Cyclodextrin nanoassemblies: a promising tool for drug delivery

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Among the biodegradable and nontoxic compounds that can form nanoparticles for drug delivery, amphiphilic cyclodextrins are very promising. Apart from ionic cyclodextrins, which have been extensively studied and reviewed because of their application in gene delivery, our purpose is to provide a clear description of the supramolecular assemblies of nonionic amphiphilic cyclodextrins, which can form nanoassemblies for controlled drug release. Moreover, we focus on the relationship between their structure and physicochemical characteristics, which is crucial for self assembly and drug delivery. We also highlight the importance of the nanoparticle technology preparation for the stability and application of this nanodevice.

Introduction

Biological membranes prevent many drugs from reaching their target, thus decreasing their therapeutic effectiveness and potentially leading to side-effects. Nanomedicine focuses on the application of nanotechnological concepts to improve diagnostics and therapies. An appealing approach in this field is the vectorization of drugs by nanometer-scale objects, called nanovectors [1]. Nanovectors can encapsulate drugs to protect them and improve their bioavailability. Furthermore, it has been demonstrated that nanovectors with an average diameter of 250 nm are compatible with parenteral administration [2], whereas supramolecular assemblies are promising in the treatment of brain diseases [3].

According to Le Droumaguet *et al.* [4], nanocarriers for drug delivery purposes should ideally be (i) biocompatible and biodegradable to allow safe administration, (ii) able to avoid the immune response, (iii) localized by, for example, a fluorescent probe, (iv) decorated by ligands to target cells or tissues.

The nanovectors (Box 1) currently used can be classified into three types in terms of their way of penetrating cells [1]. The first type is composed of capsules containing drugs, which can penetrate by passive transport. Numerous applications have been described for cancer treatments using the enhanced permeability and retention (EPR) effect [5–7]. The second type of nanovector, such as antibody-functionalized liposomes, is able to target tissues [1]. The third type is a complex device, which is programmed to interact with targeted cells of the vascular endothelium. Nanoparticles (NPs) encapsulated inside the device are then delivered to infected cells [8].

The structure and biophysical properties of nanovectors are of great importance for their cell-penetrating capacity. In fact, it has been shown that size, charge, surface hydrophilicity and the nature and density of the ligands on their surface impact the circulating half-life and biodistribution of NPs [9]. Long NPs interact better with endothelial cells than spherical ones do, probably because of their larger contact area [10]. Furthermore, NPs less than 500 nm in diameter are internalized efficiently by endocytosis, either caveolae-mediated for smaller NPs or clathrin-mediated for bigger ones. These two processes require only a modest local rearrangement of the cell cytoskeleton whereas large particles are internalized through a phagocytic process with an extensive rearrangement of the cell cytoskeleton [11,12].

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BOX 1

Nanoobjects

A few supramolecular devices are already known. Among them, vesicles are composed of an amphiphilic compound bilayer with an aqueous compartment. Nanospheres (Fig. 1) are matrices in which the drug is dispersed. They can be constituted of natural polymers, such as albumin, or synthetic biodegradable ones [12]. Finally, nanocapsules [61] (Fig. 1) are formed by a membrane surrounding either an oily or an aqueous core. This membrane can be polymeric or a nanoassembly of amphiphilic compounds.

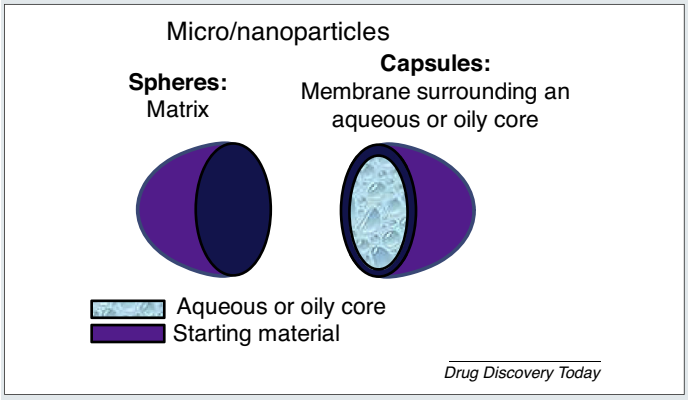

FIGURE 1

Schemes of spheres and capsules.

