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Background review for cyclodextrins used as excipients

In the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1)

Draft report published in support to the propylene glycol Q&A document.
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Executive summary

Cyclodextrins (CDs) are cyclic oligosaccharides used for the improvement of water-solubility and bioavailability of medicinal products. At least six types are already available on the market. Because cyclodextrins at high doses have active properties and may show adverse effects, it is recommended to add information on these excipients in the package leaflet of medicinal products.

Introduction

Cyclodextrins are cyclic oligosaccharides used for the improvement of water-solubility and bioavailability of drugs. Because of the diverse types of application of cyclodextrins, several types of medicinal products may contain cyclodextrins. They are used for example 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 [7]. Cyclodextrins are currently not included in the European Commission Guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00 Rev. 1) [15].

Table 1: Use of cyclodextrins in type of products

	α-CD	β-CD	γ-CD	HP-β-CD	SBE-β-CD	RM-β-CD
Oral		X	X	X	X	
Nasal						X
Rectal		X		X		
Dermal		X	X	X		
Ocular		X		X		X
Parenteral	X			X	X	

Both α-CD (Alphadex) and β-CD (Betadex) are listed in the European Pharmacopoeia (Ph.Eur.) and γ-CD is referenced in the Japanese Pharmaceutical Codex (JPC) and will be included in the Ph.Eur. A monograph for HP-β-CD (Hydroxypropyl-betadex) is available in the Ph.Eur. In 2000-2004, α-CD, β-CD and γ-CD were introduced into the generally regarded as safe (GRAS) list of the FDA for use as a food additive. Alpha- and beta-CD are approved as novel food ingredients by the Commission. Beta-CD is approved in Europe as a food additive (E459) with an ADI (acceptable daily intake) of 5 mg/kg/day. SBE-β-CD and HP-β-CD are cited in the FDA's list of Inactive Pharmaceutical Ingredients.

1. Characteristics

Cyclodextrins 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). 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), and the randomly methylated β-CD (RM-β-CD).

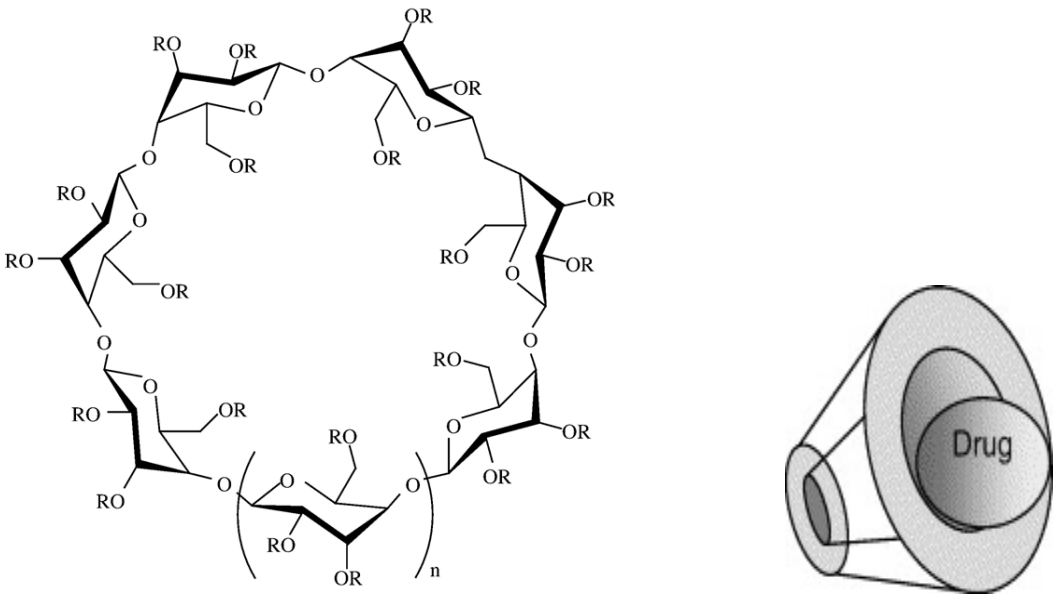

Figure 1: β-Cyclodextrin structure and depiction of an inclusion complex of a drug residing in the cavity formed by the cyclodextrins.

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. In addition, cyclodextrins can be used to reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent 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 [5].

