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Mixed DPPC/POPC Monolayers: All-atom Molecular Dynamics Simulations and Langmuir Monolayer Experiments

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ABSTRACT

To elucidate the consequences of the saturated-unsaturated nature of lipid surface films, monolayers formed by an equimolar mixture of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine (POPC) and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) lipids are investigated in a wide range of surface pressures. As such mixtures share some features with naturally-occurring surfactants, for example the lung surfactant, the systems are studied at the temperature relevant for human body. All-atom molecular dynamics simulations and Langmuir trough experiments are employed. The binary lipid mixture is compared with the corresponding one-component systems. Atomistic-level alterations of monolayer molecular properties upon lateral compression are scrutinized. These involve elevation of lateral ordering of lipid chains, modulation of chain and headgroup orientation, and reduction of lipid hydration. The presence of the unsaturated POPC in the DPPC/POPC mixture reduces the liquid expanded-liquid condensed coexistence region and moderates the phase transition. Simulations predict that nanoscale lipid de-mixing occurs with small transient DPPC clusters emerging due to local fluctuations of the lateral lipid arrangement. A vertical sorting of lipids induced by lateral compression is also observed, with DPPC transferred toward the water phase. Both the conformational lipid alterations due to monolayer compression as well as the existence of lateral dynamic inhomogeneities of the lipid film are potentially pertain to dynamic and non-homogeneous lipid interfacial systems.

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1. Introduction

Mixed lipid monolayers are interesting in biophysical context because both complex lipid films and multilayers occur on such biological interfaces as lung surfactant, tear film, and skin. In this respect, lung surfactant (LS) is of particular importance because of its crucial role during respiration [1]. LS is a surface active substance which is secreted by the type II cells of the alveolar epithelium and covers the air-water interface of alveoli [2]. It is a complex mixture consisting predominantly of lipids (~90% by weight) and proteins [3]. Its main function is reduction of surface tension at alveoli-air interface in order to increase lung compliance. Moreover, LS prevents the collapse of lungs at the end of expiration. LS is also a first barrier in the transfer of exogenous factors from the inhaled air to lungs. The deficiency of the lung surfactant in premature infants leads to the respiratory distress syndrome (RDS). This condition is routinely treated by the surfactant replacement therapy where exogenous surfactant preparations are administered. Protein-free synthetic surfactants were initially used but they are presently replaced by animal-derived modified formulations. Peptide-containing synthetic surfactants are currently under development [4]. In this light, a molecular-level understanding of basic physicochemical properties of the LS seems essential not only for understanding of the natural surfactant in lungs but also for supporting and guiding the development of synthetic surfactants.

Among the lipids that constitute the LS, the most abundant (~70–80%) are phospahtidylcholines (PCs) [5–7]. Approximately half of PCs are molecules with both chains saturated, namely dipalmitoylphosphatidylcholine (DPPC). It is generally accepted that DPPC makes the LS withstand high surface pressures due to the fact that at the lung temperature it is able to form a highly packed liquid condensed (LC) phase [8]. Another property of DPPC is that, due to its saturation, it is relatively invulnerable to oxidation by ozone and free radicals present in the inhaled air [9]. A non-negligible fraction of phosphatidylcholines in the LS, up to 50% of all PCs, consists of unsaturated lipids, mainly 16:0–16:1, 16:0–18:2, and 16:0–18:1 PC [7]. It is assumed that these lipids increase LS fluidity and help with surfactant respreading [10]. The remaining minor lipids in the LS are mainly polar anionic, mostly phosphatidylglycerols (PG) and non-polar lipids (cholesterol). Due to its composition, LS exhibits a complex behavior in compression-decompression cycles during breathing. In particular, it

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is able to withstand high surface pressures without irreversible collapse [11]. The origin of this phenomenon at the molecular level is still debated. Early theories suggest squeezing-out of the less durable non-DPPC components from the LS [12] while some of later studies opt for formation of meta-stable supercompressed phases during the relatively fast breathing cycles [13]. Regarding the dynamics, a strong time-dependence of lateral domain formation and coexistence was experimentally demonstrated in pulmonary surfactant films [11].

Numerous experimental and simulation studies were conducted for monolayers consisting of PC lipids for over forty years [14–28]. Such lipid systems can be employed as minimalistic models of the LS [19]. In contrast to natural LS extracts, they allow for a precise control of surfactant composition while studying film properties. This feature can be particularly useful for design of artificial LS systems. Of note, one should be always aware that pure lipid mixtures lack the full complexity of the actual lung surfactant and they cannot reproduce some of naturally observed LS phenomena. This is particularly important for protein-assisted processes such as formation of multilayered lipid structures in alveoli.

In most of previous model studies, the focus was on saturated DPPC monolayers. However, as unsaturated components constitute almost half of lipids in the LS, unsaturated lipids should be also included in an LS model. A one step further toward more complex and hence realistic LS models are two-component lipid monolayers. Such systems, formed by binary mixtures of saturated and unsaturated lipids, have been studied for long time [15,29]. However, binary lipid monolayers with a physiologically relevant composition in the context of the lung surfactant were only recently addressed, mostly in simulation studies [11,19,22,23,25,30–32]. In some of those works, monolayers of DPPC mixed with unsaturated POPG were studied with the main focus on the role of the PG headgroup [11,19,22,23,30,31]. Note however, that PGs, in contrast to PCs, are only a minor unsaturated lipids class in the LS [6,7]. Therefore, the DPPC/POPC mixture seems to better represent the saturation-unsaturation nature of the surfactant present in lungs.

