CYCLODEXTRIN NEWS
VOLUME 29. No. 5. MAY 2015 ISSN 0951-256X

EMA Review on Cyclodextrins 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) the European Medicines Agency (EMA) published an evaluation on cyclodextrins as pharmaceutical excipients [1]. The toxicology data are summarized according to the administration routes and the safety threshold values are established. These data might be useful for those developing cyclodextrin-based pharmaceutical formulations.

In the introduction the medicinal products containing CDs are overviewed (citing also the 02/2013 issue of *Cyclodextrin News* on the approved pharmaceutical products containing cyclodextrins [2]). The following CDs are compared: α-, β- and γCD, HPBCD, SBEBCD and RAMEB. Concerning the administration routes HPBCD is the most versatile used in oral, rectal, dermal, ocular and parenteral formulations. The only marketed nasal formulation is with RAMEB. The αCD is applied only for parenteral route (excipient in prostaglandin E1 infusion), while γCD is for oral and dermal formulations and SBEBCD is for oral and parenteral routes.

Concerning the kinetic/toxicological data and clinical safety the various administration routes are discussed separately.

The low ***oral*** bioavailability is the basis of the safety of CDs. Adverse effects (diarrhea, cecal enlargement) can be observed only at high doses (>1000 mg/kg). The total daily oral dose of α-, β- and γCD as dietary supplement may reach 6000 mg/day, 500 mg/day and 10 000 mg/day, respectively, and for HPBCD this value is 8000 mg/day as oral pharmaceutical [3].

Dimethyl βCD (DIMEB) facilitates the drug absorption through ***nasal*** mucosa. In animal experiments at higher doses DIMEB was detected in urine [4]. HPBCD has no absorption enhancing effect, its absorption, however, is highly improved by commercial absorption enhancer HPE-101. While βCD and HPBCD are harmless even at high concentrations (1.5% and 20%, resp.), RAMEB at 20% level caused severe damage of nasal mucosa.

CDs (βCD, RAMEB, HPBCD) are absorbed when administered ***pulmonary***: the bioavailability was 66%, 74% and 80%, respectively [4].

βCD, RAMEB and HPBCD are absorbed from the rat rectum due to their interaction with the lipid components of the ***rectal*** mucosa [5]. RAMEB and αCD caused reversible damage at higher concentrations.

CDs themselves are poorly absorbed through the skin, but from formulations containing absorption enhancer there might be significant ***dermal*** absorption at least into the skin. Up to

0.1% no harmful effects were observed in HaCaT keratinocytes, while at 0.5% and 1% level significant cytotoxicity was observed in the order of RAMEB > βCD > HPBCD > αCD > (γCD) [6].

In ***ocular*** delivery CDs enhance the absorption of drugs through the aqueous mucin layer, αCD through the layers of cornea, too. Also, αCD was found to interact with the membrane components, destabilize it this way increasing its own permeability [7]. Concentrations of 4% αCD and 5% RAMEB can be toxic to the corneal epithelium of rabbits. Solutions of 10% SBEBCD and 12.5% HPBCD were found not to be toxic or irritating in rabbit eyes [1].

The fate of the ***parenterally*** administered CDs is summarized by EMA as follows:

IV-administered cyclodextrins disappear rapidly from systemic circulation and are renally excreted intact. The $t_{½}$ varies from 20 to 100 minutes. Only RAMEB has a longer $t_{½}$ compared to other cyclodextrins derivatives (7h), probably related to its ability to interact with cellular membranes.

Among the parent CDs both α- and βCD show renal toxicity, while γCD is harmless up to 600 mg/kg. In spite of its safety no medicinal products with γCD for intraveneous administration are used. Similarly to α- and βCD, RAMEB is not suitable for parenteral application because of kidney damage. HPBCD and SBEBCD are considered safe at relatively high doses (250 mg/kg/day for 21 days and 6 months, respectively). They are, however, not recommended for new born babies and patients with renal impairment.

Based on the NOAEL data (no adverse effect concentration) the Permitted Daily Dose (PDE) values were calculated. Unfortunately not all the necessary data are available as a lot of experiments were performed with not the pure CDs but their complexes. As there are no data where CDs enhance the toxic effects of active substances, the data with or without active substances were considered. For treatment duration, at least a 3-week period was calculated.