2. Kinetic / toxicological data and clinical safety

2.1. Oral products

Kinetics

The oral bioavailability of cyclodextrins is very low in animals and humans (0.1 – 3%), except for RM-β-CD, which has a bioavailability of 12% in rats. Because of their bulky and hydrophilic nature only insignificant amounts of cyclodextrins are absorbed from the gastrointestinal tract by passive diffusion [27,22]. The increase in solubility of drugs by cyclodextrins also can increase dissolution rate and thus improve the oral bioavailability of drugs with high permeability and low solubility, and drugs with low permeability and low solubility (i.e. BCS Class II and IV materials) [5]. Interactions of ingested cyclodextrins with the absorption of fat-soluble vitamins or other lipophilic nutrients is not to be expected because the formation of inclusion complexes is a reversible process, γ-CD is readily digested in the small intestine, and studies with the poorly digestible α-CD and β-CD have shown that the bioavailability of vitamins (A, D, and E) is not impaired [4,24,28,19].

Safety

Orally administered cyclodextrins at high doses (> 1000 mg/kg/day) may cause reversible diarrhea and cecal enlargement in animals. These effects represent physiologically adaptive responses to a large load of poorly digestible carbohydrates and other osmotically active nutrients, of which the relevance to humans is minimal [27].

All parent cyclodextrins are accepted as food additives and “generally recognized as safe” (GRAS). As dietary supplement the total daily oral dose of α-CD may reach 6000 mg/day, for β-CD 500 mg/day and for γ-CD 10 000 mg/day, and for HP-β-CD as oral pharmaceutical 8000 mg/day [22]. Preclinically, oral NOELs after a year of HP-β-CD are 500 mg/kg/day for rats and 1000 mg/kg/day for dogs [12]. Oral NOAELs of SBE-β-CD in rats and dogs after 3 months are both 3600 mg/kg/day [27]. RM-β-CD has no oral application.

Conclusion

The oral availability of cyclodextrins is very low. Adverse interactions with vitamins or other nutrients are not to be expected with the parent cyclodextrins. At high doses (> 1000 mg/kg/day) cyclodextrins may cause reversible diarrhea and cecal enlargement in animals, and therefore also in humans to some small extent. There are no data on children under two years old.

2.2. Nasal and pulmonary products

Kinetics

Cyclodextrins at high doses can increase drug permeability by direct action on mucosal membranes and enhance drug absorption and/or bioavailability. These effects are possibly caused by solubilisation of membrane lipids through inclusion complexation with cyclodextrins and the ability of cyclodextrins to cause perturbation of membrane integrity. However, unlike detergents, cyclodextrins solubilize membrane components without entering into the membrane, therefor the perturbing effects of cyclodextrins are mild and reversible [6]. Cyclodextrins are absorbed poorly via mucosal membranes, but at the higher concentrations necessary to achieve substantial permeation enhancement of drugs, cyclodextrins may facilitate also their own absorption. For instance, when 80 mM DM-β-CD (dimethyl-β-cyclodextrin, not in pharmaceutical products) was administered nasally to rats, a relatively high amount of 16% of DM-β-CD was recovered in the urine [18].

HP-β-CD has not a substantial effect on the nasal permeability, but it potentiates strongly the lipophilic absorption enhancer HPE-101 in making the cyclodextrins and drugs bioavailable. In rats 45% of HP-β-CD was absorbed via the nasal cavity when combined with HPE-101 against 3% without the combination [18].

Nasal administration of highly water-soluble cyclodextrins complexes of steroid hormones provides a rapid rise of drug levels in systemic circulation, avoiding intestinal and hepatic first-pass metabolism of the drugs. The effects of cyclodextrins on the nasal epithelial membranes seem to be of minor importance for the absorption enhancement, because cyclodextrins would lose their abilities to interact with the membranes when their cavities are occupied with the steroids [18].

Cyclodextrins improve the pulmonary delivery of drugs, but are also absorbed themselves. When β-CD, RM-β-CD, or HP-β-CD was administered intratracheally in rabbits, the bioavailability of the cyclodextrins was 66%, 74%, and 80% respectively [18].

