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Influence of the cyclodextrin nature on the decompaction of dimeric cationic surfactant-DNA complexes

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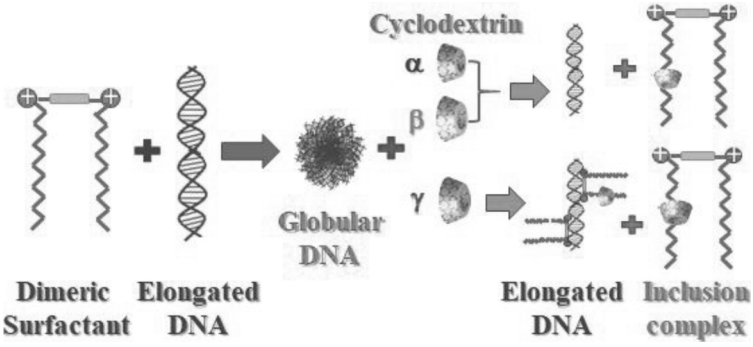
GRAPHICAL ABSTRACT

Cyclodextrin nature affects the decompaction of dimeric cationic surfactant-DNA complexes.



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ABSTRACT

In this work, the influence of the cyclodextrin, CD, nature on the decompaction of positively charged compacted dimeric surfactant-DNA complexes was investigated. First, the condensation of calf thymus DNA by addition of three cationic dimeric surfactants with different spacer groups was studied by fluorescence, zeta potential, circular dichroism and atomic force microscopy measurements. Electromotive force experiments provided quantitative information about the influence of the spacer group on the DNA surfactant compaction efficiency. Cytotoxicity was evaluated to determine the biocompatibility of the cationic lipids. Subsequently, the decompaction of the surfactant-DNA complexes was achieved by adding α-, β-, and γ-cyclodextrin, the experimental observations being analogous for the three surfactants investigated. α- and β-cyclodextrin were found to behave similarly. These CDs completely hinder the interactions between the surfactant and the nucleic acid and provoke the DNA morphological change from a globular to an elongated form. A concentration of γ-CD higher than those of α- or β-CD is necessary in order to decompact the nucleic acid. Besides, zeta potential measurements show that in the presence of γ-CD, surfactant-DNA interactions are only partially hindered, some of the surfactant molecules remaining bound to the DNA.

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1. Introduction

Gene therapy is the therapeutic delivery of genetic material for the treatment of a disease that enables the patient's cells to produce the lacking proteins [1,2]. Usually the genetic material is combined with a delivery vehicle, or vector, which helps the nucleic acids to go into the cells achieving the therapeutic effect. Vectors make possible that the nucleic acid crossed barriers such as cell and nucleus membranes [3–5] since the anionic character of DNA limits its permeation across negatively charged cell membranes, and the steric restriction inside the cell prevents its transportation to the nucleus [6]. The use of vectors avoids these problems by condensing the nucleic acids into a neutral o positively charged complex with a compact globular conformation of reduced size [7]. Nonetheless, if DNA compaction is necessary for protecting the nucleic acid from degradation by nucleases as well as to facilitate cell uptake, once the nucleic acids have reached the cell nucleus, decompaction is indispensable for the release of the genetic material inside the cells. This allows the recovering of its properties and permits to proceed to the following transcription [8]. For this reason the interest of many researchers have been attracted by the decompaction process of DNA. Different reagents, such as non-ionic, anionic and zwitterionic surfactants, β-cyclodextrin, or electrolytes, among others [9–13], have been investigated as decompacting agents.

A large variety of reagents has been used as non-viral vectors: cationic lipids, surfactants, polymers, etc. [3,14–21]. Among them, cationic surfactants have been shown to be efficient DNA compacting agents [16,15–21]. In particular, the use of dimeric cationic surfactants is of special interest not only for the unique relation they show between the surfactant structure and its activity [22,23], but also because several dimeric surfactants have been found to be efficient non-viral vectors [17,15–21,24].

Cyclodextrins, CDs, are cyclic oligosaccharides formed by six to eight (α-, β-, and γ-CD) α(1-4) ether linkages of glucopyranoside units [25]. Their shape is like a truncated cone and the internal cavity has a relatively hydrophobic character. This favors the formation of host-guest inclusion complexes with hydrophobic species of adequate size. The hydrophobic tails of surfactants have a strong tendency to intercalate into the hydrophobic CDs cavity forming highly stable inclusion complexes [26–33]. Therefore, CDs are able to strip the bound surfactant molecules from the surfactant-DNA complexes, this resulting in the DNA decompaction process.

