50% and up to 80% mol polymer) when the lipid is in the gel state (DPPC). When associated with fluid lipids (≥50% mol of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC)), PDMS-*g*-PEO spontaneously form vesicles with micrometric lipid domains that progressively evolve into separated liposomes and polymersomes through a budding and fission process [10]. This phenomenon of total demixing of a hybrid vesicle into two daughter vesicles can be viewed as a ''poor-man model'' of the cellular division.

Furthermore, in most of the studies reported so far, the copolymers used form membranes thicker than 8 nm, and the spontaneous formation of domains (at least at the optical microscope scale) was reported as a rare event occurring only for narrow composition ranges. For instance in one of these studies [13], giant unilamellar vesicles (GUV) presenting micrometric domains were spontaneously obtained using DPPC and PIB_{87}-*b*-PEO_{17}, but only in a very narrow composition range (20–28 mol% polymer). The large hydrophobic block in that case limits the conformational adaptation at the polymer–lipid boundary. On the contrary, the large hydrophobic thickness plays in favor of a single-phase membrane for a large composition range (all polymer contents larger than 30 mol%) as sketched in Fig. 2b. But a decrease of the hydrophobic block length (to enable domains) must be accompanied by a concomitant reduction of the hydrophilic block length; otherwise the hydrophilic-to-hydrophobic volume ratio becomes too high to form stable (unperforated) membranes. This is the most likely explanation for hole-defects observed in vesicles

formulated with high DPPC content (≥60%) and block copolymer with a shorter hydrophobic block and a longer hydrophilic one (PIB_{37}-*b*-PEO_{48}), stabilizing bilayers edges with a local micellar structure.

Among the different polymer/lipid hybrid systems, there is a special interest in the formation of polymer-rich vesicles with stable lipid-rich domains of controlled size, with regard to different kinds of applications in drug delivery, bio-targeting or biophysical fundamental studies, such as the modeling of nanoparticles/membrane interactions and cellular internalization (artificial endocytosis). When lipids are used in the fluid state, only homogeneous hybrid vesicles (at the micrometric scale) can be obtained. Additional components are then needed to generate a stable phase-separated membrane. For instance, micrometric domains were generated in hybrid vesicles by reacting streptavidin (in solution) with biotinylated head-groups of the lipids, the protein with multivalent binding sites ''working as a zipper'' to gather the lipid together in monodomains. However, such a protein coating limits the further biofunctionalization of the domains [16]. Cholesterol, which is well-known to promote compaction of fluid phase lipids and the lateral phase separation into ''raft-like'' domains within liposomes for certain lipid compositions [26] induces the same effects when added to lipid/polymer mixtures. Hence, hybrid vesicles with round shaped micrometric domains were obtained with various lipids of low T_m (DLPC, POPC, $DC_{13}PC$) complemented with cholesterol, the domain size varying with the exact polymer/lipid/cholesterol composition [17].

Moreover, it has been shown that working at temperature where lipids are in gel state favors the formation of lipid domains in the polymer vesicle membrane. Nam et al. proposed a method which consists in forming hybrid vesicles from PBut-*b*-PEO and DPPC above the lipid melting temperature and then cooling the system below the melting point at a controlled cooling rate [17]. Such an approach offers the possibility to control the number and the size of lipid domains. When the cooling is fast, the domains become smaller and with a large number, as expected for a typical

FIGURE 3

Impact of the cooling rate on the structure of the membrane of hybrid vesicles based on PBut-*b*-PEO/DPPC (60/40) adapted from [17]. The arrow indicates the increase of the cooling rate from to −0.1 °C/min to −0.4 °C/min.

nucleation-growth process (Fig. 3). It is also worth noticing that the surface fraction of domains decreases when the cooling rate increases, as observed by optical microscopy on giant vesicles. Under such quenching conditions, lipid molecules tend to be homogeneously dispersed in the polymer matrix or may form domains too small to be detected by optical microscopy (*i.e.* smaller than typically 300 nm).

