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Mixed monolayers involving DPPC, DODAB and oleic acid and their interaction with nicotinic acid at the air–water interface

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Abstract

The behaviour of binary mixtures involving dipalmitoylphosphatidylcholine (DPPC), dioctadecyldimethylammonium bromide (DODAB) and oleic acid (OA) was investigated at the air–water interface by surface pressure–area (π–A) measurements and by Brewster angle microscopy (BAM). Thermodynamic analysis indicates for the system DPPC/DODAB miscibility with strong negative deviations from the ideal behaviour, from low to high surface pressures over all the composition range. For systems DODAB/OA and DPPC/OA, thermodynamic analysis and BAM observation indicate miscibility from low to intermediate surface pressures, and phase separation in a limited range of composition at high surface pressures. The interaction of nicotinic acid (NA) with pure lipids and with selected compositions of mixed systems was investigated. Significant positive deviations of π–A isotherms in the presence of NA indicate attractive interactions between NA and the polar groups of DPPC and DODAB. NA easily penetrates in expanded regimes while it tends to be segregated from condensed regimes in mixed monolayers.

Keywords: Mixed monolayers; Model systems; BAM observation; Drug/lipid interaction; Nicotinic acid in lipid monolayers

1. Introduction

Monolayers and mixing behaviour of components of biomembranes have attracted considerable interest over the years for both fundamental research and applications. The encapsulation of biologically active molecules in the membrane-like drug carrier systems (liposomes) is one among many applications evidencing the huge importance of this subject. Properties and functioning of membranes are closely related to the lipid composition and microstructure (Jørgensen et al., 2001). Examples include the stability of liposomes, the trans-membrane permeability and fluidity, as well as the interaction of biomolecules and drugs with lipid membranes. Phospholipids, fatty acids and sterols are the structural components of biological membranes. Monolayers of phospholipids on aqueous subphase and liposomes in aqueous dispersion are often used as model systems to study the structure and properties of native biological membranes and to investigate

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biological processes (Brezesinski and Möhwald, 2003). The Langmuir monolayer, as half of a lipid bilayer, is the very convenient first step to approach the two-dimensional structure of biomembranes. Biomembranes also contain lipids that carry an electrical excess charge. Such lipids are crucial for the binding of proteins to membrane as well as for its morphology and integrity. On the other hand, the inclusion of charged lipids strongly contributes to the stability of liposomes and to the incorporation of drugs or biomolecules in ionic bilayers (Campbell et al., 2001b).

This paper focuses on the study of mixtures involving dipalmitoylphosphatidylcholine (DPPC), dioctadecyldimethylammonium bromide (DODAB) and oleic acid (OA), and their interaction with niacin or nicotinic acid (NA), a water-soluble B vitamin. NA is an anticholesterol and vasodilatory drug that lowers the "bad" LDL-cholesterol and triglycerides levels, while raising the "good" HDL-cholesterol level, when administered in doses well above the vitamin requirement (Bhattacharyya et al., 1988). The effect of NA on the fluidity profile of a liposomal system was studied (Bhattacharyya and Nandy, 1989); NA creates a more fluid environment. To our best knowledge the interaction of NA with model membranes at the air–water interface has not been reported. On the other hand, due to some adverse effects of niacin it is recommended in specific cases the time-released administration. Therefore, the encapsulation of NA in liposomes for drug delivery is a matter of current interest.

DPPC is an important constituent of cell membranes, it is the major component in lung surfactants, and often used as the main phospholipid to prepare liposomes to a wide range of applications due to its neutral charge and inertness. This explains the enormous interest and the high number of studies reporting on this phospholipid and their mixtures with a large range of other components. Some examples are the relevant studies on the molecular interactions of DPPC with cholesterol (Albrecht et al., 1981; Kim et al., 2001), fatty acids (Bringezu et al., 2001; Cockshutt et al., 1991), proteins (Bringezu et al., 2002; Chang et al., 2000) and in multicomponents mixed monolayers (Miñones et al., 2002; Ding et al., 2003).

DODAB is a dialkyl cationic lipid with two saturated alkyl chains bonded to the hydrophilic group, resembling the typical membrane-forming phospholipids. DODAB forms stable monolayers at the air–water interface (Gonçalves da Silva et al., 2004) and also forms bilayer structures or liposomes when dispersed in aqueous solution (Scarpa et al., 2002). The incorporation of additional charged materials in liposomes can provide electrostatic repulsive forces between the suspended liposomes, preventing fusion or aggregation. In particular, the inclusion of cationic lipids improves the stability of liposomes containing paclitaxel (taxol) compared with those negatively charged or neutral (Campbell et al., 2001a; Bordi et al., 2003). Several studies involving the mixture DODAB/DPPC in aqueous suspension or on solid supports have been performed (Linseisen et al., 1996; Rapuano and Carmona ribeiro, 2000) but none reported the thermodynamic characteristics of DPPC/DODAB mixed monolayers in order to provide information on the molecular interactions between DPPC and DODAB molecules.

Oleic acid, a *cis*-monounsaturated fatty acid, is also a natural component with relevant effects on membrane properties (Roach et al., 2004). The presence of fatty acids in lipid membranes modulates their fluidity and permeability and a high intake of OA has been consistently associated with a reduced risk of developing cardiovascular and tumoral pathologies (Funari et al., 2003).

The purpose of this study is the characterization at the air–water interface of mixed lipid systems relevant as model systems and potential drug delivery systems. Miscibility of binary mixtures involving DPPC, DODAB and OA are investigated by π–A measurements and Brewster angle microscopy (BAM) observation at the air–water interface. Selected compositions of mixed monolayers are studied in the presence of niacin in order to evaluate the interaction of NA molecules with lipid monolayers.

2. Experimental

2.1. Materials

Dioctadecyldimethylammonium bromide was obtained from Fluka with purity higher than 98%. 1,2-Dipalmitoyl-rac-glycero-3-phosphatidylcholine was supplied by Sigma with purity higher than 99%. *cis*-9-Octadecenoic acid (oleic acid) (>99%) and nicotinic acid (>98%) were purchased from Aldrich. The solvent chloroform was of spectroscopic grade