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Questions and answers on cyclodextrins used as excipients in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [1].

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1. What are cyclodextrins and why are they used as excipients?

Cyclodextrins (CDs) are cyclic oligosaccharides made up of a number of dextrose units of (α-1,4)-linked α-D-glucopyranose. These cyclic structures contain a lipophilic central cavity and a hydrophilic outer surface (Fig. 1). Cyclodextrins are made up of six, seven or eight dextrose units (α-, β-, and γ-CDs, respectively; the so-called parent cyclodextrins. Ph.Eur names of α- and β-CD: alfadex and betadex). Cyclodextrins interact with hydrophobic drug molecules to form inclusion complexes and can be used e.g. to improve the aqueous solubility of the drug molecule. For β-CD, which itself has a relatively low aqueous solubility, substitution of any of the hydrogen bond-forming hydroxyl groups, even by lipophilic functions, results in a dramatic improvement in the aqueous solubility of the derivative. Examples of β-CD derivatives used as excipients in medicines are the sulfobutylether of β-CD (SBE-β-CD), the hydroxypropyl derivative of β-CD (HP-β-CD, hydroxypropylbetadex), and the randomly methylated β-CD (RM-β-CD).

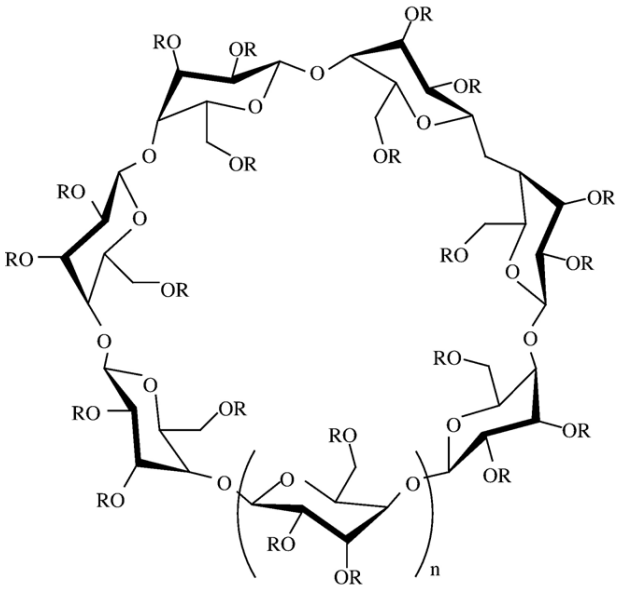

Figure 1: β–Cyclodextrin structure

SBE-β-CD: R = $-(CH_2)_4–SO_3^-Na^+$

HP-β-CD: R = $-CH_2–CHOH-CH_3$

RM-β-CD: R = $-CH_3$

In the pharmaceutical industry, cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of active substances poorly soluble in water, in order to increase their bioavailability and to improve stability. Cyclodextrins can lower the free concentration of the drug and therefore the pharmacokinetics/pharmacodynamics of the active substance may be changed significantly. In addition, cyclodextrins can be used to reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent pre-systemic drug-drug or drug-additive interactions within a formulation (all these properties are based on reduction of the free drug in solution), or to convert oils and liquid drugs into microcrystalline or amorphous powders [3].

2. Which medicinal products contain cyclodextrins?

Because of the diverse types of application of cyclodextrins, several types of medicinal products can contain cyclodextrins. They are used e.g. in tablets, aqueous parenteral solutions, nasal sprays and eye drop solutions. Examples of the use of cyclodextrins in medicines on the European market are β-CD in cetirizine tablets and cisapride suppositories, γ-CD in minoxidil solution, and examples of the use of β-cyclodextrin derivatives are SBE-β-CD in the intravenous antimycotic voriconazole, HP-β-CD in the antifungal itraconazole, intravenous and oral solutions, and RM-β-CD in a nasal spray for hormone replacement therapy by 17β-estradiol. In Germany and Japan there are infusion products on the market, containing alprostadil (prostaglandin E1, PGE1) with α-CD [4].

Cyclodextrins used as an active substance, rather than excipients, will not be discussed in this document (not in the scope).

3. What are the safety concerns?

3.1. Oral products

The oral availability of cyclodextrins is very low. Adverse interactions with vitamins or other nutrients are not to be expected [10, 17]. At high doses (> 200–1000 mg/kg/day) cyclodextrins may cause reversible diarrhoea and cecal enlargement in animals, and therefore also in humans to some extent [16]. An oral study of HP-β-CD up to 2000 mg/kg/day for ca. 4 weeks in juvenile rats did not show more toxicity than in adult rats [6]. Few data on children under two years old treated with oral solutions of itraconazol with up to 200 mg HP-β-CD/kg/day for 2 weeks were well tolerated and considered safe. The oral availability of HP-β-CD was less than 1% [7, 12].

3.2. Nasal and pulmonary products

Cyclodextrins are absorbed poorly via mucosal membranes, but at high doses they can increase nasal and pulmonary drug permeability by direct action on mucosal membranes and facilitate also their own absorption. They can also strongly potentiate lipophilic absorption enhancers.

Less than 10% HP-β-CD or RM-β-CD solutions, and less than 1.5% β-CD solutions do not induce tissue damage in rats and can keep the integrity of the nasal mucosa [14].

