International Journal of Pharmaceutics 516 (2017) 278–292

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Review

γ-Cyclodextrin

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ARTICLE INFO

Article history:
Received 19 September 2016
Received in revised form 24 October 2016
Accepted 26 October 2016
Available online 29 October 2016

Keywords:
γ-Cyclodextrin
ADME
Complexing agent
Inclusion complex
Solubilization
Aggregation

ABSTRACT

γ-Cyclodextrin (γCD) is a cyclic oligosaccharide formed by bacterial digestion of starch and used as solubilizing agent and stabilizer in a variety of pharmaceutical and food products. γCD is a large (molecular weight 1297 Da) hydrophilic molecule that does not readily permeate biological membranes and is rapidly digested by bacteria in the gastrointestinal tract. In humans γCD is metabolized by α-amylase that is found in, for example, saliva, bile fluid and tears. Thus, bioavailability of γCD is negligible. Also, γCD is readily excreted unchanged in the urine after parenteral administration. Like other cyclodextrins, γCD can form water-soluble inclusion complexes with many poorly-soluble compounds. In comparison with the natural αCD and βCD, γCD has the largest hydrophobic cavity, highest water solubility and the most favorable toxicological profile. The focus of this review is production, physiochemical properties, pharmacokinetics, toxicity and applications of γCD and its derivatives. Also, the aggregation behavior of γCD in aqueous media is discussed.

Contents

1. Introduction

Cyclodextrins (CDs) are a group of natural occurring oligosaccharides that are formed by bacterial digestion of starch (Kurkov and Loftsson, 2013; Szejtli, 1988). Two most common natural CDs (αCD and βCD) were discovered in 1891 by Villiers (Villiers, 1891). This was followed by the discovery of the natural γCD in 1935 (Freudenberg and Jacobi, 1935). These doughnut shaped molecules contain 6 (αCD), 7 (βCD), 8 (γCD) or more glucopyranose monomers linked via α-1,4-glycoside bonds with a hydrophilic outer surface and a somewhat lipophilic central cavity. Although CDs with more than 8 glucopyranose units do exist they can be hard to produce and have limited ability to form water-soluble complexes with poorly-soluble drugs and, thus, are of limited interest as pharmaceutical excipients. The natural CDs are hydrophilic with numerous hydroxy groups on their outer surface. However, their solubility in water is somewhat limited due to intermolecular hydrogen bonding in their crystalline state. Random substitution of the hydroxy groups, even by lipophilic methyl moieties, will enhance their solubility in water. CDs of pharmaceutical interests include the natural αCD, βCD and γCD and their hydroxypropylated derivatives, 2-hydroxypropyl-αCD

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http://dx.doi.org/10.1016/j.ijpharm.2016.10.062
0378-5173/

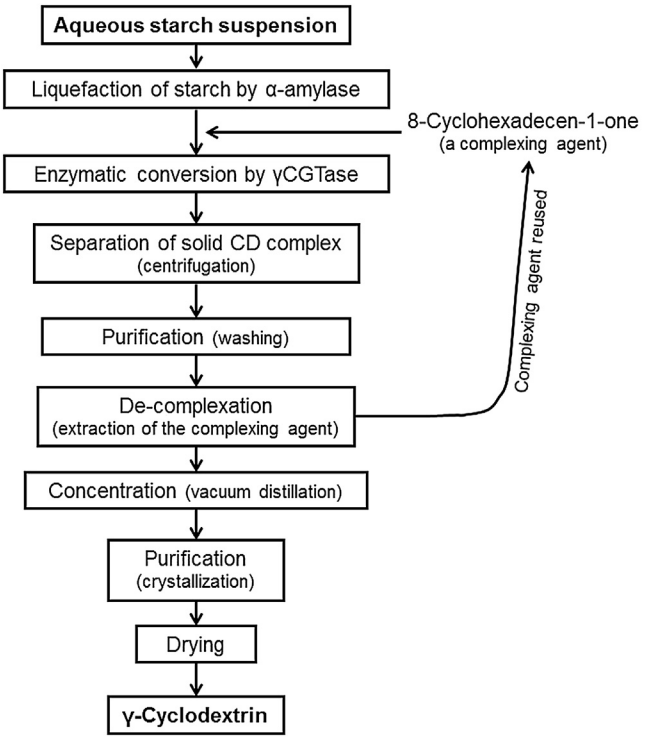

Fig. 1. Flow diagram showing production of γ-cyclodextrin.

(HPαCD), 2-hydroxypropyl-βCD (HPβCD) and 2-hydroxypropyl-γCD (HPγCD), the randomly methylated βCD (RMβCD) and γCD (RMγCD), and the sulfobutyl ether derivatives of βCD (SBEβCD) and γCD (SBEγCD) (Loftsson and Duchêne, 2007). Other CD derivatives are available as fine chemicals including CD polymers. CDs can presently be found in over 35 marketed drug products world-wide as well as in numerous food and toiletry products, cosmetics and textiles. The natural βCD is the most commonly used CD in industrial products. βCD is about 70% of the global CD production while αCD is about 15% and γCD is about 5%. Although the pharmaceutical industry frequently favors the water-soluble CD derivatives over the less soluble natural CDs the combined production of the various CD derivatives is only about 10% of the global CD production.

