

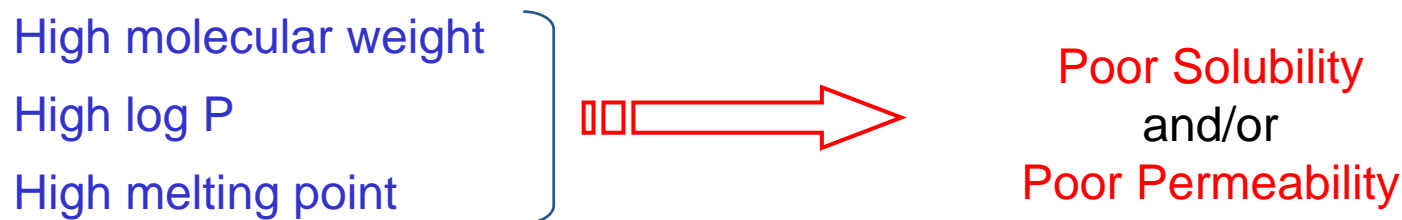
Poorly water soluble substances: challenges, options and limitations for children

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Why increasing numbers of poorly soluble compounds?

Tendency of present drug discovery methodology to produce candidate drugs of increasing molecular size and lipophilicity

- molecular motifs often derived from molecular modelling on reseptor
- molecular motifs derived from natural compounds
- activity screens utilising solutions diluted from DMSO stock
- PK lead optimisation will increase molecular weight



Solubility and permeability major barriers for oral absorption
Both linked to concept 'maximum absorbable dose'

Retrospective analysis of properties producing good or bad absorptive behaviour

Lipinsky's 'Rule of 5'

- based on a retrospective analysis of World Drug Index
- poor intestinal permeability is predicted for compounds exhibiting two or more of following
 - sum of hydrogen-bond donors (OH and NH) > 5
 - sum of hydrogen-bond acceptors (N and O) > 10
 - MW > 500
 - $\log P > 5$
- applies only to passively permeated compounds that are not substrates of gut wall enzymes or active transporters

General formulation approaches for parenteral products of poorly soluble compounds

- Salt form (or pH adjustment/buffering)
- Co-solvents (ethanol, propylene glycol, PEG 400, glycerol)
- Cyclodextrins (hydroxypropyl-, sulfobutyl- β -cyclodextrin or other cyclodextrin derivatives)
- Micellar solubilisation (eg. Cremophor EL/RH 40, Vit-E-TPGS, polysorbates, phospholipids)
- Emulsions (MCT, LCT, phospholipids)
- Liposomes (phospholipids)
- Nanosizing (stabiliser eg albumin, polymer, surfactant)
- Nanoparticles (polymeric micelles, nanosized solid dispersions)

