International Journal of Pharmaceutics 531 (2017) 457–469

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review Article

Amphiphilic cyclodextrin nanoparticles

Gamze Varan[a], Cem Varan[a], Nazlı Erdoğar[b], A. Atilla Hıncal[b], Erem Bilensoy[b,*]

[a] Department of Nanotechnology and Nanomedicine, Institute of Graduate Studies in Science, Hacettepe University, 06800 Beytepe-Ankara, Turkey
[b] Department of Pharmaceutical Technology, Faculty of Pharmacy, Hacettepe University, 06100 Sıhhiye-Ankara, Turkey

ARTICLE INFO

Article history:
Received 1 March 2017
Received in revised form 29 May 2017
Accepted 3 June 2017
Available online 6 June 2017

Keywords:
Amphiphilic cyclodextrin
Synthesis
Nanoparticle
Targeting
Gene delivery

ABSTRACT

Cyclodextrins are cyclic oligosaccharides obtained by enzymatic digestion of starch. The α-, β- and γ-cyclodextrins contain respectively 6, 7 and 8 glucopyranose units, with primary and secondary hydroxyl groups located on the narrow and wider rims of a truncated cone shape structure.

Such structure is that of a hydrophobic inner cavity with a hydrophilic outer surface allowing to interact with a wide range of molecules like ions, protein and oligonucleotides to form inclusion complexes. Many cyclodextrin applications in the pharmaceutical area have been widely described in the literature due to their low toxicity and low immunogenicity. The most important is to increase the solubility of hydrophobic drugs in water. Chemically modified cyclodextrin derivatives have been synthesized to enhance their properties and more specifically their pharmacological activity. Among these, amphiphilic derivatives were designed to build organized molecular structures, through selfassembling 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. The purpose of this review is to summarize applications of amphiphilic cyclodextrins in different areas of drug delivery, particularly in protein and peptide drug delivery and gene delivery. The article highlights important amphiphilic cyclodextrin applications in the design of novel delivery systems like nanoparticles.

1. Introduction

Cyclodextrins are cyclic oligosaccharides obtained by enzymatic digestion of starch. The α-, β- and γ- cyclodextrins contain respectively 6, 7 and 8 glucopyranose units, with primary and secondary hydroxyl groups located on the narrow and wider rims of a truncated cone shape structure (Fig. 1).

Such structure is that of a hydrophobic inner cavity with a hydrophilic outer surface allowing to interact with a wide range of molecules like ions, protein and oligonucleotides to form inclusion complexes (Irie and Uekama, 1999; Lysik and Wu-Pong, 2003). Many cyclodextrin applications in the pharmaceutical area have been widely described in the literature due to their low toxicity and low immunogenicity. The most important is to increase the solubility of hydrophobic drugs in water. Chemically modified cyclodextrin derivatives have been synthesized to enhance their properties and more specifically their pharmacological activity (Challa et al., 2005; Uekama, 2004). Among these, amphiphilic derivatives 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. The purpose of this review is to summarize applications of amphiphilic cyclodextrins in different areas of drug delivery, particularly in protein and peptide drug delivery and gene delivery. The article highlights important amphiphilic cyclodextrin applications in the design of novel delivery systems like nanoparticles.

2. General overview of cyclodextrins

2.1. History

Cyclodextrins, also known as cellulosines or Schardingers dextrins, were discovered by French scientist Villiers in 1891. He determined a crystal structure called ‘cellulosine’ from the isolation of starch via bacterial digestion (Villiers, 1891). Then, Austrian microbiologist Franz Schardinger described crystalline dextrins (α-cyclodextrin and β-cyclodextrin), which were isolated from bacterial digest of potato starch in the early 20th century. At

* Corresponding author
E-mail address: eremino@hacettepe.edu.tr (E. Bilensoy).

