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Cyclodextrins: structure, physicochemical properties and pharmaceutical applications

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ABSTRACT

Since their discovery over 100 years ago cyclodextrins (CDs) have been the subject of numerous scientific publications. In 2016 alone CDs were the subject of over 2200 research articles published in peer-reviewed journals and mentioned in over 2300 patents and patent applications, many of which were on pharmaceutical applications. Natural CDs and their derivatives are used as enabling pharmaceutical excipients that enhance aqueous solubility of poorly soluble drugs, increase drug permeability through biological membranes and improve drug bioavailability. Unlike conventional penetration enhancers, their hydrophilic structure and high molecular weight prevents them from penetrate into lipophilic membranes leaving biological membranes intact. The natural CDs and some of their derivatives have monographs in pharmacopeias and are also commonly used as food additives and in toiletry products. CDs form inclusion complexes with lipophilic moieties of hydrophobic drugs. Furthermore, CDs are able to form non-inclusion complexes and self-assembled aggregates; small and large complex aggregates with micellar-like structures that can enhance drug solubility. Excipients commonly used in pharmaceutical formulations may have additive or inhibiting effect on the CD solubilization. Here various methods used to investigate CD aggregate formation are reviewed as well as techniques that are used to increase the solubilizing effects of CDs; methods that enhance the apparent intrinsic solubility of drugs and/or the complexation efficacy and decrease the amount of CD needed to develop CD-containing pharmaceutical formulations. It will be explained how too much or too little CD can hamper drug bioavailability, and the role of CDs in solid dosage forms and parenteral formulations, and examples given on how CDs can enhance drug delivery after ocular, nasal and pulmonary administration.

1. Introduction

The first publication describing cyclodextrins (CDs) was by Antoine Villiers (Villiers, 1891). He discovered crystalline dextrins (cellulosines) which were obtained by enzymatic digestion of potato starch by *Bacillus amylobacter*. At the beginning of the 20th century, Franz Schardinger described the preparation, separation and purification of cellulosines, dextrin A and B (Schardinger, 1903). His research on the fundamental properties of these crystalline dextrins indicated that they were “cyclic polysaccharides” (Schardinger, 1911). Their structure was 30 years later described by Freudenberg and his co-workers (Freudenberg and Cramer, 1948; Freudenberg and Meyer-Delius, 1938; Freudenberg et al., 1939). At the end of the 1940s, the word “cyclodextrin” was used to define the dextrin characteristics by Friedrich Cramer (Cramer, 1949). Cramer investigated the procedure to purify and separate the natural CDs (i.e. αCD, βCD, and γCD) and he performed numerous studies on solid and solution state of guest/CD inclusion complexes (Cramer, 1954). CDs have been used in pharmaceutical industry since the 1970s with the first product prostaglandin E2/βCD (Prostarmon E^{TM} sublingual tablet) marketed in Japan in 1976 (Loftsson and Duchêne, 2007). Since then pharmaceutical applications of CD inclusion complexes to enhance solubility, improve stability and increase bioavailability of drugs have been described in numerous scientific publications and patents (Brewster and Loftsson, 2007; Loftsson and Brewster, 1996; Uekama et al., 1998). CDs act as true carriers by dissolving and delivering hydrophobic drug molecules through the aqueous exterior of lipophilic biological membrane barriers (e.g., mucosa). In general, only dissolved drug molecules can partition into the barrier and then penetrate through it. In addition, CDs are known to self-assemble to form nanosized aggregates in aqueous solutions and, thus,

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have the potential of being developed into novel drug delivery systems (Loftsson et al., 2004a; Messner et al., 2010).

CDs are common food additives and are frequently included in both pharmaceutic and cosmetic products as well as in various other industrial products, and they are applied in various analytical techniques. The annual CD production is now over 10,000 metric tons, about 70% of which is βCD, about 15% αCD, about 5% γCD and about 10% CD derivatives (based on information from Roquette Frères, Lestrem, France). About 30% of the annual CD production is used in pharmaceutics, about 20% in food products and about 50% in various consumer products. CDs can currently be found in over 50 marketed pharmaceutical products.

2. Cyclodextrins and cyclodextrin derivatives

CDs are cyclic oligosaccharides consisting of (α-1,4)-linked D-glucopyranose units. The most common natural CDs, and the only ones used in pharmaceutical products, are αCD, βCD and γCD consisting of 6, 7 and 8 D-glucopyranose units. Larger CDs do exist but they are difficult to produce and have limited ability to form inclusion complexes. αCD, βCD and γCD are doughnut-shaped molecules with hydrophilic outer surface and a somewhat lipophilic central cavity. In aqueous solutions CDs are able to form water-soluble inclusion complexes of lipophilic poorly-soluble drugs by taking up some lipophilic moiety of the drugs into the central cavity (Fig.1). In aqueous solutions complex bound drug molecules are in dynamic equilibrium with free drug molecules with rates of formation and dissociation close to the diffusion-controlled limits (Stella et al., 1999). Drug/CD complexes are continuously being formed and dissociated. Consequently, drug molecules are rapidly released from the complex upon, for example, media dilution or by molecules competing with the drug for a space in the cavity such as by bile acids and lipids in the gastrointestinal tract (Ono et al., 1999; Stappaerts and Augustijns, 2016; Stella et al., 1999). CDs are known to stabilize supersaturated drug solutions (Brewster et al., 2008). The physiochemical and biological properties of CDs are similar to their linear counterparts (Table 1). There are however some differences. Due to their cyclic structure CDs are less susceptible towards enzymatic degradation than the linear dextrins and CDs are better complexing agents and solubilizers.