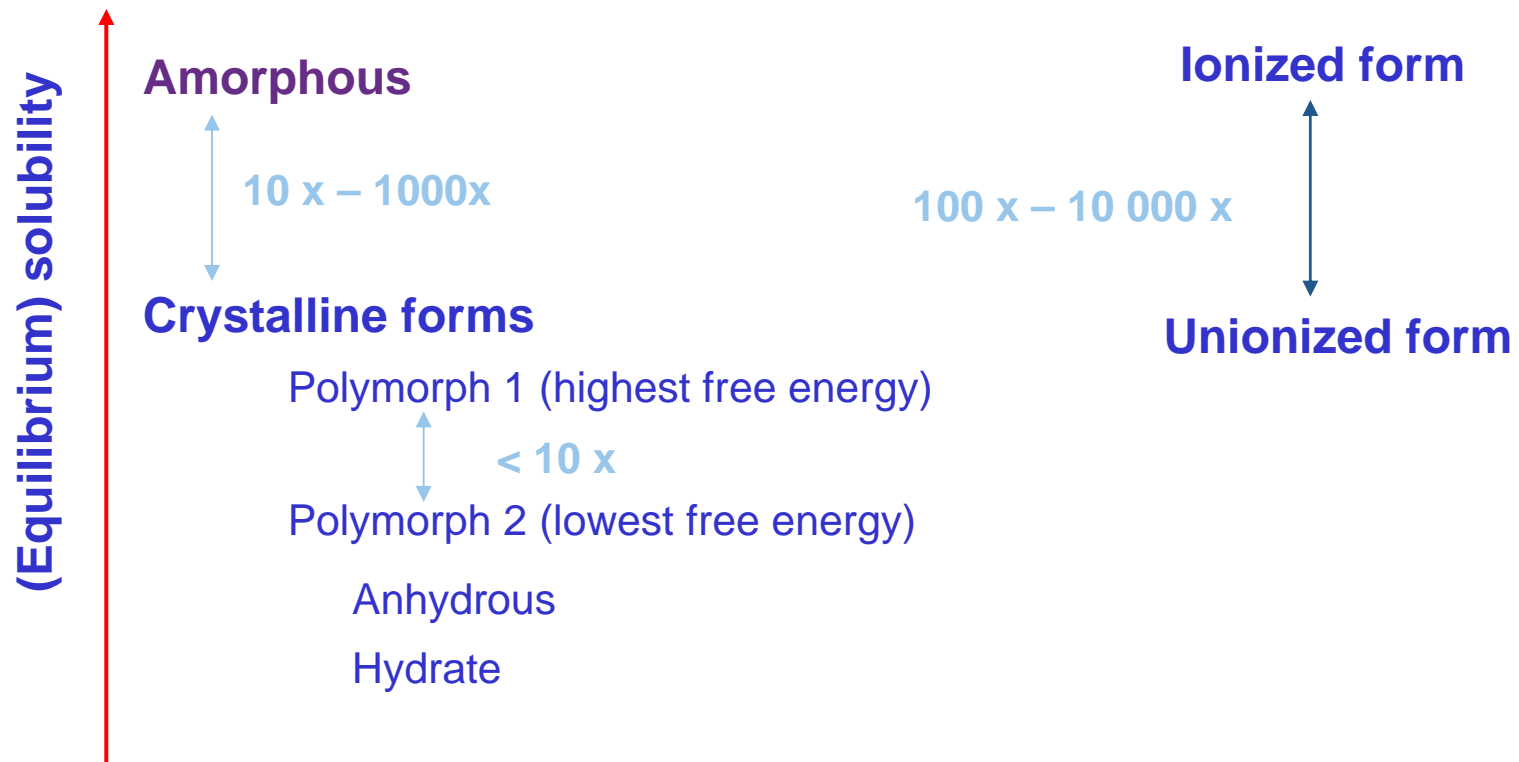
General formulation approaches for oral products of poorly soluble compounds

- Salt form (or pH adjustment/buffering)
- Micronization } + highly soluble excipients
- Nanosizing } and surfactans (wetting, micellar solubilization)
- Cyclodextrins (β - or γ -cyclodextrin, hydroxypropyl-, sulfobutyl ether- β -cyclodextrin, or other cyclodextrin derivatives)
- Co-solvents (ethanol, propylene glycol, PEG 400, glycerol)
- Liquid/Semi-solid lipid formulations (oils, SEDDS, SMEDDS)
- Solid dispersions / co-precipitates (HPMC, PEG, lipid based)
- Nanosizing (stabiliser eg polymer, surfactant)
- Nanoparticles (polymeric micelles, nanosized solid dispersions, SLN)

Solid phase properties vs range of solubility increase

Physical stabilisation of amorphous state?
Chemical stability?
→ Amount and type of excipients needed

Common ion effect (Na, K, HCl)!
Organic salts may be better
(eg choline vs Na upto 4 x)
Toxicity of salt form?
Toxic reactants of salt former?



The fatty food effect → lipid formulations?

