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Oil and drug control the release rate from lyotropic liquid crystals

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ABSTRACT

The control of the diffusion coefficient by the dimensionality *d* of the structure appears as a most promising lever to efficiently tune the release rate from lyotropic liquid crystalline (LLC) phases and dispersed particles towards sustained, controlled and targeted release. By using phosphatidylcholine (PC)- and monolinoleine (MLO)-based mesophases with various apolar structural modifiers and water-soluble drugs, we present a comprehensive study of the dimensional structural control of hydrophilic drug release, including 3-*d* bicontinuous cubic, 2-*d* lamellar, 1-*d* hexagonal and 0-*d* micellar cubic phases in excess water. We investigate how the surfactant, the oil properties and the drug hydrophilicity mitigate or even cancel the effect of structure variation on the drug release rate. Unexpectedly, the observed behavior cannot be fully explained by the thermodynamic partition of the drug into the lipid matrix, which points out to previously overlooked kinetic effects. We therefore interpret our results by discussing the mechanism of structural control of the diffusion rate in terms of drug permeation through the lipid membrane, which includes exchange kinetics. A wide range of implications follow regarding formulation and future developments, both for dispersed LLC delivery systems and topical applications in bulk phase.

1. Introduction

Lyotropic liquid crystalline (LLC) particles, so-called cubosomes and hexosomes, are submicron-sized dispersions of self-assembled reverse mesophases, in which the inner structure is at thermodynamic equilibrium with the excess of water, while the high external surface area is stabilized by a secondary emulsifier [1]. Since their discovery in the 1980s, these particles offer promising prospects for drug or nutrient delivery system applications, including hydrophilic, hydrophobic or amphiphilic drugs [2–4]. However, only few of such products have been so far commercialized. Concerning hydrophilic drugs, the tuning of the inner structure of the particles appears critical for achieving both sustained and controlled release of the drug. Order-of-magnitude differences in release rates have been reported when varying the structure of loaded mesophases [5].

One of the primary functionalities of a drug delivery system is generally to optimize the therapeutic window of the drug formulation by substantially increasing the time period over which the drug is set free in solution at a suitable concentration, in other words to enable a sustained release of the drug. The main obstacle to application of LLC delivery systems for hydrophilic drugs currently remains the burst release often observed from sub-micrometer particles [6,7]. This issue has been addressed mainly by privileging more hydrophobic drugs [6,8] or large molecules such as proteins [9,10] in the choice of the load, or by designing ionic interactions or covalent bonds between the drug and the mesophase matrix [6,11]. There are still needs to optimize the release of active molecules from LLC mesophases to be able to design delivery systems adapted to given applications, including also sustained release from dispersed LLC particles.

Order-to-order phase transitions in the mesophase structure have been so far the most commonly explored strategies to achieve controlled release of hydrophilic drug [2,12–14], along with variation of the drug affinity [8,15,16] and water domain size [17]. Stimuli-triggered phase transitions therefore open the way to environment-triggered targeted drug release, due to their potentially large dynamic range of release rates [2,14]. However, no systematic study of the influence of the formulation parameters on the dynamic range of release rates attainable by phase changes has yet been carried out.

The release of a hydrophilic drug from a mesophase matrix has been essentially described as a Fickian diffusion phenomenon. The Higuchi equation (Eq. (1)) predominates in release modeling, although more detailed models have been applied [15]. Molecularly speaking, the release of a hydrophilic drug from a mesophase is a dynamic phenomenon, in which the drug molecules diffuse through the water domains, partition into the lipid domains and eventually cross them. The lipid–water partition coefficient of the drug has been recognized since the initial release studies as an important parameter contributing to the effective release rate observed for a given drug, since the most hydrophilic

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drugs were observed to be released faster from bicontinuous cubic phases [6,16,18]. The structural control of the release rates results from the resistance of the lipid domains against drug transfer, i.e. how efficiently the lipid walls confine the drug into the water domains. The diffusion behavior then strongly depends on the dimensionality of the water domains [2].

Here, the dimensionality d of a mesophase structure is defined as the number of dimensions, i.e. independent directions that can be explored in space without leaving the water domain (within a single crystalline grain). In a hexagonal phase, the drug molecules can only move along the cylindrical water channels, therefore $d = 1$. In a lamellar phase, they can move along the planar bilayers ($d = 2$). In bicontinuous cubic phases, the diffusion is regarded as a pseudo-3-d process [5], although it is possible to increase the connectivity in the structure and thereby the diffusion rate by inserting pores in the membrane [19]. In a micellar cubic mesophase, the drug is essentially confined in the micelles ($d = 0$).

In this study, we thoroughly investigate the efficiency of the control of the release rate by the structure for different drugs in various LLC surfactant–oil systems. The model drugs were selected for their different hydrophilicities: caffeine, a wide spread stimulant of the central nervous system [20–22], the antiseptic dye proflavine [15], and glucose, a model analyte used in a number of release studies from LLC systems [5,6,22]. Phosphatidylcholine (PC) and monolinoleine (MLO) were used as LLC surfactants, limonene, cyclohexane and tocopherol as apolar phase modifiers [12,23–29]. In this model study, the release experiments were carried out in bulk phase, which enables a reliable determination of the diffusion coefficients, while excluding effects other than those of the mesophase structure and drug partitioning. Our results are therefore also directly relevant for bulk phase formulations.

