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REVIEW

Self-assemblies of amphiphilic cyclodextrins

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Abstract Cyclodextrins are natural cyclic oligosaccharides widely used as "molecular cages" in the pharmaceutical, agrochemical, food and cosmetical industries. The optimization of their pharmacological properties has led to the synthesis of numerous analogues. Amphiphilic derivatives were designed to improve the cell targeting of the drug-containing cyclodextrin cavities through their transportation in the organism, within self-assembling systems. Amphiphilic cyclodextrins can self-assemble into water-soluble aggregates such as mono or polydisperse micelles, or insert in lipid membranes and liposomes. Polysubstituted amphiphilic cyclodextrins are briefly reviewed, and monosubstituted derivatives of native and methylated β-cyclodextrins are presented in more details, with an emphasis on their self-organization within lipid membranes.

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Introduction

Cyclodextrins are natural cyclic oligosaccharides obtained by enzymatic digestion of starch. The α-, β- and γ-derivatives contain respectively 6, 7 and 8 D-Glucose units, with primary and secondary hydroxyl groups located on the narrower and wider rims of an asymmetric torus-shaped structure (truncated cone) (Fig. 1). Such structure is that of an hydrophilic molecular cage with an hydrophobic interior allowing the inclusion of hydrophobic molecules. Many cyclodextrin applications have been described in literature. The most important is the solubilization of hydrophobic drugs in water. But cyclodextrins can also protect guest molecules from chemical degradation. Cyclodextrin applications are very abundant, in pharmaceutical, agrochemical and food industries as well as in cosmetics. They are used also in wrapping materials and textiles (Dodziuk 2006). A large variety of chemically modified cyclodextrin analogues have been synthetized to enhance their properties and more specifically their pharmacological potency (Uekama 2004; Challa et al. 2005). Among these, amphiphilic derivatives (Fig. 2) were designed to build organized molecular structures, through self-assembling systems or by incorporation in lipid membranes, expected to improve the vectorization in the organism of the drug-containing cyclodextrin cavities. These derivatives can form a variety of supramolecular structures such as micelles, vesicles and nanoparticles. Two classes of substituted cyclodextrins can be considered: amphiphilic cyclodextrins bearing multiple hydrophobic chains, extensively investigated, and amphiphilic cyclodextrins obtained by grafting a single hydrophobic anchor.

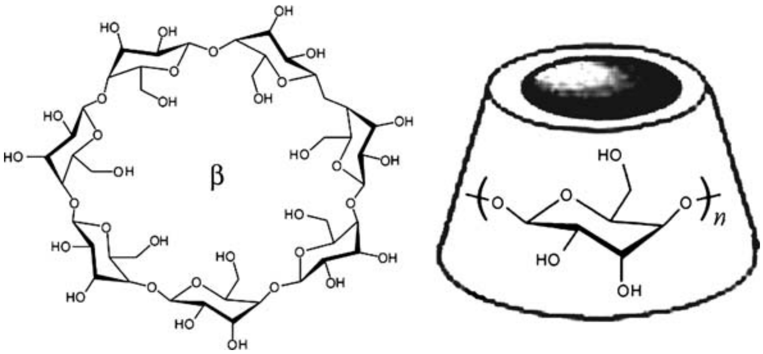

Fig. 1 Cyclodextrins: the α, β and γ derivatives contain respectively n = 6, 7 and 8 glucose residues