Increased solubilization of poorly water-soluble compounds

- slower gastric emptying (lipid chain length dependent; LCT > MCT)
- increased gastric and intestinal secretion (lipid chain length dependent)
 - increased volume
 - increased BS and PL concentration
- digestion products of lipids incorporated into mixed micelles

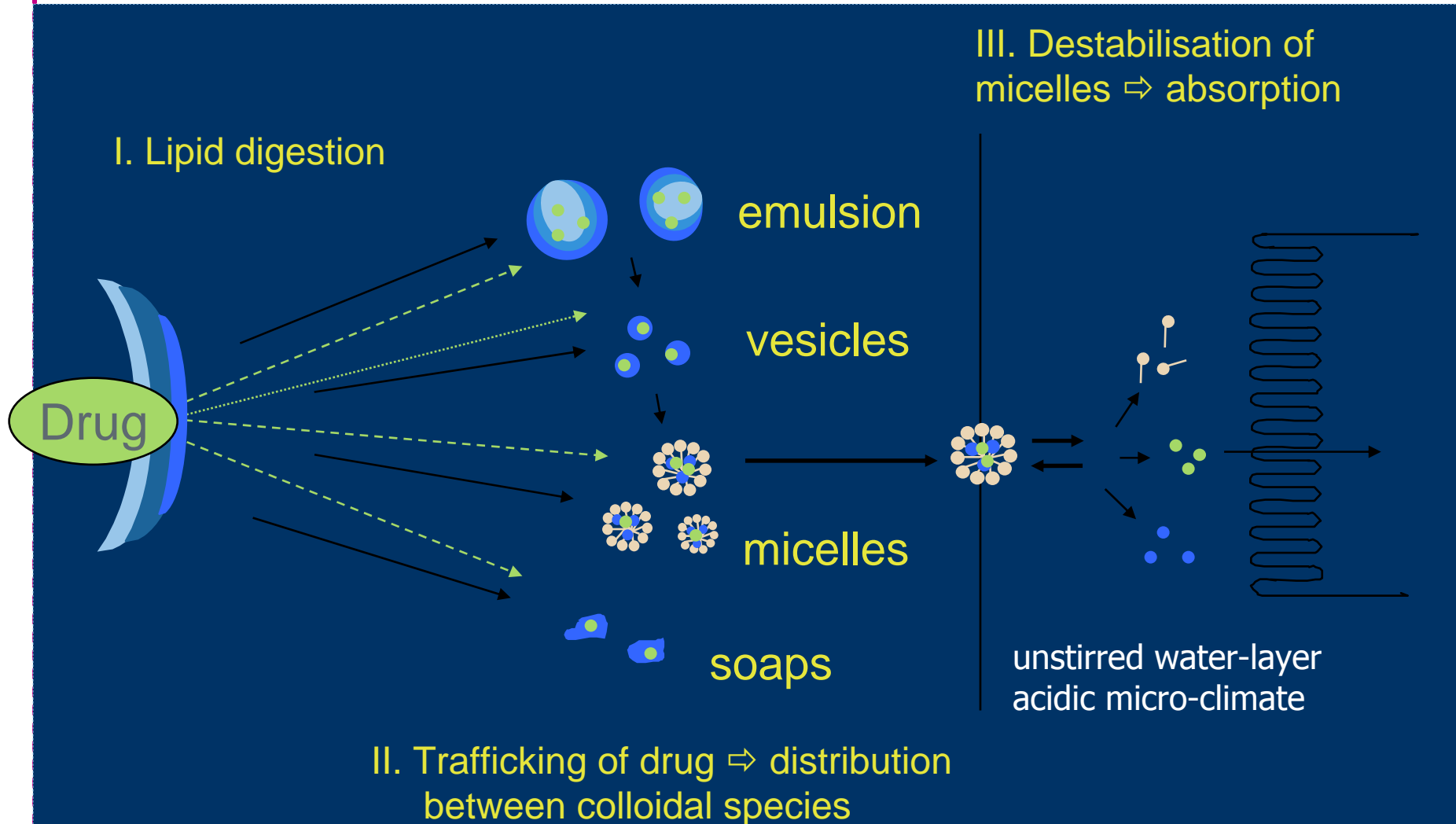
Potential changes to the biochemical barrier function

- effects on P-GP
- effects on intestinal metabolism

Stimulation of intestinal lymphatic transport of lipids

- lipid chain length dependent – LCT more than MCT
- potential absorption pathway for highly lipophilic (lipid soluble) compounds
- high lymphatic transport → potential 'bypass' of intestinal metabolism?