Rose et al. investigated binary equimolar DPPC/POPC and DPPC/POPG monolayers by means of atomistic MD simulations [22]. A response to the lateral compression was of main interest. Squeezing-out of lipids to the water phase was observed upon compression of the DPPC/POPC monolayer. The order parameter of lipid acyl chains in the mixture was similar to that of POPC while the mixture's surface area-pressure isotherm reminded that of pure DPPC. In general, no significant differences between the binary and pure lipid systems were observed regarding basic structural properties of the monolayer. Concerning the squeezing-out of lipids, a series of work by Tieleman's lab was conducted employing the coarse-grain lipid models where transfer of lipids to the water sub-phase and formation of complex monolayer-associated structures was demonstrated at the tens of nanometers length-scale [21,33,34] .

The issue of phase transitions in DPPC/POPC monolayers was addressed employing coarse-grain MD simulations by Duncan et al. [30]. That work was motivated by earlier experimental studies that reported on the LC and LE nano- and microdomains coexistence in model lipid surfactants [6,17]. MD simulations demonstrated that the addition of unsaturated POPC to DPPC results in the decrease of LE-LC transition temperature and prevents LC domains formation at high temperatures. Segregation of lipids in DPPC/POPC monolayer was observed in the LC phase while a good lipid mixing was obtained in the LE phase.

Detailed simulations studies of lung-related mono-component lipid films were recently conducted employing atomistic MD simulations [27,35]. In the case of DPPC monolayers, the experimentally observed existence of LC and LE phases was reproduced and the detailed properties of lipid molecules in these phases were investigated [35]. In the study concerning POPC, both the experimental isotherm and structural properties of the film were reproduced by simulations [27]. Encouraged by these recent studies, we investigate mixed 1:1 DPPC/POPC monolayers at the atomistic scale. MD simulations are conducted employing the newly-developed all-atom Slipids force field that was shown to very well reproduce the behavior of lipid bilayers [36,37]. In order to study the role of lipid components of the film and a possible synergy effects, we compare the DPPC/POPC system with its mono-component (DPPC and POPC) counterparts. To connect with macroscopic features of the lipid films, we measure surface area-pressure isotherms of the corresponding monolayers employing Langmuir through experiments and compare it with the simulated ones. Our goal is to probe how the properties of the lipids constituting the monolayer, in particular their saturated-unsaturated character, influence structural features of the mixed DPPC/POPC system.

2. Methodology

2.1. MD Simulations

Monolayer systems were prepared based on equilibrated bilayers of 128 lipids composed of DPPC, POPC, or an equimolar mixture of DPPC with POPC. Bilayer leaflets were translated and placed at a water slab with lipid headgroups oriented toward the water phase. Thus, for each lipid system two independent symmetric monolayers, each composed of 64 lipids, were present in the simulation box. The box of a rectangular prismatic shape was employed with periodic boundary conditions applied in all directions. The lateral dimensions of the box varied depending on the system from approximately 5.4×5.4 to 7.9×7.9 nm^2. In order to prevent interactions between periodic images, the box was elongated in the direction perpendicular to monolayers to the size of 28 nm resulting in the vacuum region which was approximately three-fold thicker than that of the water-lipid system. The three systems (DPPC, POPC, DPPC/POPC) were energy-minimized and then initially equilibrated for 10 ns in the NpT (isothermal-isobaric) ensemble at 310 K employing a semi-isotropic pressure coupling algorithm with pressure of 1 bar controlled independently in the directions perpendicular and parallel to the monolayers. The resulting box sizes corresponded to area per lipid of approximately 0.53 nm^2. The equilibrated configurations were used in several further lateral compression and expansion preparatory MD simulations in order to obtain monolayers with varying area per lipid. In these preparatory MD runs, the lateral pressures (π) employed were system-dependent and varied between -25 and 25 bar and simulation time was in the range between 8 and 20 ns. For each system, six configurations with varying area per lipid (APL), between 0.47 and 1.00 nm^2, along compression-expansion trajectories were selected and used for subsequent simulations along of pressure-area isotherm. Higher lateral compressions were tested, but such trajectories were numerically unstable during further equilibration. On the other hand, more laterally expanded systems were not employed as monolayers were already ruptured at APL $= 1.00$ nm^2. The selected π-APL isotherm points were simulated employing the NVT (canonical) ensemble, i.e., with fixed box size. The NVT ensemble was shown to provide a good agreement between simulated and experimental DPPC isotherms [22]. However, due to relatively slow lateral pressure relaxation, the NVT ensemble may give unphysical increase of pressure in the case of systems with not-enough-equilibrated initial configurations (see the comprehensive discussion in Ref. [32]). Here, well equilibrated bilayers and further equilibrated monolayers were used for initial conditions generation, hence we do not expect any significant ensemble-related artifacts. All systems were simulated at the temperature of 310 K to mimic physiological conditions in lungs. Equilibration was checked by means of both the convergence of lateral pressure and the convergence of the lateral lipid arrangement. In the case of single lipid component monolayers, simulations were performed for 100 ns at each lateral compression with the trailing 50 ns used for analysis. In the case of mixed DPPC/POPC systems, 200 ns-long trajectories were simulated with the trailing 100 ns used for analysis. In each case, we observed no significant drift of lateral pressure and no significant changes of lateral radial distribution functions after equilibration. Note that equilibration times reported in previous MD studies of DPPC and

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