Safety

With a 5 min exposure of CD solutions to the nasal mucosa of rats, no tissue damage was visible for 1.5% β-CD and 5 and 20% HP-β-CD. However, 20% RM-β-CD showed severe damage of nasal mucosa. Exposures of 30 or 60 min to 10% HP-β-CD or RM-β-CD resulted in no obvious mucosal damage. In addition, in vivo repeated dosing of RM-β-CD did not show any toxicity up to 20%. These results suggest that at least, less than 10% cyclodextrins solutions do not induce gross tissue damage and can keep the histological integrity of the nasal mucosa [3].

The twice daily administration during one month of a nasal spray containing oestradiol and progesterone solubilized by 6.2% RM-β-CD was well tolerated in patients [18].

An excellent tolerance of HP-β-CD by nasal mucosa was shown in irritation studies with rabbits that did not show any local or systemic toxic effects from nasal administration for 3 months of a maximum applicable volume of 10% HP-β-CD. The nasal administration of an antirhinovirus drug with HP-β-CD at doses of 2.4 g HP-β-CD for 4 days caused no significant changes in haematological and biological measures in human volunteers [18].

Conclusion

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. Also, they strongly can 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.

2.3. Rectal products

Kinetics

When oleaginous suppositories containing β-CD, RM-β-CD, or HP-β-CD were inserted into rat rectums, considerable amounts of intact HP-β-CD or RM-β-CD were excreted into the urine up to 24 h after administration. Moreover, when β-CDs were co-administered in vivo with ethyl 4-biphenylyl acetate (EBA, an anti-inflammatory prodrug), rather high amounts of HP-β-CD (> 26% of dose) and RM-β-CD (> 21% of dose) compared with β-CD (> 5% of dose) were absorbed from the rat rectum [2]. The relatively high absorption observed for β-CD derivatives is ascribed to a change in permeability of the rectal mucosa and/or the interaction between the surface active β-CDs and glycerides, which are principal components of the suppository bases. Cyclodextrins can act as rectal absorption enhancers [18].

Safety

β-CD has been used as a solubiliser for diazepam or naproxen in micro-enemas, thereby enhancing the rate of rectal absorption of each drug in human volunteers. None of the volunteers reported any irritation associated with the micro-enemas, even at the highest amount of β-CD (230 mg). Primary rectal irritation was compared between polyethylene glycol suppositories and oleaginous suppositories containing 12% HP-β-CD in rabbits. Polyethylene glycol suppositories caused severe irritation with erosion of the rectal mucosa, but no detectable irritation on the mucosa could be observed for the HP-β-CD containing suppositories [18].

In contrast, the irritating effects of cyclodextrins on rectal mucosa and the potential for systemic absorption of pathogenic substances and the cyclodextrins themselves need to be considered when

using cyclodextrins as rectal absorption enhancers. RM-β-CD is reported to enhance the rectal absorption of insulin from the hollow-type oleaginous suppository in rabbits. This formulation seems to be mildly irritating to the rectal mucosa as indicated by the fact that the hyper permeable state of the rectal mucosa mediated by RM-β-CD returned to a normal physiological level within 24hrs after rectal administration. Studies have shown that a combination of α-CD and xanthan gum, a viscosity-enhancing polymer, is effective in improving the rectal absorption of morphine from hollow-type suppositories in rabbits. The ability of α-CD to increase the trans-epithelial conductance of rectal mucosa suggests that α-CD potentially causes damage to the epithelial cell layer. This damage is confirmed by histological evaluation in which the morphine suppository containing α-CD caused partial degeneration and desquamation in the mucous epithelium and slight cellular infiltration in the lamina propia, which was probably due to the rapid transfer of an excess amount of the cyclodextrins to the rectal mucosa. Favourably, the combination of α-CD with xanthan gum resulted in the sustained release of the CD as well as the opioid from the suppository, and hence made it less irritating to the rectal mucosa [18].

Conclusion

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.

2.4. Dermal products

Kinetics

Cyclodextrins are poorly absorbed transdermally by themselves. When HP-β-CD in an aqueous solution was applied to the skin of hairless mice, its percutaneous absorption was extremely low at 0.02% of the amount applied 24 hours after topical application. In contrast, when cyclodextrins are applied under the occlusive dressing conditions and/or with vehicles containing absorption-promoting agents, they are able to permeate the skin. When hydrophilic ointment containing complexes of the prodrug EBA and β-CDs were applied to the skin of rats under occlusive conditions, significant amounts of cyclodextrins were lost from the vehicle into the skin in the order β-CD < RM-β-CD < HP-β-CD, a sequence that corresponds to the order of the enhancement of EBA release. The percentages of the cyclodextrins remaining in the vehicle 24 h after the application were 88%, 57%, and 47% for β-CD, RM-β-CD, and HP-β-CD, respectively [20,18].