Intestinal Pre-absorptive Processes



Some age specific issues for lipid formulations or drugs with enhanced absorption with fatty food

Lower bile salt levels

- Prematures, neonates and young infants
 - Reduced/slower digestion of lipids, especially long chain
 - Reduced solubilisation capacity in the intestinal media
 - Applies also to other situations where bile function not normal (eg liver transplant patients etc)
- Fed response and intestinal motility pattern not developed/different than in adults

Effects of excipient on barrier properties may be higher

- Relative dose of excipients may be higher than in adults, especially at ages where higher doses of active (mg/kg) used than in adults (2- 6 years)
- Expression levels efflux transporters and metabolic enzymes may be lower
- Use of different type of formulation or different excipient composition may affect BA differently in adults than in children
- Food effect may be different (also other than lipid formulations)

Types of oral lipid formulations and excipients

Formulation type	Materials	Characteristics	Advantages	Limitations
Type I	Oils without surfactants (eg. tri-, di-, and monoglycerides)	Non-dispersing, requires digestion	GRAS, simple, good capsule compatibility	Poor solvent capacity unless drug highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Rather coarse o/w dispersion, digestion likely but not crucial
Type III	Oils, surfactants and co-solvents (both water soluble and insoluble excipients)	SEDDS/SMEDDS formed with water-soluble components	Clear or almost clear dispersion; digestion not necessary for absorption	Possible loss of solvent capacity on dispersion and/or digestion
Type IV	Water-soluble surfactants only or with co-solvents (no oils)	Typically disperses to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity when dispersed; may not be digestible

Potential effects of excipients on intestinal wall

Lipid excipients/ surfactants	Examples	Comments	References
Polyoxyethylated/pegylated			
Polyoxyl 35 caster oil	Cremophor	CYP3A and P-gp inhibitors	[2,31,32,67,68]
PEG-15- hydroxystearate	Solutol HS-15	CYP3A and P-gp inhibitors	[2,67]
Medium chain glycerol and PEG esters	Labrasol, Softigen 767, Acconon	P-gp inhibitor	[2]
Polysorbates	Tween 80, Tween 20	CYP3A and P-gp inhibitors	[2,67,68,69]
Sucrose esters	Sucrose monolaurate	P-gp inhibitor	[2]
Tocopherol esters	Vitamin E-TPGS ^a	P-gp inhibitor	[2,37,68,70]
Polymers	Pluronic block copolymers	CYP3A and P-gp inhibitors	[2,71,72,73]

^a TPGS: D-alpha-tocopheryl polyethylene glycol 1000 succinate.

Problematic co-solvents in parenteral and oral formulations (1)

• Ethanol

- neurotoxic, adverse CNS effects, children below 6 years more susceptible, effects on developing brain! (prematures, neonates, infants)
- exposure should be assessed as potential blood level after ingestion
- CNS effects reported already at 0.01 g/L
- What is a safe level after single dose/over treatment period?
- Existing guidelines not very useful / **cannot be used to set safe levels!**
 - Guideline on Excipients in labeling thresholds:
 - LT 100 mg per dose (reassurance of low level)
 - 100 mg – 3 g per dose; should be converted to volume of beer etc; "To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver-disease, or epilepsy."
 - no differentiation between age groups or route of administration
 - Reflection paper on ethanol content in herbal medicinal products; recommendation that a 0.125 g/L blood ethanol concentration should not be exceeded following a single dose of **herbal medicinal product**

Problematic co-solvents in parenteral and oral formulations (2)

- Propylene glycol

- Alcohol like CNS effects, slower metabolism below 4-5 years, metabolites renally excreted; seizures possible
- May contribute to lactic acidosis and hyperosmolality, (hyperosmolality of formulation also risk in oral dosing for prematures; NEC)
- What is a safe level after single dose/over treatment period?
- Existing guidelines not very useful / **cannot be used to set safe levels!**
 - Guideline on Excipients in labeling thresholds:
 - Oral/parenteral: 200 mg/kg children; may cause alcohol like symptoms
 - Does not differentiate between age groups or route of administration
- WHO ADI upto 25 mg/kg (food additive; oral administration)

