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Lamellar self-assemblies of single-chain amphiphiles and sterols and their derived liposomes: Distinct compositions and distinct properties

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ABSTRACT

Typically, single-chain amphiphiles and sterols do not form fluid lamellar phases once hydrated individually. Most of the single-chain amphiphiles form actually micelles in aqueous environments, while sterols display a very limited solubility in water. However, under certain conditions, mixtures of single-chain amphiphiles and sterols lead to the formation of stable fluid bilayers. Over the past decade, several of these systems leading to fluid lamellar self-assemblies have been identified and this article reviews the current knowledge relative to these non-phospholipid bilayers made of single-chain amphiphiles and sterols. It presents an integrated view about the molecular features that are required for their stability, the properties they share, and the origin of these characteristics. It was also shown that these lamellar systems could lead to the formation of unilamellar vesicles, similar to phospholipid based liposomes. These vesicles display distinct properties that make them potentially appealing for technological applications; they display a limited permeability, they are stable, they are formed with molecules that are relatively chemically inert (and relatively cheap), and they can be readily functionalized. The features of these distinct liposomes and their technological applications are reviewed. Finally, the putative biological implications of these non-phospholipid fluid bilayers are also discussed.

1. Introduction

Bilayers made of phospholipids and sterols have been studied extensively [1–6]. These self-assemblies are biomimetic models for plasma membranes, and several findings inferred from these models have influenced our understanding of the physicochemical behavior of membranes, as well as of several biochemical cellular processes. Inspired from biological membranes, these thin, impermeable, and fluid bilayers also constitute nanoscale elements that are valuable for technological applications in several fields, including controlled release, drug targeting [7–9], and biosensors [10,11]. In parallel to phospholipid-based bilayers, it has been established that some mixtures of single-chain amphiphiles and sterols can self-assemble to form similar lamellar structures. Typically, single-chain amphiphiles and sterols do not form fluid lamellar phases once hydrated individually. Most of the single-chain amphiphiles form actually micelles in aqueous environments, while sterols display a very limited solubility in water. However, under certain conditions, mixtures of single-chain amphiphiles and sterols lead to the formation of stable fluid bilayers. In the past decade, several of these systems leading to fluid lamellar self-assemblies have been identified and these findings brought insights into the interactions leading to their formation. It was also shown that these lamellar systems could lead to the formation of unilamellar vesicles, similar to phospholipid-based liposomes. These vesicles display distinct properties that make them potentially appealing for technological applications. The present article reviews the current knowledge relative to these non-phospholipid bilayers made of single-chain amphiphiles and sterols.

2. Mixtures of single-chain amphiphiles and sterols forming fluid bilayers

2.1. Single-chain amphiphiles

A fair number of reports indicate or suggest the formation of fluid lamellar phases from single-chain amphiphile/sterol mixtures. In most cases, cholesterol is the selected sterol while a considerable variety of single-chain amphiphiles have been used. Table 1 lists the main single-chain amphiphiles reported to form fluid lamellar phase in the presence of sterols.

Lysophosphatidylcholine (lysoPC), a single-chain phospholipid bearing a phosphocholine head group, and cholesterol form probably the first single-chain amphiphile/sterol couple for which the

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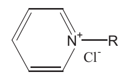
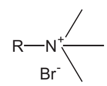
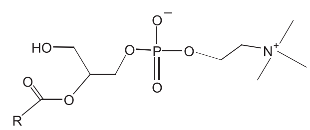
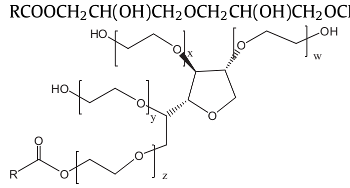
Table 1
Chemical structure of the main single-chain amphiphiles forming fluid bilayers in the presence of sterol ($R = C_nH_{2n+1}$).