In cosmetic preparations, the use of surfactants as a solubiliser sometimes meets with several drawbacks, such as cutaneous irritation, cloudiness of the preparation, and foaming. HP-β-CD has a significant advantage over the surfactants with respect to solubilizing fragrance materials and retaining them at the skin surface. When compared with existing cosmetics, HP-β-CD-containing cosmetics sustain a scent for a prolonged period of time [18].

Safety

Cyclodextrins may interact with some components of the skin. For instance, DM-β-CD is known to extract cholesterol and triglyceride from powdered hide and from rabbit skin in vitro, a process that may reduce the function of skin as a barrier and eventually may contribute in part to the enhancement of drug absorption. In such a case, particular attention should be directed toward the possible irritation effects of cyclodextrins on the skin. Some studies have demonstrated that the parent cyclodextrins at

sufficiently higher concentrations caused skin irritation in guinea pigs in the order γ-CD < α-CD < β-CD, a result that depends largely on the abilities of the cyclodextrins to extract lipids from the skin [18]. By means of different independent in vitro tests could be confirmed that α-, β- and γ-cyclodextrins in concentrations up to 0.1% (w/v) do not show any antiproliferative influence on HaCaT keratinocytes. It could be confirmed that β-CD and RM-β-CD trigger the activity of the effectors caspases -3 and -7. A significant increase of LDH release could be found for β-CD and RM-β-CD in concentrations of 0.5 and 1% (w/v). The calculated cytotoxicity amounted 45 and 79%, respectively [17].

Studies in human volunteers have shown that cyclodextrins have a significant safety margin in dermal application, in which cyclodextrins in water or vaseline were applied on the skin for 24hrs and their effects on cutaneous microcirculation were evaluated by laser Doppler velocimetry. Moreover, β-CD is proven not to induce either irritation or allergic contact dermatitis as evaluated by a repeated insult occlusive patch test in human volunteers. 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 [18].

Conclusion

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.

2.5. Ocular products

Kinetics

Cyclodextrins increase the water solubility of the drug, enhance drug absorption into the eye, improve aqueous stability and reduce local irritation. Cyclodextrins enhance drug penetration into the eye by carrying the lipophilic water-insoluble drug molecules through the aqueous mucin layer and thereby increasing drug availability at the lipophilic eye surface [21]. Alpha-CD might be able to mediate the drug transport through the layers of the cornea. Also, α-CD might interfere directly with membrane structures, especially with the lipoidal epithelial cell layers causing some kind of barrier destabilization, resulting in an enhanced permeability for itself and the drug molecule [26].

Safety

Alpha-CD has been used to solubilize cyclosporin, an immunosuppressive agent, in an ophthalmic solution where α-CD at concentrations > 4% caused superficial epithelial toxicity, such as loss of microvilli and microerosion in the cornea of rabbits. Ocular administration of RM-β-CD at concentrations of 5 and 12.5% was irritating to the conjunctival and corneal surface of rabbit eyes, whereas HP-β-CD even at a concentration of 12.5% was well tolerated. However, according to Cyclodextrin News [7] there is one ocular product which contains RM-β-CD (Clorocil, Oftalder, Poland). Studies have shown that 10% SBE-β-CD did not cause any significant damage to bovine corneal epithelium in vitro and was equally well tolerated in the case of rabbit eyes in vivo [18]. SBE-β-CD caused no toxicological findings after 6 months of ocular exposure to 25 mg/day in rabbits and after 52 weeks in dogs [27].

Conclusion

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.

2.6. Parenteral products

Kinetics

IV-administered cyclodextrins disappear rapidly from systemic circulation and are renally excreted intact. Systemically absorbed cyclodextrins distribute mainly in the extracellular compartments, and no deep compartments or storage pools are involved. The total plasma clearance for HP-β-CD and SBE-β-CD in all species tested is similar to the glomerular filtration rate. The t½ varies from 20 to 100 minutes. Only RM-β-CD has a longer t½ compared to other cyclodextrins derivatives (7h), probably related to its ability to interact with cellular membranes [27].