BOX 2

Cyclodextrins

Cyclodextrins are cyclic oligosaccharides composed of glucose units connected by α(1-4) glycosidic linkages to form a toroidal structure. This family of natural compounds is obtained from starch by *Bacillus macerans* hydrolysis. Three of them, α-, β-, γ-, are widespread and composed of 6, 7 and 8 glucoses, respectively. They are very useful for many industrial applications in chemistry, in pharmaceutical science and in the food, cosmetic and textile sectors. These compounds are considered safe and eco-compatible (Fig. 2).

Many reviews [54–57], a special issue of *Chem. Rev.* [58] and books [59,60] have been published on the properties and applications of these very interesting molecules. Readers can find therein information about chemical modifications, complexes and characterization.

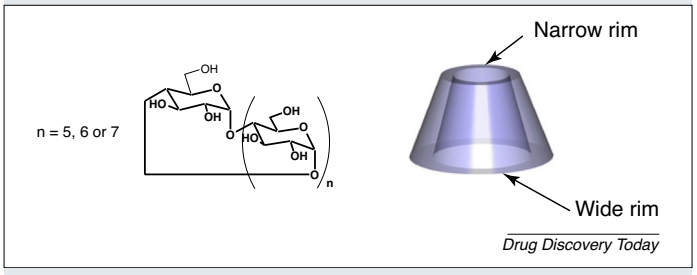

FIGURE 2

Structure of cyclodextrins and their three-dimensional toroidal shape.

Native cyclodextrins (CDs) are already used for drug delivery because of their hydrophobic cavity (Box 2). In fact, they are used extensively in pharmaceutical formulations to encapsulate drugs to protect them or to enhance solubility [13]. CDs are cyclic oligosaccharides composed of 6 (α-), 7 (β-) or 8 (γ-) glucose units linked by α-1,4 glycosidic bonds. They have the shape of a truncated cone with a hydrophobic cavity that can encapsulate a hydrophobic drug. Chemical modification of the native CDs can render them amphiphilic, which has been used to impart self-assembling properties [14]. After self-assembly, three domains of CD NPs could be used to encapsulate drugs: the aqueous core, the lipophilic rim or the surface by interaction with the cavity of CDs. Thus, hydrophobic and hydrophilic drugs could be vectorized by these devices.

Many interesting reviews have been published on cationic amphiphilic CDs for gene delivery, for example [15–17], whereas only a few anionic amphiphilic CDs have been studied for their self-assembly properties [18,19]. In this overview, our purpose is to provide a state-of-the-art of the supramolecular assemblies of nonionic amphiphilic CDs and their physicochemical characteristics, which are crucial for drug delivery (Table 1). Indeed, an analysis of their structure–activity relationships as well as the parameters influencing the preparation of NPs is very useful to understand the potential of these biodegradable, sustainable and nontoxic oligosaccharides.

Driving forces for CD nanoassemblies

Several parameters are highlighted here such as cavity size (α, β, γ), position and number of lipid moieties on the narrow or wide rim of CDs, grafted chain length, technology used for the preparation of nanoassemblies, concentration of CDs, use of surfactant and type of solution medium (water or buffer).

First, some articles showed that using α-, β- or γ-CDs in which amphiphilic moieties were grafted onto the wide rim led to the preparation of the same NPs with diameters in the range 105–130 nm in water to deliver diazepam slowly, which is a sedative of low solubility [20]. Other results with hydrophobic chains on the narrow rim of CDs (α-, β- or γ-) also showed no difference in vesicle size [21]. In the case of persubstituted β- or γ-CDs with C_6 chains on the narrow rim, no significant difference in NP size was shown [22,23]. In conclusion, the cavity size of CDs (external diameter 1.37 nm, 1.53 nm and 1.69 nm for α, β, γ-CDs, respectively) seems a negligible parameter in self-assembly properties.

The effect of the position and number of lipid moieties on the narrow or wide rim of CDs is difficult to correlate with the properties of nanovectors because many parameters differ between studies. Some studies on CDs grafted with seven chains (C_6) on the narrow rim or an average degree of substitution of 12 chains on the wide rim showed the preparation of similar nanospheres with diameters around 250–275 nm [24,25].

Nevertheless, it should be noted that the chemical approach to synthesizing amphiphilic CDs is very different for narrow or wide rim modifications as well as for the different number of grafted moieties [26]. Moreover, polysubstitution leads to a statistical mixture of compounds [27,28] whereas persubstitution or monosubstitution provide single compounds [22,29–31]. In addition, as the aliphatic chains are perpendicular to the air–water interface,