Specific properties of hybrid vesicles

What benefits have been derived from hybrid vesicles so far? Even if the membrane composition and the structure of the hybrid vesicles reported in literature are not yet fully controlled and understood, several studies already highlighted interesting features of these systems. For instance it was observed that the encapsulation of proteins in hybrid vesicles composed of PMOXA$_{1.8k}$-*b*-PDMS$_{5.4k}$-*b*-PMOXA$_{1.8k}$ and egg phosphatidyletha-nolamine (EPE) by freeze–thaw cycles was greatly decreased when the block copolymer content was above 20 mol% [11]. Since the encapsulation yield relies on the membrane destabilization ease during freeze–thaw cycles, this experiment actually highlights that the presence of copolymer improves the membrane stability. This has been confirmed by direct measurement of the mechanical properties of homogenous hybrid vesicle membranes. Globally, even if there is no complete systematic study on the effect of membrane composition yet, it seems that lysis stress, lysis strain and stretching elastic moduli present intermediate values for hybrid vesicles compared to those respectively of pure liposomes and polymersomes, and that the resulting toughness of hybrid vesicles is increased compared to liposomes [15,16].

The membrane viscosity also appears much higher as demonstrated by fluorescence recovery after photo-bleaching (FRAP) experiments on hybrid lipid/polymer giant vesicles [16]. Such an improvement of the visco-elastic properties compared to pure liposomes is of interest for future developments of hybrid vesicles in drug delivery. A current limitation of liposomes is indeed their relative low membrane stability under osmotic shocks or high shearing rates. Here, hybrid polymer/lipid vesicles are expected to withstand relatively high osmotic pressure and strong shear flow in blood circulation without damage. Besides, preliminary results obtained on nano-size hybrid vesicles bearing the folate ligand

show enhanced tumor targeting properties compared to pure folate-functionalized polymersomes, even if the origin of this effect is not understood yet [15]. Preliminary results obtained on hybrid vesicles made of poly(ethylene oxide)-*block*-polycapro-lactone (PEO-*b*-PCL) mixed with gel state lipids (DPPC), indicate that the release rate of encapsulated species could be modulated *via* the ratio of the two components [22]. Recently a milestone was reached in the quest of robust vesicles endowed with bio-functionality. It was indeed demonstrated that lipids bearing the gang-lioside GM1 receptor keep their binding ability to the cholera toxin whatever the degree of membrane organization of hybrid vesicles, *i.e.* the membrane structure can be homogeneous or having micrometric lipid domains [21]. However, this ability was lost above 40 mol% of block copolymer as ascribed to a steric hindrance of the PEO chains. It has to be noted that mixed and phase separated polymer–lipid films were recently evaluated to direct the positional control of membrane proteins [27]. It was also shown that the preferential incorporation of nanoparticles in a given phase of polymer–lipid hybrid vesicles could be realized by appropriate nanoparticles' surface modification [12].

Conclusions and perspectives

Up to now, polymers have mostly been used with liposomes as surface additives [28], either grafted to the lipid head-groups [29] or adsorbed onto the lipid bilayers thanks to hydrophobic anchors [30–32] or encapsulated inside the aqueous lumen as gels to mimic the cytoskeleton of biological cells [33,34]. In the last few years, polymers have truly entered inside the lipid membrane, and this new paradigm paves the way of a variety of new perspectives.

The design of hybrid polymer/lipid vesicles with good control over the molar composition and the membrane structure at the micro- and nano-scales remains highly challenging. It is of particular interest to build a vesicular membrane with lipid ''raft-like'' nanodomains (from a few tens to hundreds of nanometers). The benefits of such structures would be bio-functionality (patchy surface effect) and the precise modulation of basic membrane properties (elasticity, permeability…). It is well-known that lipid rafts naturally occurring in the cell membrane, with relatively small size (∼50–500 nm), play a key-role in a wide range of biological processes [35,36] including lateral protein organization, virus uptake [37],