Even though the natural γCD is only about 5% of the global CD production its favorable toxicological profile and physiochemical properties makes it very attractive as a pharmaceutical excipient in topical, oral and parenteral products. Following is a review on the physicochemical and biological properties of γCD and its pharmaceutical applications.

2. Preparation and physicochemical properties of γ-cyclodextrin and its derivatives

In nature CDs are formed during bacterial digestion of starch, amylose, and other polysaccharides and the product is a crude mixture containing αCD, βCD and γCD together with linear dextrins, glucose and small traces of CDs with 9 or more D-glucopyranose units (Terada et al., 1997). Cyclodextrin glucosyltransferase (CGTase), an extracellular enzyme produced by many bacterial species, catalyzes polysaccharide cleavage and then joins the two ends of a linear product to form a cyclic oligosaccharide (*i.e.* cyclodextrin) (Biwer et al., 2002; Hedges, 2009). Different bacteria produce different CGTases that differ in relative amounts of αCD, βCD and γCD. They produced but, in general, the main product is βCD with smaller amounts of αCD and some γCD together with linear dextrins and glucose. The final CD ratio in the crude mixture depends on both the origin of CGTase used and the reaction condition (Han et al., 2014; Hedges, 2009; Li et al., 2014). Commercial CD manufacturing is a three step process. First, CGTase is manufactured by bacterial fermentation. For γCD production a γCGTase is manufactured that predominantly produces γCD (Li et al., 2007). Second, aqueous starch slurry is liquefied by addition of α-amylase, or by heating, and then the γCGTase is added. In order to shift the CD ratio further towards γCD the γCGTase starch degradation is performed in presence of complexing agent such as 8-cyclohexadecen-1-one that has relatively high affinity for γCD. The complexing agent forms poorly soluble complex with γCD that is separated from the crude aqueous mixture as 8-cyclohexadecen-1-one/γCD precipitate (Schmid, 1991). In the final step, the solvent is removed from the precipitate by boiling the complex in an aqueous solution followed by distillation. Pure γCD is then recovered by crystallization (Fig. 1).

Due to the chair conformation of the glucopyranose units, CD molecules are cone-shaped with the secondary hydroxy groups extending from the wider rim of the torus and the primary hydroxy groups from the narrower rim (Table 1). The result is very hydrophilic molecules ($LogK_{octanol/water}$ is well below −10) with a central cavity that has lipophilicity comparable to 55% (v/v) aqueous ethanolic solution (*i.e.* the dielectric constants of the βCD and γCD cavities have been estimated to be 48 and 55, respectively) (Street and Acree, 1988). Physicochemical properties of CD derivatives, including their aqueous solubility and ability to form drug/CD complexes, depend not only on the structure of the attached substituents but also on their number and location within the CD molecule. The molar degree of substitution (MS) is defined as the average number of substituents per one glucopyranose repeat unit. For methylated CDs, the MS has a value between 0 (no substitution) and 3 when all hydroxy groups have been methylated. In other cases, such as hydroxypropylation of CDs, the hydroxy groups on the substituents can also be substituted to form oligomeric or polymeric side chains. In such cases the MS value can be greater than 3. For optimal solubility and complexation efficiency, the MS value is, in general, kept somewhat low. Fully substituted CDs can possess both poor aqueous solubility and less than an optimal ability to form inclusion complexes due to substituent obstruction of the central cavity. In carbohydrate chemistry, degree of substitution (DS) is defined as the number of hydroxyl groups per glucose repeat unit that have been substituted and, thus, the maximum obtainable DS is 3. One novel γCD derivative, sugammadex, has recently been registered as active pharmaceutical ingredient (API). It was obtained by substituting the 6-position of the γCD molecule by negatively charged eight carboxylthioether groups (Davuluri et al., 2014). The main physiochemical properties γCD, SBEγCD, HPγCD and sugammadex are listed in Table 2.

CDs possess many of the same physicochemical and biological characteristics as the analogous water-soluble linear dextrins. However, due to their cyclic structure, they are more resistant towards both enzymatic and non-enzymatic hydrolysis than the linear dextrins (Frömming and Szejtli, 1994). The hydrolytic rate of CDs in aqueous solutions depends on the ring size and fraction of free CD. In the solid state, CDs are at least as stable as sucrose or starch and can be stored for several years at room temperature without any detectable degradation (Szejtli, 1988). Non-enzymatic degradation of CDs in aqueous solutions is specific acid catalyzed hydrolysis of the α-acetal linkages to form glucose, maltose and non-cyclic oligosaccharides (Hirayama et al., 1992). The half-lives ($t_{1/2}$) for the ring-opening of αCD, βCD and γCD in aqueous 0.2 M hydrochloric acid solution at 70 °C were determined to be about 25, 15 and 7 h, respectively (Schönberger et al., 1988). While αCD and βCD were somewhat less susceptible towards acid hydrolysis than