This careful and comprehensive release study shows that the structural control of the diffusion coefficient is strongly influenced by the type of oil and drug, in a complex way. In extreme cases, a complete absence of control by the structure was obtained, a result that goes far beyond expectation from previous reports. Modulations of the release behavior are usually accounted for by drug partitioning the lipid regions. The release behavior was therefore confronted to the effective affinity of each drug for each lipid system, determined in case-by-case partitioning experiments. We show that the expected direct correlation between partition and structural control release is not observed. However, the observed effects can be reasonably rationalized by considering the *drug permeability of the lipid bilayer*, a concept that is crucial in drug transport across biological barriers. This more subtle parameter includes not only the thermodynamic partition coefficient but also the diffusion coefficient of the drug in the lipid domain, in other words the kinetics of exchange. The bilayer permeability of the drug appears therefore as the most meaningful descriptor available to predict and interpret the controlled release behavior by phase transitions in complex ternary LLC surfactant/water/oil systems in bulk phase or in dispersion.

2. Materials and methods

2.1. Materials

Soybean phosphatidylcholine (PC) was purchased from Cargill, Germany, under the product name Epikuron 200. Industrial grade monolinoleine (MLO), with product name Dimodan U/J, was a gift from Danisco (Copenhagen, Denmark). Composition details for PC and MLO are given in the Supporting information. (R)-(+)-limonene, hexadecane, caffeine, proflavine (3,6-diaminoacridine hydrochloride), α-tocopherol, glucose oxidase (GO) from *Aspergillus niger*, horseradish peroxidase (HRP), 2,2′-azino-bis(3-ethybenzothiazoline-6-sulphonic acid) (ABTS) and buffer solutions or materials were purchased from Sigma-Aldrich. D-(+)-Glucose and analytical grade ethanol were obtained from Fluka. MilliQ water was used for all sample and solution preparations. Relevant chemical structures are given in Fig. 1.

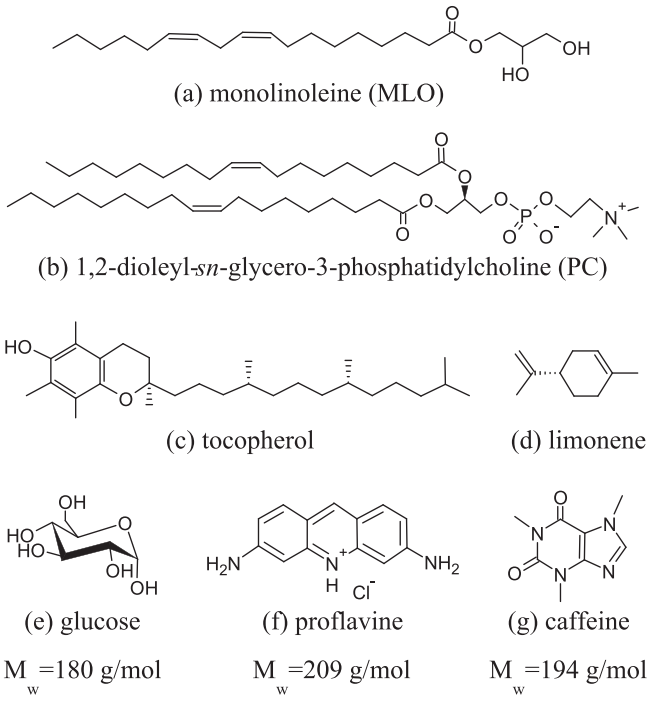

Fig. 1. Chemical structure of LLC surfactants (a, b), oil modifiers (c, d) and drugs (e–g) used in this study.

2.2. Release studies

The following drug solutions were prepared: 0.1 wt.% or 0.2 wt.% glucose in 150 mM sodium acetate buffer at pH 5, 0.1 wt.% or 0.2 wt.% proflavine in 150 mM phosphate saline buffer (PBS) at pH 7.4, and 0.7 wt.% or 1 wt.% caffeine in MilliQ water. Mesophases (0.3 g) were prepared in Pyrex tubes just below the excess water conditions (Table 1) following previous reports [12,23–28]. The drug-loaded mesophases were obtained by using the corresponding drug solution as aqueous phase. For MLO phases, the lipids and aqueous phase were weighted in a tube. The mixture was homogenized by heating, vortexing, cooling and hand-centrifuging several times. A flat surface was obtained at the end of the last cycle and the tubes were stored at 37 °C. For PC–limonene and PC–cyclohexane phases, the lipids were weighted in the tube and the lipid mixture was homogenized by vortexing. After a few hours of equilibration, the aqueous phase was added and the tube was vortexed. For PC–tocopherol phases, the lipids were codissolved in ethanol. The ethanol was completely removed with a rotary evaporator. The

Table 1
Compositions and lattice parameters of the mesophases of dimensionality d prepared for the release studies, just below the excess water limit. For the cyclohexane phases, the conditions are identical to the limonene phases, except the water content of the $Fm\bar{3}m$ phase, which was 25%.

Surfactant	Oil	Phase (d)	α_{oil}	Water content (wt.%)	Lattice param. (nm)
PC	–	Lα (2)	0	35	6.4
PC	Limonene	H_2 (1)	36	28	8.1
PC	Limonene	$Fm\bar{3}m$ (0)	55	35	19.4
PC	Tocopherol	H_2 (1)	35	20	6.3
PC	Tocopherol	$Fd\bar{3}m$ (0)	68	17	14.4
MLO	–	$Pn\bar{3}m$ (3)	0	35	8.4
MLO	Limonene	H_2 (1)	17	15	5.4
MLO	Limonene	$Fd\bar{3}m$ (0)	35	12	15.5
MLO	Tocopherol	H_2 (1)	25	15	4.8
MLO	Tocopherol	$Fd\bar{3}m$ (0)	45	10	14.0