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Opinion paper

Amphiphilic cyclodextrins as enabling excipients for drug delivery and for decades of scientific collaboration: Tribute to a distinguished scientist, French representative and friend – A historical perspective

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ABSTRACT

As a result of the long term collaboration and friendship between Prof. Dominique Duchene and Prof. Atilla Hıncal, several co-supervised Ph.D. theses were conducted in the frame of a co-tutelle PhD programme within the period of 2000–2007, based on the joint Ph.D. agreement between the Hacettepe University in Ankara, Turkey, and the Universite Paris XI in Chatenây-Malabry, France. The first of these scientific collaborations was based on the synthesis, characterization and evaluation of amphiphilic cyclodextrins as nanoparticulate material for the delivery of drugs with bioavailability problems, such as poor solubility, poor stability and side effects. This direct collaboration between Prof. Dominique Duchene and Prof. Atilla Hıncal was further followed on by different research teams from both universities, collaborating on brain delivery and ocular drug delivery with different polymeric nanoparticles resulting in two more Ph.D. theses and several publications. This paper is a historical perspective of this fruitful collaboration and acknowledges the support and supervision of the honorable Prof. Dominique Duchene in this scientific union between two countries and two universities.

1. Introduction

Since 1980s, Prof. Dominique Duchene has been a good friend and colleague. This friendship has led to several projects and resulted in 3 PhD theses and dozens of publications where teams from Hacettepe University worked together with research teams from Universite Paris XI. Due to the rising interest in nanomedicines and their potential in formulating drugs with bioavailability problems such as poor aqueous solubility, instability under physiological conditions, side effects and incompatibility problems, research in this field was the focus of this collaboration. The nanotechnology approach was also incorporated into targeting of drugs in order to improve or control the biodistribution of drugs used in the therapy of severe diseases such as cancer or stroke. Nanoparticulate drug delivery also helps to prolong the residence of drugs at mucosal membranes thus improving the bioavailability at target site, improvement of corneal absorption being one of the key applications.

The goal of this historical perspective is to briefly summarize the results of decades of scientific collaboration between two universities pioneered and lead by Prof. Dominique Duchene with amphiphilic cyclodextrin nanoparticles followed by other polymeric nanoparticles of different structures and in vitro-in vivo properties.

2. Amphiphilic cyclodextrins for nanomedicine

Cyclodextrins (CD) have been discovered through the end of 19th century from the enzymatic degradation of starch which results in cyclic oligosaccharides. Cyclodextrins consist of glucopyranose units linked with α [1, 4] bonds. Based on the number of glucopyranose units, natural cyclodextrins are named alpha-, beta- or gamma-cyclodextrins possessing 6, 7 or 8 units respectively.

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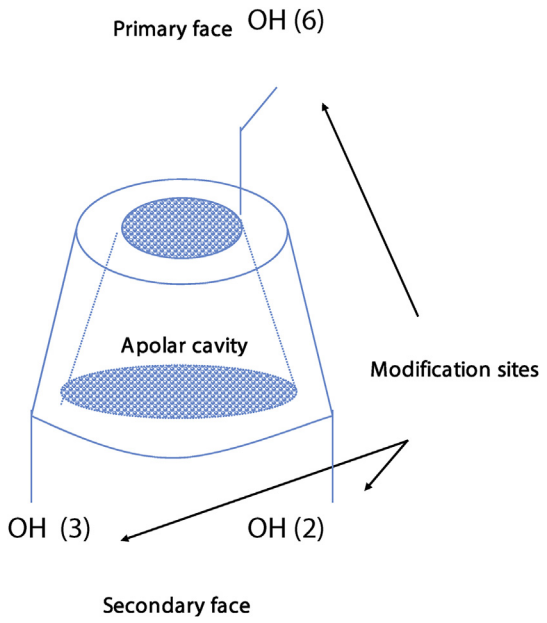

Fig. 1. Schematic diagram of natural cyclodextrins and modification sites.

With shape of a truncated cone or torus, cyclodextrins are polar on the outside due to the primary and secondary hydroxyls groups as seen in Fig. 1. What is of interest from the pharmaceutical point of view especially for drug delivery is that cyclodextrins also possess an apolar cavity lined with protons of H-2, H-3 and H-6. This dual structure gives the cyclodextrin molecule the unique ability to include hydrophobic molecules in the cavity, forming an inclusion complex with molar ratio of 1:1, 1:2 or 2:1 drug: CD. The inclusion complex helps to mask the physicochemical properties of the guest molecule such as the solubility, stability, taste, odor, side effects and physical state. Thus, cyclodextrins have been extensively used as excipients to increase the water solubility of drug molecules or improve the physical or chemical stability of active ingredients as well as to mask the side effects of drugs in parenteral, oral, nasal, buccal, topical and mucosal formulations [1–3].