signaling, trafficking [38,39] or membrane tension regulation [40]. The biophysical mechanism that maintains small lipid domains in equilibrium and opposes their ripening expected from thermodynamic consideration is not yet completely understood. Experimental and theoretical developments (until now conducted exclusively on liposomes) have shown that a subtle balance between several parameters governs the domain size. One of prime importance is the energy cost by the domain to create a boundary with the surround (line tension $\mathfrak{I}$ in pico Newton), which arises from the thickness mismatch between the domain and the surrounding membrane: $\mathfrak{I}$ opposes domain nucleation and favors domain coalescence (once nucleation size is reached) to minimize the boundary length [24,41]. This is balanced by other mechanisms such as entropic trap [42] stabilizing nanodomains, the elastic interaction between dimpled domains due to deformation of the surrounding membrane [43], the long range electrostatic dipolar interaction [44] and the natural vesicle curvature [43,45,46]. All these aspects have been discussed in recent reviews focusing on the stability of lipid domains [47], and phase separation in biological membranes [48]. There are currently only few experimental examples of lipidic nanodomains (*i.e.* below the optical microscopy resolution) in model liposomes [49–53] and their existence has not yet been proven on hybrid polymer/lipid vesicles. It is believed that block copolymer molecules of low T_g play a role in adjusting the line tension $\mathfrak{I}$ at the lipid–polymer boundaries because of their flexibility and of their molar mass tunability during the synthesis.

Finally, an emphasis should be given about the control of the membrane structure through physico-chemical pathways such as playing with entropic parameters (polymer/lipid adaptation at the boundaries), interactions (chemical nature of the polymer blocks), incorporation of additional reactants and environmental parameters (temperature, pH...), and lipid gel phase structures which may play a role on the domain morphologies of polymer/lipid vesicles, as they do for mixed lipid vesicles [54]. It is also important to remember that the membrane curvature can greatly influence the membrane structure. Therefore a series of experiments can give various results depending on the size of the vesicles. In other words, the results may differ significantly between studies on vesicles of nanometric size, also called large unilamellar vesicles (LUVs), and micrometric size giant vesicles (GUVs).

A better understanding of the hybrid thermodynamics and the addition of specific functionalities (selective permeability, magnetic properties by incorporating magnetic nanoparticles, membrane disruption with stimuli-responsive polymer block or lipids, incorporation of channel proteins...) should lead to the creation of nano- and micro-structures that are very useful in drug delivery (as preliminary illustrated in [15,22]) and as templating agents [14], or for the development of compartmentalized chemistry and biochemistry (bio-mimicry and synthetic biology) and as fundamental systems to understand complex biological behaviors in cells.