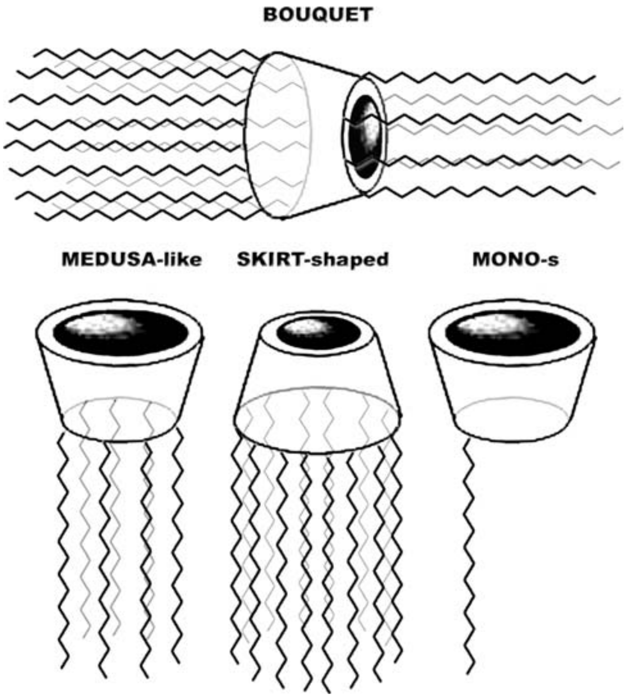

Fig. 2 Schematic structures of amphiphilic cyclodextrins

Polysubstituted amphiphilic cyclodextrins

The polysubstituted amphiphilic cyclodextrins (Fig. 2) are obtained by persubstitution of the cyclodextrin primary and/or secondary hydroxyl groups.

Medusa-like

Persubstitution of the primary side with amino-, amido-, sulfo- or thio-alkyl chains, lead to "medusa-like" compounds which are able to form stable Langmuir–Blodgett (LB) layers (Kobayashi et al. 1999; Nakahara et al. 1996; Memisoglu et al. 2003a, b; Matsuzawa et al. 2006) and even give rise to thermotropic liquid crystals with the full persubstituted thio derivatives (Ling et al. 1993). Cyclodextrin inclusion of naphtalene derivatives were found to occur with LB Films of an amino medusa-like derivatives (Nakahara et al. 1996). *β*-cyclodextrin amido derivatives self-assembling into nanospheres by nanoprecipitation techniques were shown to incorporate antimycotics (Memisoglu et al. 2003a) and progesterone (Memisoglu et al. 2003b). More recently, novel medusa-like amphiphilic cyclodextrins self-assembling into nanospheres were obtained by persubstitution on the primary side with ester of thio-perfluoroalkyl chains (Peroche et al. 2005; Lim et al. 2006).

Skirt-shaped

Cyclodextrin derivatives obtained by attaching alkyl chains via an ester link, to the secondary alcool groups on the other side leading to "skirt-shaped" derivatives. They were also found to self-organize into cyclodextrin nanospheres (Choisnard et al. 2005) allowing the encapsulation of drugs such as metronidazole an antimicrobial agent (Lahiani-Skiba et al. 2006) or tamoxifen used in breast cancer treatment (Memisoglu-Bilensoy et al. 2005). More recently, a preparation of nanoparticles has been described using an enzymatically prepared mixture of poly-esterified skirt-shaped *β*-cyclodextrins (Choisnard et al. 2006). A *β*-cyclodextrin heptakis (hexanoyl derivative) was incorporated in lipid membranes to give stable mono- and multilayers with dimyristoyl phosphatidylcholine (DMPC) (Lesieur et al. 2000). The negatively charged analogue obtained by sulfation of the cyclodextrin primary hydroxyl group was shown to insert in cholesterol-containing DPPC liposomes (Sukegawa et al. 2002).