The need to modify the structure of mother CDs was mainly a result of the limited water solubility of the β-CD which is a direct outcome of its geometry of 7 glucopyranose units leading to a rigid "belt" on the molecule making it more difficult to solubilize in water. Another reason for chemical modification of CDs is to increase interaction with biological membranes. Undoubtedly, it was also aimed to alter the complex forming ability of CDs to reduce nephrotoxicity and hemolysis associated with injectable β-CD [4].

The idea of rendering cyclodextrins with amphiphilic property to obtain self-assembling CDs at interfaces was promising to prepare nanoparticles directly from CDs. Natural or hydrophilic CDs were already incorporated in nanoparticles as coating material or in conjugation with polymer in order to control the release of therapeutic load. However, amphiphilic CDs could also be used as nanoparticle material without the use of another polymer or surfactant. Obtained by the chemical grafting of long aliphatic chains to the primary and/or secondary faces with ester, ether, thio, fluoro or amido bonds, amphiphilic CDs were still able to form inclusion complexes with lipophilic drugs and form nanoparticles with techniques like nanoprecipitation, double emulsion and detergent dialysis techniques [5–9].

Keeping this as a starting point, a series of amphiphilic cyclodextrins were synthesized by grafting 6C chains to the primary face with ester or amide bonds (named 6-O-CAPROBCD and 6-N-CAPROBCD respectively), a branched 6C ester called Ramified BCD, 6C chains on the secondary face with ester bonds (β-CDC6) and 14C chain on the primary face named 6-N-MYRISTOBCD as seen in Fig. 2 [10,11].

These series of amphiphilic CD derivatives were obtained in high purity and characterized thoroughly for selective substitution to ensure reproducibility of data. CD modification often results in statistical substitution giving a mixture or over- and under-substituted CDs, which was tried to be overcome by rigorous controlling of reaction conditions in order to obtain selectively substituted (per-substituted) meaning the substitution of each and every hydroxyl on the primary (7 OHs) or secondary (14 HOHs) faces which was further demonstrated by H NMR spectroscopy, FTIR spectroscopy, FAB MS, DSC and elemental analysis.

The molecular weight of the new amphiphilic CDs varied between 1800 and 2600 Da. All derivatives had melting points between 200 and 300 °C and the surface active properties were also demonstrated by theoretical HLB values calculated as changing between 8 and 11 suggesting good surfactant properties. In order to be used in the preparation of nanoparticles, solubility in relevant water-miscible solvents is an important parameter. Amphiphilic CDs synthesized were soluble in both acetone and ethanol with highest solubility values for β-CDC6 and 6-O-CAPRO-β-CD and lowest for Ramified β-CD (See Table 1).

After obtaining selectively substituted pure amphiphilic CDs, the next step was to demonstrate the amphiphilic nature and the surface active properties of the CDs. Interfacial tension studies of spread amphiphilic CD films at oil-water interface revealed all new derivatives had the ability to reduce the interfacial tension of the oil-water interface. This tensioactive effect was significantly higher with amphiphilic CDs modified on the primary face with 6C chains. The lowest reduction at the Miglyol-water interface was caused by β-CDC6 modified on the secondary face. The presence of an NH amine function in the skeleton of the hydrocarbon chain conferred to the studied amphiphilic molecules an increased performance in lowering the tension of the system. Surface pressure (π)–area (A) compression isotherms of the modified CDs at the air/water interface elucidated the interfacial behavior of the new amphiphilic CDs and suggested that derivatives substituted at the primary face with a relatively short aliphatic chain possessed favorable packaging properties [11].

As demonstrated capable of surface active and self-aligning properties at interfaces, all amphiphilic CDs were able to form nanospheres and nanocapsules to be used as drug delivery systems especially for lipophilic drugs. Nanocapsules were formed using Miglyol 812, Miglyol 840 or benzyl benzoate as oil using nanoprecipitation technique to obtain nanocapsules of size governed by the size of oil droplet formed during the precipitation [10]. Nanospheres were able to form spontaneously with both nanoprecipitation and emulsion/solvent evaporation techniques. Nanoprecipitation technique resulted in smaller nanoparticles with lower polydispersity indices. In fact, formulation parameters and technological factors affecting nanoparticle final properties were evaluated as seen in Table 2 [12]. Particle size was mostly found to be influenced by modification face and length and linearity of alkyl chain grafted to the CD. Longer chains and branching increased mean diameter as well as substitution on the secondary face. Drug loading efficiency and in vitro release behavior were on the other hand largely influenced by preparation technique. When CD nanospheres or nanocapsules were prepared directly from preformed drug: amphiphilic CD inclusion complexes, 2–8 fold increase in drug loading and significant slowing down of the release profile were observed [13,14]. Technological parameters such as stirring rate and temperature did not have a significant effect of