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Thirty years with cyclodextrins

Dominique Duchêne*, Amélie Bochot

Institut Galien Paris-Sud, CNRS UMR 8612, Univ. Paris-Sud, Université Paris-Saclay, 92290 Châtenay-Malabry, France

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ABSTRACT

This paper reviews the work carried out on cyclodextrins during some thirty years at the Institut Galien Paris-Sud, UMR CNRS 8612, Université Paris-Sud. It represents the normal evolution of this domain of science and the numerous possibilities of cyclodextrins for being a tool adaptable to the most complex situations. The works which have been carried out concern: the investigation of general characteristics of cyclodextrins and derivatives, the preparation and evaluation of inclusion complexes, the use of cyclodextrins in the preparation of drug delivery systems, the various possibilities offered by cyclodextrins and their derivatives for nanoparticle preparation and finally the use of cyclodextrins for the preparation of biomaterials is evoked.

1. Introduction

The main objective of this paper is not to review all the different uses described for cyclodextrins (CDs) during the past thirty years, but to explain how our laboratory started working on and with CDs, despite the fact that some among us, and not the least, said sententiously “cyclodextrins have no future”.

In fact, in the early eighties, we were asked by a company to verify if all what started to appear in the literature about the potential uses of CDs was credible. Of course, our first approach was to review the literature (Duchêne et al., 1984, 1985a,b, 1986; Duchêne and Wouessidjewe, 1990, 1992), an activity that we permanently have (Duchêne and Wouessidjewe, 1996; Loftsson and Duchêne, 2007; Duchêne et al., 2009; Duchêne and Bochot, 2011), and then we started working with CDs. The main research domain of our laboratory is pharmaceutical technology, drug delivery systems, drug targeting, *etc*. But, being a CNRS (Centre National de la Recherche Scientifique) unit, some groups inside the laboratory are constituted by pure scientists mostly in the domain of chemistry, but also physics and biology, this explains some more fundamental aspects of the works which were carried out on CDs along the years. Anyhow, in the present review, we will mainly focus on pharmaceutical technology aspects.

Abbreviations: CDs, cyclodextrins; DMPC, dimyristoylphosphatidylcholine; DPPA, dipalmitoylphosphatidic acid; DPPC, dipalmitoylphosphatidylcholine; DSC, differential scanning calorimetry; Et-β-CD, ethyl-β-CD; HP-β-CD, hydroxypropyl-β-CD; IM, indomethacin; IR, infrared; ITC, isothermal titration microcalorimetry; Me-β-CD, methyl-β-CD; MD, modified dextran; MOF, metal-organic frameworks; NMR, nuclear magnetic resonance; PACA, poly(alkylcyanoacrylates); pβ-CD, polyβ-CD; PBLG, poly(γ-benzyl-L-glutamate); PIBCA, poly(isobutylcyanoacrylate); PIHCA, poly(isohexylcyanoacrylate); P-Gp, P-glycoprotein; RA, all-*trans*-retinoic acid; RAMEB, randomly methylated β-CD; RHOE, reconstituted human oral epithelium; SEB-β-CD, sulfobutyl ether-β-CD; XRD, X-ray diffractometry.

* Corresponding author.
E-mail address: dominique.duchene@u-psud.fr (D. Duchêne).

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2. Characteristics of CDs and CD derivatives (Table 1)

Chemically, native CD are cyclic oligosaccharides produced by enzymatic degradation of starch. The main natural CD (α, β and γ) are constituted of 6, 7 and 8 glucopyranose units connected by α(1,4)-linkages, respectively but larger ones have been also isolated. They present a truncated cone structure, in which the internal cavity diameter increases as a function of the number of glucopyranose units, from 5.7 to 7.8 and 9.5 Å, when the height of the truncated cone is 7.8 Å. The external faces of CDs are hydrophilic with the primary hydroxyl groups of the glucopyranose units on the narrow side of the ring molecule, and the secondary hydroxyls on the wider side. On the other hand, the internal cavity is relatively apolar but contains water molecules, the quantity of which varies with relative humidity. This special conformation allows the inclusion of apolar molecules or parts of molecules inside CD's cavity, conferring on them new physico-chemical characteristics among which the apparent water solubility of the guest molecule is increased and very often, as a consequence, its bioavailability. The water solubility of natural CDs is 145, 18.5 and 232 g/L for α, β and γ-CD respectively. β-CD being the CD presenting most often the best aptitude for inclusion of drug molecules, its poor water solubility led to the preparation of more soluble derivatives among which methyl- and hydroxypropyl-β-CDs (Me-β-CD and HP-β-CD) and the sulfobutyl ether (SEB-β-CD). There are also poorly water soluble derivatives such as ethyl-β-CD (Et-β-CD).