The natural αCD, βCD and γCD have somewhat limited solubility in water which limits their applications as solubilizing complexing agents. Like starch CDs can be reacted with wide variety of reagents to obtain water-soluble CD derivatives. For example, hydroxypropylated CD derivatives (e.g., HPβCD and HPγCD) are obtained by treating the natural CDs with propylene oxide, carboxymethylated CDs (e.g., CMβCD) by treating the natural CDs with monochloroacetic acid, randomly methylated CDs (e.g., RMβCD) by treating the natural CDs with methyl iodide and sulfobutylether CDs (e.g., SBEβCD and SBEγCD) by treating the natural CDs with 4-butane sultone. CD derivatives that currently can be found in marketed pharmaceutical products are listed in Table 2. In general, the substitution of the hydroxy groups is random resulting in an isomeric mixture that has aqueous solubility well above 500 mg/ml (Pitha et al., 1986). Even random substitution of the hydrophilic hydroxy groups by more lipophilic methoxy moieties, like in RMβCD, will result in dramatic improvements in their solubility. The random substitution converts the natural CDs from crystalline solids to physically stable, amorphous mixtures of isomers. Converting the crystalline natural CDs to mixture of isomers not only increases the solubility of the CDs themselves but also that of their complexes (Fig. 2). Amorphous CDs form amorphous complexes with poorly soluble, lipophilic, crystalline drugs.

Table 1
The physiochemical properties of β-cyclodextrin (βCD) and its linear analog, maltoheptaose (Dona et al., 2011; Gould and Scott, 2005; Stella and He, 2008; Szejtli, 1988).

Property	βCD	Maltoheptaose
Structure	Cyclic (α-1,4)-linked	Linear (α-1,4)-linked
Formula	$C_{42}H_{70}O_{35}$	$C_{42}H_{72}O_{36}$
Molar mass (g/mol)	1135	1153
$LogP_{octanol/water}$ (calculated)[a]	−14	−14
Solubility in water at room temperature (mg/ml)	18.5	about 50[b]
H-acceptors[c]	35	36
H-donors[d]	21	23
Human α-amylase	Essentially stable towards α-amylases	Hydrolyzed by α-amylases
Bacterial digestion in the gastrointestinal tract	Susceptible to bacterial digestion in the GI tract	Susceptible to bacterial digestion in the GI tract

[a] Logarithm of the octanol/water partition coefficient. Calculated value (2017).
[b] The solution becomes cloudy at approximately 50 mg/ml at 25 °C.
[c] H-acceptor: the electronegative atom that possesses a lone electron pair capable to non-covalently bind the hydrogen atom participating in the hydrogen bond.
[d] H-donor: the atom to which the hydrogen atom participating in the hydrogen bond is covalently bounded.

3. ADME and toxicology of cyclodextrins

CDs are resistant to β-amylases that hydrolyze starch from the non-reducing end, but they are slowly hydrolyzed by α-amylases that hydrolyze starch from within the carbohydrate chain. Human α-amylase present in the saliva and bile, as well as in other bodily fluids such as the tear fluid, hydrolyze linear dextrins quite readily but the cyclic structure and substituents on the CD molecules prevent their catalyzed hydrolysis by this enzyme. The only CD that is readily hydrolyzed by α-amylase is the unsubstituted γCD (Lumholdt et al., 2012, 2015; Munro et al., 2004; Saokham and Loftsson, 2017; Szejtli, 1987). Substituted γCDs are hydrolyzed much more slowly and formation of inclusion complex prevents α-amylase hydrolysis of CDs. CDs not digested by human α-amylase undergo bacterial digestion in the lower sections of the gastrointestinal tract (Antlsperger, 1992; Antlsperger and Schmid, 1996; De Bie et al., 1998; Irie and Uekama, 1997; Stella and He, 2008; Van Ommen et al., 2004; Zhou et al., 1998). After oral administration, γCD is completely digested in the gastrointestinal tract, whereas both αCD and βCD, as well as the CD derivatives, are predominantly digested by bacteria in the colon. αCD is digested more slowly than βCD. After parenteral administration CDs are mainly (> 90%) excreted unchanged in the urine via glomerular filtration with the rest eliminated by other excretion pathways, such as liver metabolism and biliary excretion (Kurkov and Loftsson, 2013). The pharmacokinetics of HPβCD, SBEβCD and sugammadex have been studied in humans and shown to be mainly

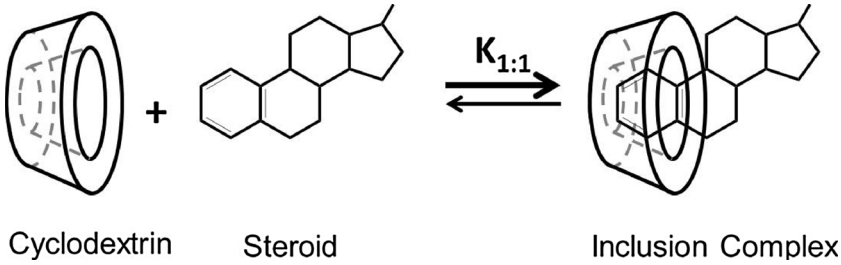

Fig. 1. Formation of an inclusion complex in aqueous solution. $K_{1:1}$ is the equilibrium constant (i.e. the stability constant) where 1:1 indicates the stoichiometry of the complex. The value of $K_{1:1}$ for a steroid/βCD complex is frequently between 1000 and 2000 M^{-1}.