Acknowledgments

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The publisher regrets that when the figures were relabelled during the final editing stage, the Fig. 3 legend was repeated in error as the legend of Fig. 2. The correct figures and legends appear below. The publisher would like to apologize for any inconvenience caused.
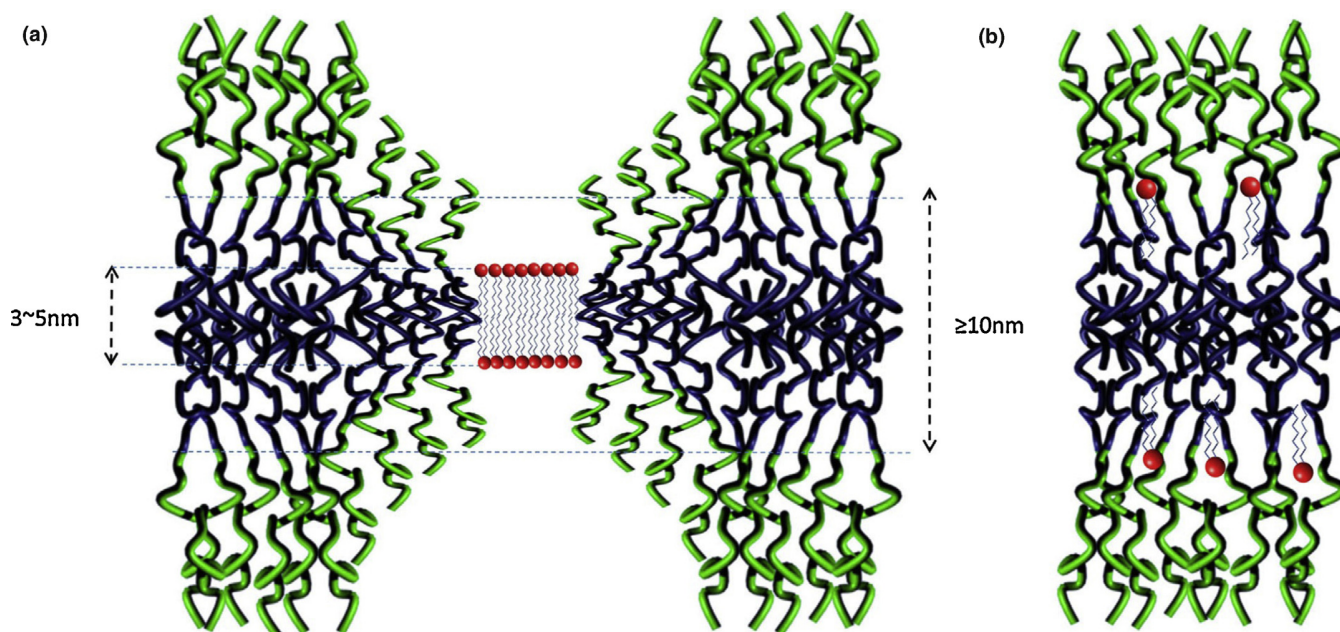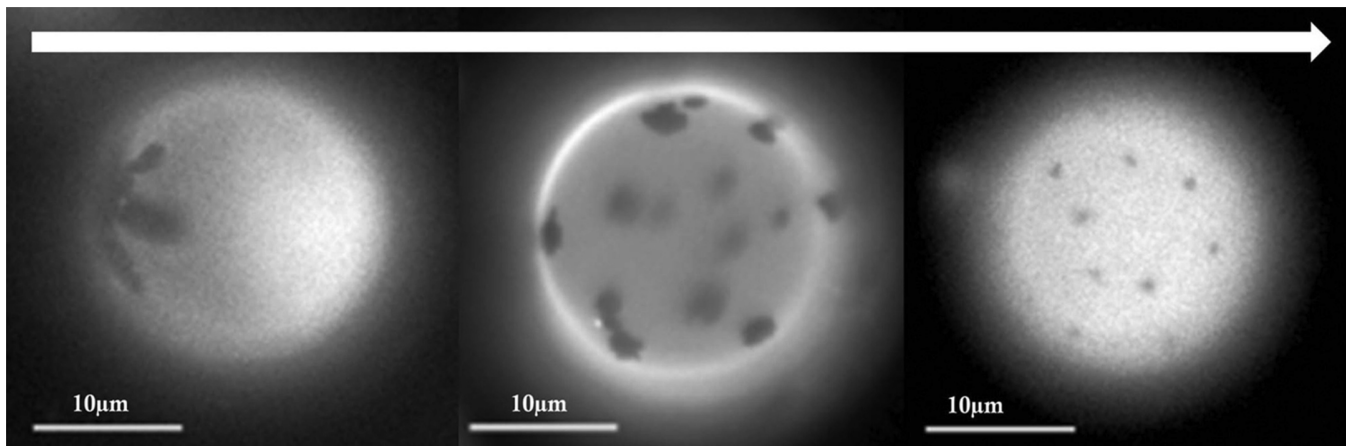

FIGURE 2

(a) Conformational adaptation expected at polymer/lipid domain boundary in hybrid vesicles in case of domain formation; (b) absence of conformational adaptation between polymer/lipid boundary leading to homogeneous mixture of the components.

FIGURE 3

Impact of the cooling rate on the structure of the membrane of hybrid vesicles based on PBut-b-PEO/DPPC (60/40) adapted from [17]. The arrow indicates the increase of the cooling rate from −0.1 °C/min to −0.4 °C/min.