Bouquet-like

Bouquet-like derivatives contain hydrocarbon chains on both sides of the cyclodextrin cavity, increasing their hydrophobicity. The derivatives obtained by grafting one poly(oxyethylene) or polymethylene as well as *O*-alkyl chain, on each side of the cyclodextrin cavity, were designed to mimick transmembrane ion channels after insertion in lipid membranes (Pregel et al. 1992, 1995). A new very promising cyclodextrin family bearing hydrophobic alkyl chains on one side and hydrophilic chain on the other side, designed to enhance their amphiphilicity, led to self-assembling derivatives able to form bilayer vesicles. These vesicles consist of bilayers of cyclodextrins, in which the hydrophobic "tails" are directed inward and the hydrophilic macrocycle "head groups" are facing water, thereby enclosing an aqueous interior. The presence of hydrophilic oligomers at the surface of the vesicles increases their colloidal stability while potentially decreasing their adverse immune response in drug delivery systems, much like "stealth liposomes" (Lasic and Needham 1995). Neutral vesicles obtained with poly(ethylene glycol) (Mazzaglia et al. 2002; Ravoo and Darcy 2000) were shown to bind small guest molecules such as adamantane (Falvey et al. 2005) and even polymers (Ravoo et al. 2003; Crespo-Biel et al. 2005) by their inclusion in the cyclodextrin cavities. Insertion of a labile disulfide bond between the hydrophobic chain and the cyclodextrin secondary side, lead to vesicles or nanoparticles which could be disrupted upon disulfide cleavage following cellular uptake (Nolan et al. 2003). Charged vesicles were also described by grafting a cationic ω-amino poly(ethylene glycol) to the cyclodextrin primary hydroxyl group (Donohue et al. 2002). Positively charged nanoparticles obtained from the same derivative were shown to encapsulate an anionic porphyrin which could be used in photodynamic cancer therapy (Sortino et al. 2006).

Monosubstituted amphiphilic cyclodextrins

The monosubtituted amphiphilic cyclodextrins (Fig. 3) are obtained by appending a single hydrophobic anchor, with the aim of improving the cell targeting of the drug-containing cyclodextrin cavities through their liposome transportation, after insertion in the lipid bilayer. Monosubstitution on the primary side was chosen to leave the secondary wider face unhindered, accessible to guest molecules known to generally enter the cavity from this side.

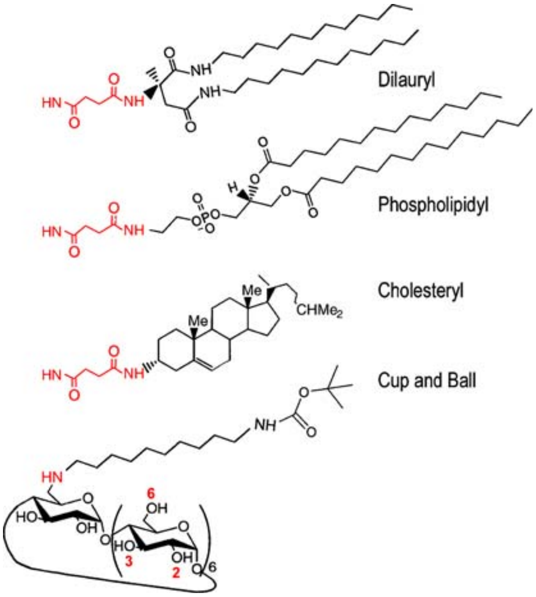

Fig. 3 Monosubstituted amphiphilic cyclodextrins

From lollipop to cup and ball

The so-called "Lollipop" is obtained by grafting a single alkyl chain on one of the primary hydroxyl group. This compound turned out to be poorly soluble and the alkyl chain tend to loop back and enter the cyclodextrin hydrophobic cavity, leading to intramolecular self-inclusion (Bellanger and Perly 1992). Adding the bulky Boc amino protective group at the end of the alkyl chain gave the "Cup and Ball" derivative much water-soluble, with a weakened self-inclusion effect, allowing the inclusion of ASANa (sodium anthraquinone-2-sulfonate) in the cyclodextrin cavity. Both "Cup and Ball" derivative and its inclusion complex with ASANa could be inserted into phospholipid membranes via the hydrophobic anchor (Lin et al. 1998).

Lipid-like

To favor the amphiphilic cyclodextrin membrane insertion, the hydrophobicity was increased by grafting a lipid-like anchor such as a cholesteryl or phospholipidyl moiety, or an aspartic acid with carboxyl groups esterified by two lauryl acyl chains. Derivatives of both native and methylated β-cyclodextrin were obtained.