Safety

Both α-CD and β-CD showed renal toxicity after parenteral administration and thus are generally not suitable for medicinal products given intravenously. Besides, β-CD has the additional disadvantage of an inherent low solubility, which makes it less suitable for medicines given parenterally [27]. However, one IV-product containing α-CD is on the market in Japan (Prostandin 500, Ono).

The intravenous administration of 2000 mg/kg/day of γ-CD to rats for 1 month caused a slight impairment of the renal function. At 600 mg/kg/day for 3 months, this was only seen in the males. Vacuolization showed in the renal tubular epithelium of some rats receiving γ-CD at doses of 630 or 600 mg/kg/day in the 1- and 3-month study, respectively. However, degenerative changes were not observed in the kidneys, and the vacuolization was fully reversible on cessation of the treatment [9]. No medicinal products with γ-CD for intravenous administration are used at the moment in Europe.

The effective intravenous dose of RM-β-CD to induce kidney damage in animals is even lower than that of β-CD, therefore, this modified CD is also not suitable for parenteral use [22].

HP-β-CD and SBE-β-CD can be found in marketed parenteral formulations with intravenous dosing of up to 16 g HP-β-CD daily in e.g. products with itraconazole and 14 g SBE-β-CD daily in products with voriconazole (in adults). In rats, a daily dose of up to 15,000 mg/kg SBE-β-CD for 14 days produced only vacuolation of the kidney tubular cells without loss of kidney function. Longer treatments caused these, mostly reversible effects, at lower doses of SBE-β-CD and HP-β-CD [18,27], indicating that duration of exposure may be an important parameter. The tubular vacuolation observed in the kidney is the result of a series of alterations in vacuolar organelles of the proximal tubule. These changes begin as an increase in size of apical vacuoles that is followed by the appearance of giant lysosomes. A 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 [10,8]. The NOEL in the rat is 50 mg/kg for HP-β-CD receiving daily IV injections for 3 months and 80 mg/kg for SBE-β-CD daily IV injections for 1 month, respectively [12,27]. In humans, no side effects were observed after parenteral administration of up to 24 g of HP-β-CD daily for 15 days [22]. HP-β-CD and SBE-β-CD are considered safe at relatively high doses and used most widely in parenteral products. Amounts of ca 250 mg/kg/day for 21 days (HP-β-CD) or 6 months (SBE-β-CD) are found safe in humans older than 2 years.

However, these products are not indicated for new-born babies and infants under 2 years old, and for patients with renal impairment, because of insufficient toxicological knowledge in juveniles, and

accumulation of cyclodextrins in the kidney at renal impairment (SmPCs Vfend, Vibativ and Sporanox). The major concern in children under 2 years old is the risk of osmotic nephrosis, because they have a lower renal function than adults. Based on ontogeny the lower glomerular filtration rate in young infants can lead to higher blood levels of cyclodextrins, leading to an increase in extra-renal adverse effects. The decreased renal tubular function might reduce the risk of renal toxicity due to lower intra-renal osmotic pressure. However, it is currently not known whether there is a risk of ontogeny-related direct tubular cell toxicity unrelated to osmotic pressure (Dr. H. van den Berg, paediatrician, personal communication). A small number of neonates treated with SBE-β-CD containing products corresponding with up to 336 mg/kg/day for 18 to 24 days did not show significant toxicity [23,11,29,25]. Two children of 5 years of age treated for Niemann-Pick Type C disease received 2500 mg/kg HP-β-CD intravenously twice weekly for more than one year, which was well tolerated [16]. Treatment of infants from 7 months up to 5 years of age with HP-β-CD containing products caused no harmful effects at 100 mg/kg/day HP-β-CD given single dose or for a few days [1,13].

Conclusion

IV-administered cyclodextrins 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.

Alpha-CD, β-CD and RM-β-CD showed renal toxicity at relatively low doses after parenteral administration and thus are not suitable for medicinal products given intravenously. High doses of ≥600 mg/kg of γ-CD showed only reversible vacuolation in the renal tubular epithelium of rats.