3.3. Rectal products

Cyclodextrins can act as rectal absorption enhancers of drugs, including themselves; at higher amounts of cyclodextrins, a higher percentage of cyclodextrins is absorbed. In rats, up to 5% of β-CD and 26% of HP-β-CD can be absorbed. Suppositories with up to 230 mg of β-CD and 12% of HP-β-CD do not cause irritation in rectal mucosa in humans and rabbits respectively. However, α-CD potentially causes damage to the epithelial cell layer, but there are no rectal products with α-CD on the market [14].

3.4. Dermal products

Cyclodextrins alone are poorly absorbed transdermally, but in combination with absorption-promoting agents, they are able to permeate the skin by 12%, 43%, and 53% for β-CD, RM-β-CD, and HP-β-CD, respectively. Concentrations up to 0.1% of α-, β-, and γ-cyclodextrins are considered safe.

Studies on antigenicity, mutagenicity, and topical irritation have proven that HP-β-CD is as safe as materials currently being used in perfumes and cosmetics [15].

3.5. Ocular products

Cyclodextrins enhance drug penetration into the eye. Concentrations of 4% α-CD and 5% RM-β-CD can be toxic to the corneal epithelium of rabbits. Solutions of 10% SBE-β-CD and 12.5% HP-β-CD are found not to be toxic or irritating in rabbit eyes [16].

3.6. Parenteral products

IV-administered CDs disappear rapidly from systemic circulation and are renally excreted intact. The t½ varies from 20 to 100 minutes, with the exception of RM-β-CD, which has a t½ of 7h [16].

Alpha-CD, β-CD and RM-β-CD showed renal toxicity in animals at doses relatively low (> 150 mg/kg) compared to other cyclodextrins after parenteral administration and therefore are rarely used in medicinal products given intravenously. High doses of ≥600 mg/kg of γ-CD showed only reversible vacuolation in the renal tubular epithelium of rats [14, 9].

In animals, HP-β-CD and SBE-β-CD at high doses (> 300 mg/kg) can cause vacuolation of the kidney tubular cells without loss of kidney function. This transient increase in size of apical vacuoles is also observed as an adaptive response to the excretion of osmotic agents such as glucose, mannitol and dextran at extremely high concentrations, e.g. 3 g/kg/day of mannitol showed osmotic nephrosis and kidney injury in humans [8]. Longer treatments cause these mostly reversible effects, at lower doses of SBE-β-CD and HP-β-CD, indicating that duration of exposure may be of importance. HP-β-CD and SBE-β-CD are considered safe at relatively high doses and used most widely in parenteral products. An in vivo study of HP-β-CD up to 400 mg/kg/day for ca. 4 weeks in juvenile rats did not show more toxicity than in adult rats [6]. Based on assessment of currently authorised products, amounts of ca 250 mg/kg/day are found safe in humans older than 2 years when given 21 days (HP-β-CD) or 6 months (SBE-β-CD). Children less than 2 years old may theoretically be less vulnerable to renal toxicity due to their lower baseline glomerular filtration rate. However, this can lead to higher blood levels of cyclodextrins potentially inducing extra-renal effects. Data related to the use of cyclodextrins in very young children is limited. In a few case reports, the use of intravenous products with high doses of HP-β-CD and SBE-β-CD in neonates and young children did not result in signs of toxicity [11, 2, 16].

4. What are the reasons for giving information in the package leaflet?

Cyclodextrins were not included in the European Commission Guideline on excipients in the label and package leaflet of medicinal products for human use dated 2003 [13].

Although the oral availability of cyclodextrins is very low, high doses (> 200–1000 mg/kg/day) cause reversible diarrhoea and cecal enlargement in animals, and may cause diarrhoea in humans also to some minimum extent.

Depending on the type of compound and the amount and type of cyclodextrins in question, the cyclodextrins may influence the permeability of compounds across membranes, and therefore also the bioavailability of (other) active substances given topically (nasal, rectal, dermal, ocular).

Some cyclodextrins, like α- and β-CD, can cause nephrotoxic effects in animals at high systemic exposure, while derivatives of β-CD (e.g. HP-β-CD and SBE-β-CD) or γ-CD are less associated with adverse effects on kidneys or on renal function of animals. Up to now, there is no proof of effects on kidneys in humans; however, data in children less than 2 years old are scarce.

In conclusion, safety information in the package leaflet is desirable in products with substantial contents of cyclodextrins as excipient. Because of the complex behaviour of cyclodextrins, the safety aspects should have been considered during the development and safety assessment of the specific drug products, and should therefore be clearly stated in the SmPC. Because there is insufficient information on the effects of CDs in children < 2 years old, a case by case judgement should be made regarding the risk/benefit for the patient.

5. Proposal for new information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Cyclodextrins e.g.: Alfadex Betadex (E 459) γ-cyclodextrin Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) Hydroxypropyl betadex Randomly methylated β-cyclodextrin (RM-β-CD)	All routes of administration	20 mg/kg/day	This medicine contains x mg cyclodextrin(s) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Do not use in children less than 2 years old unless recommended by your doctor.	Cyclodextrins (CDs) are excipients which can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC. There is insufficient information on the effects of CDs in children < 2 years old. Therefore, a case by case judgement should be made regarding the risk/benefit for the patient. Based on animal studies and human experience, harmful effects of CDs are not to be expected at doses below 20 mg/kg/day.
	Oral	200 mg/kg/day	Cyclodextrins may cause digestive problems such as diarrhoea.	At high doses cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals.

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
	Parenteral	200 mg/kg/day and use for > 2 weeks	If you have a kidney disease, talk to your doctor before you receive this medicine.	In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins. In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur.

Further scientific background is available in the report entitled ‘Cyclodextrins used as excipients’ [5].

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