The PDE values are summarized below.

Table 1. PDE (mg/kg/day) or safe amount (mg/kg/day or %) values above which adverse effects may occur

CD/route	αCD	βCD	γCD	RAMEB	HPBCD/SBE-BCD
oral	120	10	200	no data	160
nasal	no data	1.5	no data	10	10
rectal	no data	5	no data	no data	12%
dermal	no data	±0.1%	±0.1%	no data	±0.1%
ocular	<4%	±1%	no data	<5%	10%
parenteral	0.2	no data	0.8	no data	300

± means estimation based on properties

For neonates (newborn babies and infants below 2) PDE or safe amount values were calculated by dividing the data in Table 1 by an extra safety factor of 10.

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Antidepressant, βCD, γCD

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Voglibose, Post-meal blood glucose lowering effect, αCD

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γ-CD, HP-γ-CD, Minimum inhibitory concentration

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Kneading, Coevaporation, Phase solubility

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Intracerebroventicular injection, HP-γ-CD, Higher biocompatibility, Wider safety margin

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Jono, H.; Inoue, M.; Fujisawa, K.; Hayashi, Y.; Anno, T.; Motoyama, K.; Ando, Y.; Arima, H.

Novel cyclodextrin-based therapeutic approaches for refractory Amyloidosis

Amyloid fibrils, Alzheimer's disease, Prion disease, Branched β-CDs, Inhibiting the misfolding of amyloid precursor protein

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Kam, J. H.; Lynch, A.; Begum, R.; Cunea, A.; Jeffery, G.

Topical cyclodextrin reduces amyloid beta and inflammation improving retinal function in ageing mice

Age-related macular degeneration (AMD), 2-Hydroxypropyl-β-cyclodextrin, Retinal pigment epithelium specific protein 65 (RPE65)

Experimental Eye Research, 2015, 135, 59-66; DOI:10.1016/j.exer.2015.03.023

Kimura, S.

2-Hydroxypropyl-β-cyclodextrin acts as a novel anticancer agent

Leukemic cell lines, Reduced intracellular cholesterol, Cell growth inhibition, Leukemia mouse models

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Maeda, Y.; Motoyama, K.; Higashi, T.; Horikoshi, Y.; Takeo, T.; Nakagata, N.; Kurauchi, Y.; Katsuki, H.; Kondo, Y.; Ishitsuka, Y.; Irie, T.; Era, T.; Arima, H.

Effects of Cyclodextrins on GM1-gangliosides in Fibroblasts from GM1-gangliosidosis Patients

Lysosomal storage disorders, Methylated cyclodextrins, Hydoxypropylated cyclodextrins, Branched cyclodextrins

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Montecucco, F.; Lenglet, S.; Carbone, F.; Boero, S.; Pelli, G.; Burger, F.; Roth, A.; Bertolotto, M.; Nencioni, A.; Cea, M.; Dallegri, F.; Fraga-Silva, R. A.; Fougère, L.; Elfakir, C.; Gassner, A.-L.; Rudaz, S.; Parissaux, X.; Wils, D.; Salomé, M.; Vuilleumier, N.; Poggi, A.; Mach, F.

Treatment with KLEPTOSE® CRYSMEB reduces mouse atherogenesis by impacting on lipid profile and Th1 lymphocyte response

Methyl β-cyclodextrin, High-cholesterol diet, Hypercholesterolemia, Reduced triglyceride serum levels, increased HDL-cholesterol levels, Reduced free fatty acids and spleen weight, Atherosclerosis, Inflammation

Vascular Pharmacology, 2015, In Press; DOI:10.1016/j.vph.2015.04.008

Moraes, E.A.; Matos, W.C.G.; Graham, J.K.; Ferrari Jr., W.D.

Cholestanol-loaded-cyclodextrin improves the quality of stallion spermatozoa after cryopreservation

Equine, Motility, Post-thaw, Viability

Animal Reproduction Science, 2015, 158, 19-24; DOI:10.1016/j.anireprosci.2015.04.004

Motoyama, K.; Tanaka, N.; Onodera, R.; Higashi, T.; Arima, H.