HP-β-CD and SBE-β-CD at high doses can cause vacuolation of the kidney tubular cells without loss of kidney function in animals. 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. 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. 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). Because of their lower renal function, children less than 2 years old may theoretically be less vulnerable to renal toxicity, whereas it is likely to lead to higher blood levels (slower elimination). However, a few cases on the use of intravenous products with high doses of HP-β-CD and SBE-β-CD in neonates and young children have been reported without signs of toxicity.

3. Risk assessment and thresholds

In order to find indications for the thresholds of triggering labelling, including quantitative information and safety statements in the package leaflet, the Permitted Daily Exposures (PDEs) are calculated according to the Guideline for Residual Solvents (CPMP/ICH/283/95) [14], see tables 2, 3 and 4. The calculations are based on estimations of no observed adverse effect levels (NOAELs) derived from the literature referred to in section 2. A complicating factor is that not all studies have been performed with the cyclodextrins only and that the cyclodextrins may have influenced the effects of the active substance of a medicinal product. For example the nephrotoxic effect of telavancin is substantially reduced by HP-β-CD (EPAR Vibativ), and bioavailability and permeability of active substances may be increased by cyclodextrins (section 2). However, since there are no data where cyclodextrins increase the toxic effects of active substances, the estimated NOAELs given below are considered reasonable, with or without active substances. The safe treatment time is considered to be at least 3 weeks, but presumably much longer.

Table 2: Oral PDEs of cyclodextrins in different species

Oral	α-CD	β-CD	γ-CD	HP-β-CD	HP-β-CD	HP-β-CD	SBE-β-CD	SBE-β-CD
Species	human	human	human	rat	dog	human	rat	dog
NOAEL, mg/kg/day	120	10	200	500	1000	160	3600	3600
F1	1	1	1	5	2	1	5	2
F2	1	1	1	10	10	1	10	10
F3	1	1	1	1	5	1	5	10
F4 = F5 = 1								
PDE, mg/kg/day	**120**	**10**	**200**	**10**	**10**	**160**	**14,4**	**18**

Bodyweight human = 50 kg
F1 = A factor to account for extrapolation between species
F2 = A factor of 10 to account for variability between individuals
F3 = A variable factor to account for toxicity studies of short-term exposure
F4 = A factor that may be applied in cases of severe toxicity
F5 = A variable factor that may be applied if the no-effect level was not established

Table 3: Parenteral PDEs of cyclodextrins in different species

Parenteral	α-CD	γ-CD	HP-β-CD	HP-β-CD	SBE-β-CD	SBE-β-CD
Species	rat	rat	rat	human	rat	human
NOAEL, mg/kg/day	100	200	50	320	80	280
F1	5	5	5	1	5	1
F2	10	10	10	1	10	1
F3	10	5	5	1	5	1
F4 = F5 = 1						
PDE mg/kg/day	**0,2**	**0,8**	**0,2**	**320**	**0,32**	**280**

Remark the difference between the calculated PDEs and established safe human use of parental administered HP-β-CD and SBE-β-CD: 10 to 1000 times! Very probably, the calculated PDEs are large overestimations of risk.

But because of insufficient data, it is still suggested to introduce an extra safety factor of 10 for new-born babies and infants below 2 years.

Data on nasal, rectal, dermal and ocular routes are mostly given in percentage, therefore the concerning PDEs could not be calculated. Because of the relatively small amounts and penetration of cyclodextrins in these types of products, there is no concern for systemic concentrations which could have nephrotoxic effects. However, cyclodextrins can show effects on tissue, so also for these products a warning may be warranted. As a starting point, the usual safety factor of 10 has been used. No data were found on dermal toxicity, but because of the properties of cyclodextrins, one can assume that a concentration below 1% will be safe.

Based on human data, and where these are not available, estimations based on animal data, table 4 shows suggested thresholds of triggering safety statements.