2.1. Crystal structure

Specogna et al. (2015) studied different physical characteristics of the three natural CDs. The water content evaluated by thermogravimetric analysis for 90%, 44% and 3% relative humidity (HR), varies from 10.15 to 10.11 and 5.26% for α-CD, 15.21 to 14 14.26 and 2.95% for β-CD and 18.18 to 9.64 and 4.55% for γ-CD. These amounts of water are not totally inserted in the CD cavity. For example for α-CD the amount of water in humidity (90 and 44% HR) represents approximately $6H_2O$ molecules per CD, and in dry conditions (3% HR) it is only $3H_2O$. The dehydration process occurs in 3 steps. The first one, between 27 and 48–50 °C, is equivalent to 2.2 H_2O/α-CD molecules. This corresponds to the H_2O molecules bonded in the inner cavity, which are less energetically stabilized and less fixed than those bonded outside, because of the apolar character of the inner cavity. The stability of the outer $4H_2O$ molecules is divided in two categories: the less stable ones desorbing between 50 and 73–79°C (2.6–2.7 H_2O/α-CD molecules), and the most strongly bonded water, 0.5 H_2O/αCD molecules. The water molecules outside the cavity may be involved in hydrogen bonding with hydroxyl groups from both sides of the CD. The water molecules interfere on the crystal structure of CDs. The molecules inside the cavity have no influence on the crystal, while the molecules outside stabilize the crystal structure.

2.2. Chemical constitution and solubility

For years, Et-β-CD was known as poorly water soluble derivative capable of being used to sustain the release and bioavailability of the included molecules. However, as demonstrated in a work carried out by Lemesle-Lamache et al. (1997), the degree of substitution and the exact position of the substitution play a major role on the Et-β-CD solubility. In fact a batch of Et-β-CD from Cyclolab (Budapest, Hungary) was compared with three batches synthesized by Orsan Comp. (Les Ulis, France). The Cyclolab Et-β-CD had been prepared by reacting β-CD with ethyl iodide in the presence of powdered sodium hydroxide in dimethyl sulfoxide at room temperature, and the Orsan batches with ethyl sulphate. The degree of substitution of Et-β-CD from Cyclolab was 1.98 and those of the Orsan batches vary from 1.91 to 2.12. The molecular weight for the Cyclolab product was 1523 g/mol and that of the Orsan ones vary from 1511 g/mol to 1577 g/mol, but the resulting water-solubilities at 25 °C were very different from each other 0.4 g/L for Cyclolab and between 24 and 30 g/L for Orsan products. It appeared that the Cyclolab and Orsan products differed by the position of the Et substituents: on C2 and C6 for Cyclolab, and on C3 for Orsan. As it had been claimed that the low solubility of β-CD could be due to strong intermolecular bonds between C3 hydroxyl protons and C2 ethoxyl group, the substitution in C3 may hinder these bonds and enhance the solubility.

2.3. Toxicity

Administered by the oral route, natural CDs behave more or less like starch but their metabolism speed decreases from γ- to β- and α-CD due to the decreasing size of their ring structure preventing hydrolysis by β-amylases (active on end of chains). When administered intravenously β-CD demonstrates a more pronounced haemolytic activity than α- or γ-CD (the less haemolytic), furthermore its low water solubility leads to its recrystallization in the kidneys resulting in nephrotoxic effect.

Leroy-Lechat et al. (1994) investigated the haemolytic effect of HP-CDs compared with that of natural CDs. The *in vitro* haemolytic effect of CDs, assessed on either erythrocytes suspension in phosphate buffer saline or whole blood, decreases in the order

Table 1
Types of CDs mentioned in this review.

Types of CDs mentioned in this review	
Natural CDs	α-CD β-CD γ-CD
Hydrophilic derivatives	Methyl-β-CD, randomly meththyl-β-CD Hydroxypropyl-β-CD Hydroxypropyl-γ-CD Sulfobutyl ether-β-CD
Poorly water soluble derivatives	Ethyl-β-CDs
Polymer of CDs	polyβ-CD
Amphiphilic CDs	Amphiphilic β- and γ- CDs grafted, by ester or amide bond, on the primary or secondary face with hydrocarbon chains of varying length (C6 to C14) linear or branched