http://dx.doi.org/10.1016/j.ijpharm.2017.06.010
0378-5173/

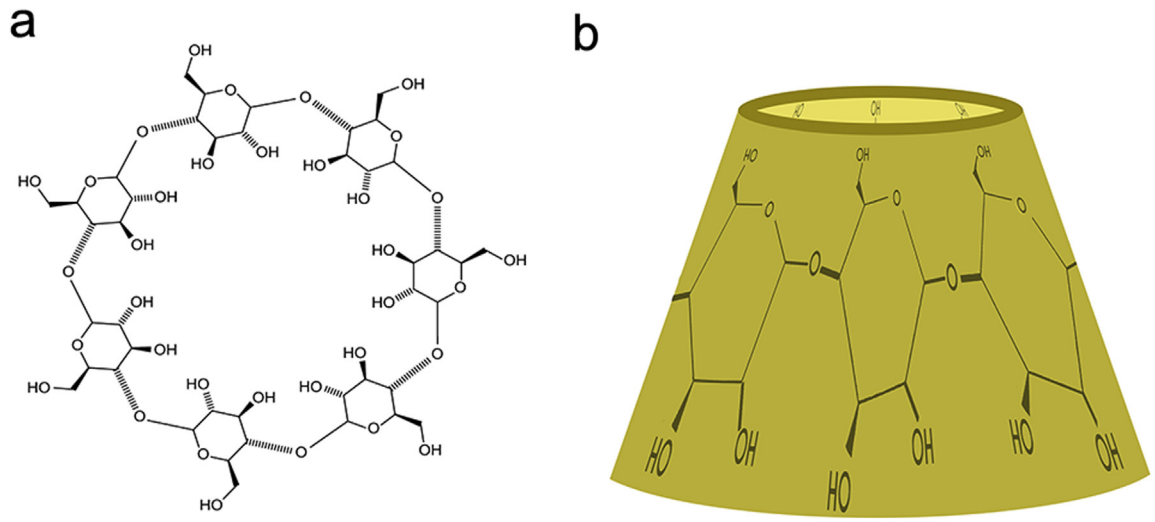

Fig. 1. The chemical structure (a) and the toroidal shape of cyclodextrin (b).

the end of the 1920s, he also performed a lot of experiments with cyclodextrins and he accepted as a founder of cyclodextrin chemistry by authorities (Schardinger, 1903a, 1903b, 1911; Szejtli, 1998). In 1935, γ-cyclodextrin was discovered by Freudenberg. During the discovery period, three main natural cyclodextrins were discovered and characterized. Between 1935–1970s, new methods had developed for the preparation of cyclodextrins at laboratory scale. However, small amounts of impure cyclodextrin could be produced which prevent the industrial investigation of these novel oligosaccharides. In this exploration period, first patent and first fundamental review on cyclodextrins had received in drug formulations by Freudenberg (Loftsson and Duchene, 2007). In the utilization period (1970 to present), biotechnological techniques were developed to obtain purified cyclodextrin products used as pharmaceutical excipients (Kurkov and Loftsson, 2013). Following this, due to the low water solubility of natural cyclodextrins, various cyclodextrin derivatives were synthesized with the substitution of hydroxyl groups. In pharmaceutical area, studies demonstrated that oral availability in cyclodextrin-containing formulations could be enhanced with cyclodextrins for FDA's Class II (poor aqueous solubility, high permeability) drugs but they can hamper bioavailability of Class I (high solubility, high permeability) and Class III (high solubility, poor permeability) drugs (Loftsson and Masson, 2004). Both the parent cyclodextrins and their derivatives have been used in dispersed systems such as emulsions, microspheres, nanospheres and liposomes (Duchene et al., 2005). Otherwise, cyclodextrins have been used to increase drug loading of polymeric microspheres or to increase drug availability from dispersed systems. Novel surface-active cyclodextrin derivatives have also been synthesized and used as drug delivery system (Memisoglu-Bilensoy et al., 2005).

2.2. Chemistry and properties

Cyclodextrins are cyclic oligosaccharides 6 D-(+) glucopyranose units linked by α-(1,4) bonds (Challa et al., 2005; Messner et al., 2010; Zhang and Ma, 2013). The chair formation of the glucopyranose units gives the truncated cone-shape with secondary hydroxyl groups extending from the hydrophilic outer surface and the primary groups from the lipophilic inner cavity (Challa et al., 2005; Saenger et al., 1998). The truncated cone-shaped cyclodextrins possess a hollow, tapered cavity of 0.79 nm in depth, while both the top and bottom diameters are increased with the number of glucose units (Li and Purdy, 1992). In aqueous solutions, hydroxyl groups form hydrogen bonds with water making cyclodextrins soluble in water. Another property of cyclodextrin structure is the hydrophobic cavity enabling them to form inclusion complexes with a large number of compounds such as small molecules, proteins and oligonucleotides via host-guest interaction in the pharmaceutical area (Messner et al., 2010; Zhang and Ma, 2013).

The pharmaceutical applications of cyclodextrins are remarkable due to their low toxicity, low immunogenicity, easy-accessible and cost-effective (Del Valle, 2004; Irie and Uekama, 1997). These applications as listed below;

- increase drug solubility and stability,
- enhance drug absorption,
- mask unwanted odors and tastes,
- control drug release,
- eliminate local and systemic toxicity,
- improve drug permeability through biological barriers (Carrier et al., 2007; Hirayama and Uekama, 1999; Loftsson and Brewster, 2011; Uekama et al., 1998).

2.3. Natural cyclodextrins and modified cyclodextrins

Cyclodextrins are a family of cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds. Cyclodextrins with less 6 units cannot be formed due to steric barriers while the higher structures with 9 or more glucose units are very difficult to purify (Miyazawa et al., 1995). Cyclodextrins are of three types: α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, considered as first generation or natural cyclodextrins, are consist of six, seven and eight glucopyranose units, respectively (Dass and Jessup, 2000; Messner et al., 2010). The physicochemical differences of natural α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin are given in Table 1.

The cavity size of α-cyclodextrin is insufficient for many drugs and γ-cyclodextrin is high cost. Generally, δ-cyclodextrin has weaker complex forming ability than other parent cyclodextrins. β-cyclodextrin has been widely used in the early stages of pharmaceutical applications due to easily accessible and suitable cavity size for the widest range of drugs. But the low water solubility and nephrotoxicity limited the use of β-cyclodextrin particularly in parenteral drug delivery (Loftsonn et al., 2005).