Table 4: Suggested thresholds (TH) above which adverse effects may occur

CD / route	α-CD	β-CD	γ-CD	RM-β-CD	HP-β-CD / SBE-β-CD[1]
Oral tox					
PDE, mg / kg / day	120	10	200	N	160
TH adult	120	10	200	-	160
TH neonate	12	1	20	-	16
Nasal					
Safe solution, %	N	1.5	N	10	10
TH adult	-	1.5	-	10	10
TH neonate	-	0.15	-	1	1
Rectal					
Safe amount, mg / kg / day or %	N	5	N	N	12%
TH adult	-	5	-	-	12%
TH neonate	-	0.5	-	-	1.2%
Dermal					
Safe amount, %	N	±0.1	±0.1	N	±0.1
TH adult	-	0.1	0.1	-	0.1
TH neonate	-	0.01	0.01	-	0.01
Ocular					
Safe solution, %	<4	±1	N	<5	10
TH adult	1	1	-	1	10
TH neonate	0.1	0.1	-	0.1	1
Parenteral					
PDE, mg / kg / day	0.2	N	0.8	N	300
TH adult	0.2	-	0.8	-	300
TH neonate	0.02	-	0.08	-	10

Yellow: used in medicinal products
N: No data and indication for respective route of administration.
±1: Estimation based on properties.
[1] Although the molecular weights of HP-β-CD and SBE-βCD differ ca. 1.5 times, they can be taken together from a property- and toxicological point of view.

4. Recommendations for the guideline

Cyclodextrins are currently not included in the European Commission Guideline on excipients in the label and package leaflet of medicinal products for human use [15].

Although the oral availability of cyclodextrins is very low, high doses may cause reversible diarrhea and cecal enlargement in animals, and therefore also in humans to some minimum extent.

Depending on the amount, cyclodextrins may influence the permeability of tissues and therefore the bioavailability of active substances given topically (nasal, rectal, dermal, ocular).

Cyclodextrins can cause nephrotoxic effects in animals at high systemic exposure. Up to now, there is no proof of these effects in humans; however, data in children less than 2 years old are scarce.

In conclusion, safety information in the package leaflet may be desirable in products with substantial contents of cyclodextrins as excipient. However, because of limited information and possible interaction with active substances, the presence of cyclodextrins should always be stated as a precaution (zero thresholds).

4.1. Current information in the package leaflet (2003 Guideline)

None.

4.2. Proposal for information in the package leaflet

Name	Route of Administration	Threshold* mg/kg/day or %	Information for the Package Leaflet	Comments (for health care professionals)
Cyclodextrins **eg.** **α-cyclodextrin** **β-cyclodextrin** **γ-cyclodextrin** **Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD)** **Hydroxy-propyl-β-cyclodextrin (HP-ß-CD)** **Randomly methylated β-cyclodextrin (RM-β-CD)**	All routes of administration	zero	The amount of cyclodextrin in each <volume/unit> is xx mg. Talk to your doctor or pharmacist before giving this medicine to your child if he/she is less than 2 years as the cyclodextrin contained in this medicine might cause undesirable effects. The presence of cyclodextrin in this medicine may alter the effects of other medicines.	Low doses of cyclodextrins are not expected to cause adverse effects. However, there is insufficient information on children less than 2 years. The interactions of cyclodextrin should be stated and documented in the SmPC section 4.5.
	Oral	zero	*As above and:* May cause intestinal disorders like diarrhoea.	At high dose (> 1000 mg/kg/day) cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals.
	Parenteral	zero	*As above (in "all routes of administration") and:* Before taking this medicine, talk to your doctor if you have a kidney disease.	At high dose (> 50-300 mg/kg/day) cyclodextrins can cause renal toxicity in animals when given intravenously. In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of

Name	Route of Administration	Threshold* mg/kg/day or %	Information for the Package Leaflet	Comments (for health care professionals)
				cyclodextrins which may lead to extra-renal adverse effects. In patients with moderate to severe renal dysfunction accumulation of cyclodextrins occurs. So far, there are no cases of kidney injury caused by cyclodextrins in humans.
	Ocular, dermal, rectal, nasal	zero	*As above (in "all routes of administration") and:* May cause irritation.	At high concentration (>> 1%) cyclodextrins can be toxic to the corneal epithelium of rabbits. At high concentration (>> 0.1%) cyclodextrins may cause damage to the skin. At high doses (>> 5 mg/kg) cyclodextrins may cause damage to the rectal mucous epithelium. At high concentration (> 10%) cyclodextrins can cause damage to the nasal mucosa of rats.

Note:

* The threshold is a value, equal to or above which it is necessary to provide the information stated for the package leaflet. This threshold is not a highest acceptable limit. A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product [15].

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