Cholesteryl methylated cyclodextrin

The cholesteryl derivative of 2,6-di-*O*-methyl β-cyclodextrin is highly water-soluble and able to self-organize in aqueous solutions, leading to perfectly spherical micelles with an average condensation number of 24 (Fig. 4). It has been demonstrated that the cyclodextrin cavities are exposed towards the aqueous medium (Auzély-Velty et al. 2000). These new nanoparticles, characterized by X-rays, neutron diffusion as well as light scattering, have been shown to retain capacity to include guests in the cyclodextrin cavity (Auzély-Velty et al. 2001). Freestanding film technique has been used to mime the cyclodextrin action on a model membrane target, and stable cyclodextrin/DMPC Black Film has been obtained in ultrapure water (18.2 MΩ) at 27°C using this cholesteryl derivative (Javierre et al. 2002). The central core of this mixed film contains the cyclodextrin cavities facing each other and embedded between two biological membrane-like walls composed of cholesterol and DMPC. Owing to the film structure derived

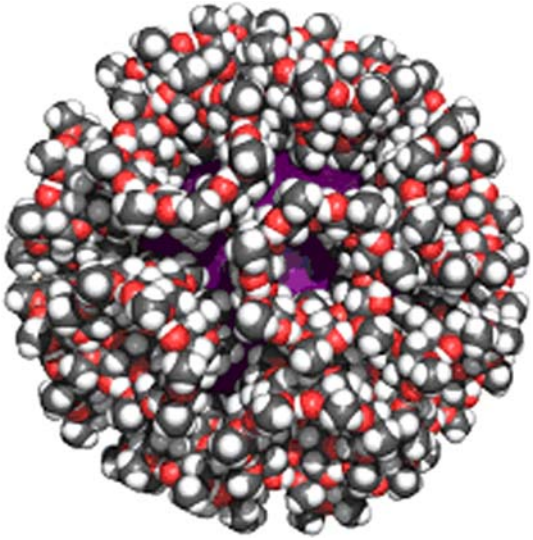

Fig. 4 Representation of cholesteryl 2,6-di-*O*-methyl-*β*-cyclodextrin micelles deduced from their neutrons and X-rays scattering length density profiles

from the electron density profile, it appears that the cyclodextrin insertion process in the DMPC bilayer can be reduced to a DMPC/cholesterol interaction with an arrangement of 3 DMPC tails around the grafted cholesterol, the cyclodextrin cavities remaining available for the inclusion of guests such as dosulepin.

Phospholipidyl methylated cyclodextrin

Phospholipidyl-cyclodextrins prepared by replacing the cholesteryl anchor by a phospholipid (DMPE), were also shown to self-organize in water with low CMC to form fluctuating micellar fibers retaining inclusion capacity of the cyclodextrin cavities (Moutard et al. 2002). They can form alone fairly stable Black Film to give a thick highly hydrated bilayer. The cyclodextrin abundant hydration core play a key-role in the stabilization process and attempt to insert a guest in the cavity results in a breaking down of the structure (Sultanem et al. 2004). These methylated phospholipidyl-cyclodextrins were also tested for dermatological delivery of xenobiotics (Piel et al. 2004).

Both cholesteryl and phospholipidyl derivatives of methylated cyclodextrins have a detergent-effect on lipid membranes leading to a disruption and a solubilization of the bilayers (Moutard et al. 2002; Perly et al. 2005). This does not occur with the lipid-like derivatives obtained with native non-methylated *β*-cyclodextrin, which are insoluble in water, and insert readily in lipid membranes without bilayer disruption. The cholesteryl and dilauryl derivatives (Fig. 3) are actually able to self-assemble within the bilayer, inducing a lateral segregation of a cyclodextrin-rich phase, the L_{CD} phase, which is reviewed in the following section.

Self-association of cyclodextrins at the membrane surface: the L_{CD} phase

The segregated L_{CD} phase was first evidenced by small angle X-rays scattering (SAXS) after insertion of cholesteryl-*β*-cyclodextrin in DMPC membranes (Auzély-Velty et al. 1999). Four Bragg peaks were observed in the DMPC fluid phase, indicating the coexistence of two lamellar phases. Two peaks correspond to the first- and second-order lines of the pure L_α phase of DMPC, while the two others were assigned to another lamellar phase with a larger swelling and a repetition distance increased by 12 Å with respect to that of pure DMPC (62 Å). The lateral segregation of a cyclodextrin-enriched L_{CD} phase was also clearly established later by deuterium NMR experiments with multilamellar membranes of chain-perdeuterated DMPC d54 (Roux et al. 2002). In addition to the pure lipid signal, a second component with reduced order parameters was attributed to the cyclodextrin-enriched L_{CD} phase. Both SAXS and NMR studies indicate that the lipid-to-cyclodextrin ratio in the L_{CD} phase was about 3 for 2.