Folate-appended methyl-β-cyclodextrin as a novel autophagic cell death inducer

Cholesterol, Phospholipids, DM-β-CD, FR-α overexpressing cell-selective cytotoxic activity, Doxorubicin

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Pulli, I.; Blom, T.; Löf, C.; Magnusson, M.; Rimessi, A.; Pinton, P.; Törnquist, K.

A novel chimeric aequorin fused with caveolin-1 reveals a sphingosine kinase 1-regulated Ca^{2+} microdomain in the caveolar compartment

Methyl-β-cyclodextrin, HeLa cells, Sphingosine-1-phosphate, Plasma membrane

Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, 2015, In Press; DOI:10.1016/j.bbamcr.2015.04.005

Rungrotmongkol, T.

Molecular modelling of flavonoid/cyclodextrin inclusion complexes

MD simulations, 2,6-Dimethyl and hydroxypropyl β-CDs, Permeation behavior of CDs, Drug transport to the membrane

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Takayama, Y.; Nasuno, E.; Iimura, K.; Matsunaga, Y. T.; Kato, N.

Inhibitory effects of fiber gel bundle immobilized with cyclodextrins on prodigiosin production in *Serratia marcescens* AS-1 due to intercepting cell-cell communication

Quorum sensing, N-acylhomoserine lactone, Microfluidic device, Hydroxypropyl cellulose, Immobilize α-CDs with glutaraldehyde

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Tamura, A.; Yui, N.

Polyrotaxane-based intracellular delivery of cyclodextrins for the therapy of intractable diseases

β-CD-threaded biodegradable poyrotaxanes Pluronic P123 and β-CD, (2-Hydroxyethoxy)ethyl groups, NPC1 fibroblasts, Formation of autolysosomes

Joint Conference of 8th Asian Cyclodextrin Conference and 32nd Cyclodextrin Symposium, 2015, Abstract book p. 80

Yamamura, H.

Antimicrobal cyclodextrin bearing polyamino groups for bacterial membrane disruption

Benzyl moieties, Microwave-assisted Huisgen 1,3-dipolar cycloaddition reaction, Click chemistry

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5. CDs in Food, Cosmetics and Agrochemicals

Ho, T. M.; Howes, T.; Bhandari, B. R.

Encapsulation of CO_2 into amorphous and crystalline α-cyclodextrin powders and the characterization of the complexes formed

Pressure, Inclusion complex, Solid encapsulation

Food Chemistry, 2015, 187, 407-415; DOI:10.1016/j.foodchem.2015.04.094

Suzuki, K.; Inoue, Y.; Murata, I.; Yokota, M.; Tokudome, Y.; Knamoto, I.

Examination of physical properties and antioxidative of caffeic acid with γ-cyclodextrin

Freeze-dried, Coprecipitation, Physical mixture, Antioxidant activity

Joint Conference of 8th Asian Cyclodextrin Conference and 32nd Cyclodextrin Symposium, 2015, Abstract book p. 106

Zhang, W.; Li, X.; Yu, T.; Yuan, L.; Rao, G.; Li, D.; Mu, C.

Preparation, physicochemical characterization and release behavior of the inclusion complex of *trans*-anethole and β-cyclodextrin

Food functional ingredient, Co-precipitation method, Phase solubility study

Food Research International, 2015, 74, 55-62; DOI:10.1016/j.foodres.2015.04.029

6. CDs for other Industrial Applications

Komiyama, M.

Cyclodextrins as eminent sources of detailed molecular information leading to precise design of highly advanced materials

β-cyclodextrin-catalyzed hydrolysis of phenyl acetates, Structural change of CD complex

from the initial state to the transition state

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Mallard, I.; Städe, L. W.; Ruellan, S.; Jacobsen, P. A. L.; Larsen, K. L.; Fourmentin, S.

Synthesis, characterization and sorption capacities towards organic pollutants of new β-cyclodextrin modified zeolite derivatives

3-Glycidoxypropyltrimethoxysilane, Toluene, Methyl orange, FIB-SEM-EDX, Adsorption, Remediation

Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2015, 482, 50-57; DOI:10.1016/j.colsurfa.2015.04.014

Mohamed, M. H.; Wilson, L. D.; Headley, J. V.