Most of the investigations about decompaction of cationic surfactant-DNA complexes have involved single-chain cationic surfactants and only few of them studied the influence of the CD nature on the process [12,26,34–36]. To the authors' knowledge the influence of the CD nature on the decompaction of cationic dimeric surfactant-DNA complexes has not been investigated yet. For this reason, in the present work the compaction of calf thymus DNA caused by the addition of the dimeric surfactants 1,3-bis-(*N,N*'-dimethyl-*N*-docecylammonium) isobutylene dichloride, 12-ib-12,2Cl$^-$, 1,3-bis-(*N,N*'-dimethyl-*N*-docecylammonium) 2-butylene dichloride, 12-bt-12,2Cl$^-$, and 1,2-bis-(dodecyldimethylammonium) dichloride, 12-2-12,2Cl$^-$ (see Scheme 1) was investigated. Subsequently, the decompaction of the dimeric surfactant-DNA complexes by α-, β-, and γ-cyclodextrin has been studied by using several techniques. The spacer group of the dimeric surfactants was varied with the goal of examining its influence on the compaction and decompaction process. The results in this work will provide valuable information regarding how to choose the most appropriate CD in order to optimize the surfactant-CD complexes decompaction.

2. Experimental methods

2.1. Materials

Most of materials were purchased from Sigma-Aldrich and Fluka, of the highest purity available, and used without further purification. α-, β-, and γ-cyclodextrin (> 99% purity) were kept under vacuum.

The dimeric surfactants 1,3-bis-(*N,N*'-dimethyl-*N*-docecylammonium) isobutylene dichloride, 12-ib-12,2Cl$^-$, and 1,3-bis-(*N,N*'-dimethyl-*N*-docecylammonium) 2-butylene dichloride, 12-bt-12,2Cl$^-$, were synthesized and kindly provided by Prof. Laschewsky [37]. The 1,2-bis-(dodecyldimethylammonium) dichloride, 12-2-12,2Cl$^-$, was synthesized from an ion-exchange of the corresponding dibromide [38], which was prepared following the method in the literature [39]. 12-2-12,2Cl$^-$ was characterized by ^{1}H NMR, ^{13}CNMR, and elemental analysis, with the results being in agreement with those previously reported.

The calf thymus DNA concentration (given by phosphate groups) was estimated spectrophotometrically at 260 nm (molar absorptivity of 6600 M^{-1} cm^{-1}) [40]. An agarose gel electrophoresis test, using ethidium bromide, EB, yielded an average number of base pairs per polynucleotide molecule of 10,000 bp [41]. The ratio $Absorbance_{260nm}$/$Absorbance_{280nm}$ of the DNA solutions varied between 1.7 and 1.8, suggesting the absence of proteins [42].

All solutions were prepared in HEPES 40 mM, at pH 7.4. Deionized distilled water Super Q Millipore (resistivity > 18 MΩ cm) was used.

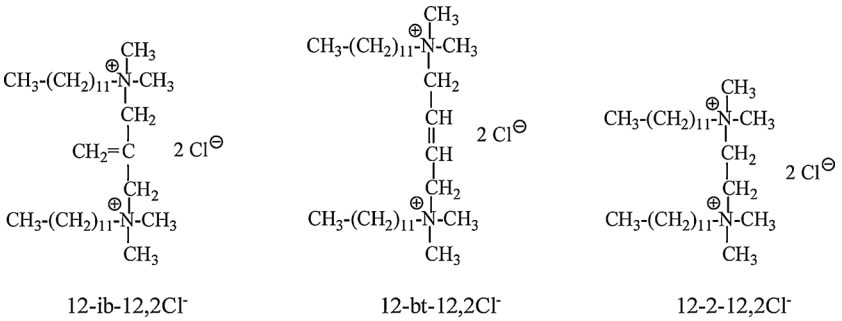
2.2. UV–vis absorption spectroscopy

Absorbance was measured using a CARY 1E UV–vis spectrophotometer (Varian), connected to a water flow Lauda cryostat. A standard quartz cell of 1 cm path length was used. Temperature was maintained at 298.0 ± 0.1 K.

The stability of the surfactant-DNA solutions was investigated keeping a fixed DNA concentration ([DNA] = 3×10^{-5} M) and varying the surfactant concentration.

2.3. Conductivity measurements

Conductivity was measured with a Crison GLP31 conductimeter as described in Ref. [43].



Scheme 1. Structure of the surfactants used in this work.