Name	Chemical structure	*n*	Ref.
Myristic acid		13	[19]
Palmitic acid (PA)	RCOOH	15	[16–18]
Stearic acid		17	[19]
α-Hydroxypalmitic acid (αOH-PA)	RCH(OH)COOH	14	[20]
α-Fluoropalmitic acid (αF-PA)	RCH(F)COOH	14	
Stearylamine (SA)	RNH_2	18	[21]
Cetylpyridinium chloride (CPC)		16	[25]
Cetyltrimethylammonium bromide (CTAB)		16	[23,24]
N-myristoylethanolamine		13	
N-palmitoylethanolamine	$R(C{=}O)NHCH_2CH_2OH$	15	[26,27]
N-stearoylethanolamine		17	
LysoPC		16–18	[12–15]
Polyoxyethylene alkylethers (C_nEO_q)	$RO[CH_2CH_2O]_mH$	16–18	[35,40,41]
Diglyceryl monolaurate (DGL)	$RCOOCH_2CH(OH)CH_2OCH_2CH(OH)CH_2OH$	11	[35]
Tetraglyceryl monolaurate (TGL)	$RCOOCH_2CH(OH)CH_2OCH_2CH(OH)CH_2OCH_2{-}CH(OH)CH_2OCH_2CH(OH)CH_2OH$	11	
Tween 20 ($w+x+y+z=20$) Tween 21 ($w+x+y+z=4$)		11	[35–39]
Tween 60; Tween 61 ($w+x+y+z=20$)		17	
Octadecyl methyl sulfoxide (OMSO)	$RSOCH_3$	18	[43]

formation of a fluid lamellar phase was reported. Hydrated lysoPC generally forms micelles. In 1975, it was shown, using X-ray diffraction, electron spin resonance, and electron microscopy, that lysoPC derived from egg-yolk lecithin interacted stoichiometrically with cholesterol to form lamellar structures [12,13]. The possibility to prepare multilamellar as well as small unilamellar vesicles was subsequently demonstrated with an equimolar mixture of 1-palmitoyl-sn-glycerol-3-phosphocholine (lysoPPC) and cholesterol [14]. Based on scanning calorimetry and ^{13}C NMR, it was concluded that a 1:1 molar ratio provided an optimal composition because all the lysoPPC existed in the fluid lamellar phase without excess of cholesterol. Similarly, a systematic study using ^{31}P NMR and X-ray scattering showed that mixtures of lysoPPC and cholesterol formed fluid bilayers [15]. The lysoPPC self-assembly was progressively modified upon the addition of cholesterol, from micelles of pure lysoPPC to fluid bilayers when the mixture included 70 mol% cholesterol.

Fluid lamellar self-assemblies of palmitic acid (PA) and cholesterol in aqueous environment have been initially reported by Paré and Lafleur [16]. The temperature–composition diagram (Fig. 1) of this system, at pH 5.5, showed a region above 55 °C where the lamellar phase was exclusively formed. The authors concluded to the existence of "eutectic-like" composition corresponding to 65–70 mol% cholesterol. Lower cholesterol amount would lead to an isotropic oily phase formed mainly by the remaining PA whereas higher cholesterol content would produce solid cholesterol domains. When the fatty acid was deprotonated (pH > 7.5), it was found that PA/Chol 30/70 mixtures formed stable fluid bilayers between 20 and 70 °C [17,18]. Therefore the presence of the carboxylic group conferred pH-sensitivity to these bilayers, a feature that has been exploited to create pH-triggered release as discussed below. The formation of fluid bilayers in the presence

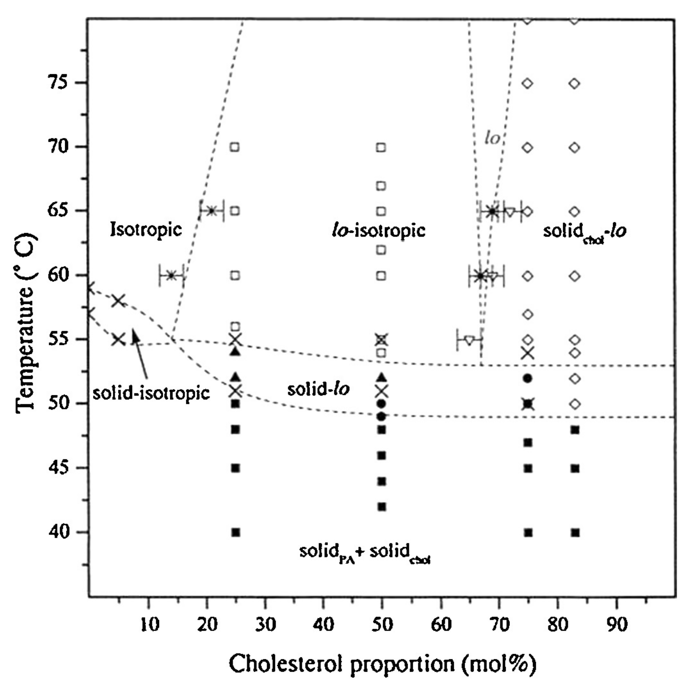


Fig. 1. Temperature–composition diagram for PA/Chol system, at pH 5.5. Reprinted with permission from Paré and Lafleur, Langmuir 17 (2001) 5587 [16]. Copyright 2001 American Chemical Society.