Tuning the physicochemical properties of β-cyclodextrin based polyurethanes via cross-linking conditions

Hexamethylene diisocyanate, 4,4'-Dicyclohexyl diisocyanate, Phenolphtalein

Microporous and Mesoporous Materials, 2015, 214, 23-31; DOI:10.1016/j.micromeso.2015.04.029

Mosivand, S.; Kazeminezhad, I.

Structural and magnetic characterization of electro-crystallized magnetite nanoparticles under constant current

β-Cyclodextrin as organic stabilizer, Nanostructures, Synthesis, Electron microscopy, Mössbauer spectrometry

Materials Research Bulletin, 2015, 70, 328-335; DOI:10.1016/j.materresbull.2015.04.053

Okano, C.; Nasuno, E.; Iimura, K.-I.; Kato, N.

Suppressive effects of cyclodextrin-immobilized core/shell polymeric microspheres on quorum sensing-dependent antibacterial production

Prodigiosin production in Serratia marcescens, Pyocyanin production in Pseudomonas aeruginosa, N-acylhomoserine lactone, Polystyrene, Poly(methacrylic acid)

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Serio, N.; Levine, M.

Efficient extraction and detection of aromatic toxicants from crude oil and tar balls using multiple cyclodextrin derivatives

Methyl-β-cyclodextrin, β-Cyclodextrin, γ-Cyclodextrin, Fluorescence detection

Marine Pollution Bulletin, 2015, 95, 242-247; DOI:10.1016/j.marpolbul.2015.04.008

Thombal, R. S.; Jadhav, V. H.

Biomass derived β-cyclodextrin-SO_3H carbonaceous solid acid catalyst for catalytic conversion of carbohydrates to 5-hydroxymethylfurfural

Solvents system, Fructose, Glucose, Sucrose, Inulin

Applied Catalysis A: General, 2015, 499, 213-216; DOI:10.1016/j.apcata.2015.04.021

7. CDs in Sensing and Analysis

Kojima, Y.; Egawa, Y.; Miki, R.; Seki, T.

Preparation of a sugar-responsive gel using rotaxane structures as cross-linkers

Phenylboronic acid, N-[3-(dimethylamino)propyl]acrylamide, Sugar-responsive swellable and shrinkable RX gels

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Li, L.; Li, X.; Luo, Q.; You, T.

A comprehensive study of the enantioseparation of chiral drugs by cyclodextrin using capillary electrophoresis combined with theoretical approaches

Carboxymethyl-β-cyclodextrin, β-cyclodextrin, Isothermal titration calorimetry, Nuclear magnetic resonance spectroscopy, Molecular modeling

Talanta, 2015, 142, 28-34; DOI:10.1016/j.talanta.2015.04.039

Nonaka, K.; Yasui, M.; Yamaguchi, M.; Fujiwara, S.; Hashimoto, T.; Hayashita, T.

Guest-induced supramolecular chirality in ditopic azoprobe-cyclodextrin complexes in water

Sensor, twisted stucture

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Seki, T.; Abe, K.; Egawa, Y.; Miki, R.; Juni, K.; Seki, T.

Preparation of a sugar-responsive polypseudorotaxane having a directly sugar-binding sensor

Sugar-responsive insulin release system, Naphthalene-modified polyethylene glycol, γ-Cyclodextrin modified with phenylboronic acid, 3-Carboxy-5-nitrophenylboronic acid

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Zhang, J.; Gan, N.; Chen, S.; Pan, M.; Wu, D.; Cao, Y.

β-cyclodextrin functionalized meso-/macroporous magnetic titanium dioxide adsorbent as extraction material combined with gas chromatography-mass spectrometry for the detection of chlorobenzenes in soil samples

Magnetic solid phase extraction (MSPE), Automated solid-phase extraction, Carboxymethyl-β-cyclodextrin, Matrix interference

Journal of Chromatography A, 2015, 1401, 24-32; DOI:10.1016/j.chroma.2015.04.057

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