Fluid at low temperatures

The L_{CD} phase is stable at cholesteryl-*β*-cyclodextrin levels as low as 5%, coexisting with pure lipid regions containing more than 90% of the total lipids. It remains fluid until 15°C while the pure lipids go through the gel state at 19.5°C, the transition temperature of DMPC d54. The L_{CD} phase stays partially fluid down to 5°C, and then displays a broad transition to reach a more ordered state at –5°C. This ordered fluid phase finally displays another transition to a gel-like state around –10°C, correlated with the complete freezing of the bulk water (Roux et al. 2002).

Boundary lipids

The pure lipid and L_{CD} phases are connected via fluid boundary lipids, which are detected on deuterium NMR spectra recorded just below the fluid/gel transition (Roux et al. 2002). The gel and L_{CD} phase boundary can be visualized through a simple graphical representation of the membrane surfaces occupied by each phases, calculated from the relative amounts of the lipids found in the gel, in the L_{CD} phase, and at their boundary (Fig. 5). In the absence of cholesteryl-*β*-cyclodextrin, all the lipids are in the gel phase at 19°C (dark-filled circle). The incorporation of the cholesteryl cyclodextrin derivative induces the segregation of the L_{CD} phase (white area) separated from the

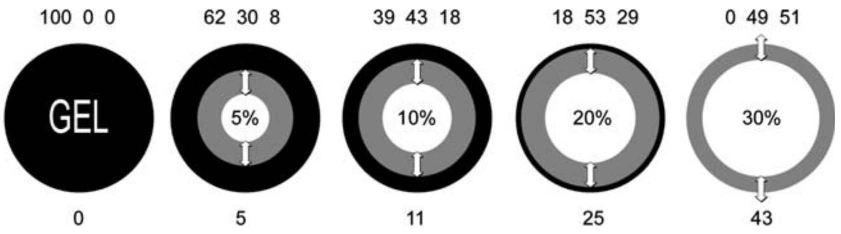

Fig. 5 *Top numbers*: lipid distribution (% of the total lipid) in the gel, fluid and L_{CD} phases calculated from the data obtained with cholesteryl-β-cyclodextrin molar concentrations of 0, 5, 10, 20 and 30%, (Table I from Roux et al. 2002.). *Bottom numbers*: unit of cholesteryl-β-cyclodextrin for 100 lipids at these concentrations. The relative membrane surfaces occupied by each phase, sketched by the *dark*-, *grey*- and *white-filled circles*, were estimated from (1) the lipid distribution, and (2) the relative average areas S occupied at the membrane surface by a lipid molecule (fluid or in the gel state) and a cholesteryl anchor (approximated by $S_{lfluid} = S_{lgel} = 2\ S_{chol}$; *see* Edholm and Nagle 2005). At 19°C in absence of cholesteryl-β-cyclodextrin all the lipids are in the gel state (*dark*). The incorporation of cholesteryl-β-cyclodextrin induce a lipid lateral segregation and formation of the L_{CD} phase (*white*). Boundary lipids (*grey*) between the gel and L_{CD} phases are in the fluid state

gel phase by the boundary lipids (grey area). When the cholesteryl-β-cyclodextrin concentration is increased, the amount of L_{CD} lipids increase at the expense of those in the gel state, while the width of the boundary region appears to remain constant, and starts to decrease at high cholesteryl-β-cyclodextrin level, when there is no more gel phase, i.e., no more boundary.

Composition depends of the hydrophobic anchor

The composition, that is the amount on lipids trapped in the L_{CD} phase, depends critically of the nature of the cyclodextrin hydrophobic anchor. The bilayer-insertion of dilauryl-β-cyclodextrin (Fig. 3), lead to a segregated L_{CD} phase containing three times more lipids (4–5 lipids per cyclodextrin) because the DMPC myristoyl acyl chains adjust more closely with the flexible lauryl chains than with the bulky and rigid sterol nucleus of the cholesteryl derivative (Roux et al. 2007). At a concentration approximately equal to the stoechiometry found for the L_{CD} phase (~20%), dilauryl-β-cyclodextrins are actually able to sequestrate all the lipid molecules, leaving a single, well-defined and stable mixed lipid/dilauryl-β-cyclodextrin phase, with only traces of free lipids. The L_{CD} phase remains fluid below the DMPC main transition, coexisting with pure lipid in the gel state, and displays a sharp transition to a gel state with frozen acyl chains at 12.5°C. With the cholesteryl derivative, the L_{CD} phase remained partially fluid at lower temperatures, likely due to the well-known cholesterol "fluidifying" effect of lipids in the gel phase (Vist et al. 1990).

Stabilized by cyclodextrin headgroup interactions

The cohesion of the L_{CD} phase appears to be governed through finely tuned intermolecular interactions of the cyclodextrin headgroups at the membrane surface. Monomers of β-cyclodextrin can form aggregates in solution through hydrogen bonds between the free hydroxyl groups of their glucose units (Coleman et al. 1992; Bonnet et al. 2002). It is very likely that the same driving forces control the formation of a membrane-bound cyclodextrin network at the membrane surface, sequestrating lipids in the L_{CD} phase. To achieve this, the membrane-bound cyclodextrin headgroups require a sufficient molecular space to adjust and interact with each other at the membrane surface, as they do freely in solution. Restraining the cyclodextrin molecular space by removing the flexible succinyl spacer inserted between the cholesterol anchor and the cyclodextrin headgroup, prevents the L_{CD} phase lateral segregation (Roux et al. 2002). Likewise, the substitution of the cyclodextrin β derivative, by the larger γ derivative inhibits the formation of the L_{CD} phase (Roux et al., unpublished results). The methylated form of the dilauryl-β-cyclodextrin can be inserted in DMPC membranes without detergent-effect and bilayer disruption as observed with the cholesteryl and phospholipidyl derivatives (see above). Indeed, the methylation of the cyclodextrin hydroxyl groups, which prevents the hydrogen bond-mediated cyclodextrin aggregation, also inhibits the formation of the L_{CD} phase (Roux et al. 2007).

Conclusion

Amphiphilic cyclodextrins can form a variety of supramolecular assemblies, such as micelles, vesicles, and nanoparticles. The obtained type of structure depends on the nature and length of the grafted chains, and also on the state of the cyclodextrin headgroups, i.e., the absence or presence of a spacer and the eventual methylation of the hydroxyl groups. In many cases, the cyclodextrin cavities retain their full capacity to include external guest, raising hope for a possible application in drug delivery.

The self-assembly of amphiphilic cyclodextrins within a lipid bilayer, provide an interesting case of microdomain formation through cyclodextrin intermolecular interactions at the membrane surface. Macroscopic techniques like fluorescence microscopy should allow a direct observation of the cyclodextrin-induced L_{CD} phase, and provide additional structural informations such as the dimensions of the segregated microdomains. What happens to the inclusion properties of the cyclodextrins segregated in the L_{CD} phase, and its pharmacological relevance regarding the potency of a drug trapped in the cavities, are questions that should also be addressed in future studies. Considerable interest has raised from the cyclodextrin ability to form mechanically-interlocked molecular structures of the rotaxane family (Wenz et al. 2006) allowing to develop functional molecular machines (Harada 2001; Qu et al. 2005). The need of interfacing these supramolecular assemblies with the "macroscopic world", such as metallic surfaces, porous materials or membranes has been recently pointed out (Clemente-Leon et al. 2006). The cyclodextrin insertion and self-organization at the surface of phospholipid membranes might turn out to be a case worth to investigate.

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