- **Case by case evaluation**

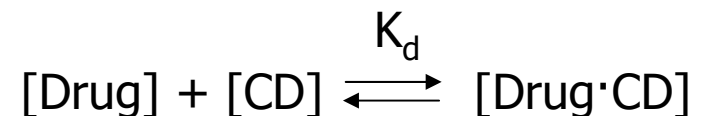
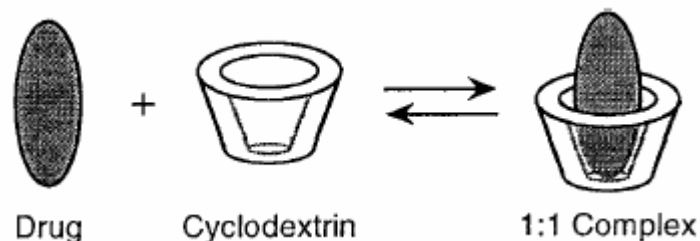
- **PK and safety assessment may be required**

Cyclodextrins as solubilisers of lipophilic compounds

Cyclodextrin cavity lipophilic, thermodynamically favorable to insert lipophilic compound and exclude water molecules

Potential utility in formulation

- increased apparent solubility
- increase of dissolution rate of poorly soluble drug
 - improvement of bioavailability
 - faster onset of action (T_{max} earlier)
- chemical and/or physical stabilisation of drug
- suppression of volatility of drugs with high vapour pressure
- transformation of liquid drugs into solid form
- elimination of incompatibilities
- alleviation of local toxicity
- taste masking

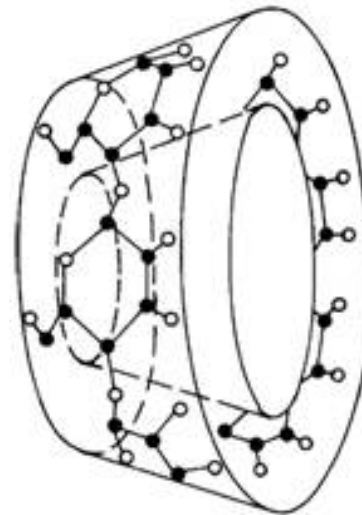
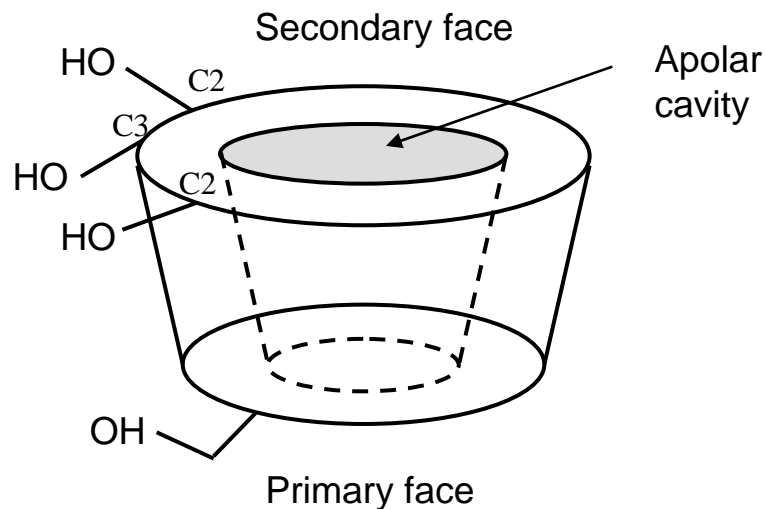


$$K_d = [\text{Drug} \cdot \text{CD}] / [\text{Drug}] [\text{CD}]$$

Cyclodextrin structure

Cyclodextrins form a torus shaped structure where the outer surface is hydrophilic and the cavity hydrophobic

- secondary hydroxyls line wider end of torus
- primary hydroxyls line narrow end of torus
- hydrogen atoms and glycosidic oxygen bridges line inside of cavity
- hydrogen bonding between glycopyranose units via OH-groups in C2 and C3 position → rigid structure, wider opening at secondary face



Regulatory status of cyclodextrins as excipients and food additives

Cyclodextrin	Food Approval			Pharmacopoeia Monographs		
	US	Europe	Japan	USP/NF	Ph.Eur.	JPC
α CD	"GRAS"	Planned	Yes	Yes	Yes	Yes
β CD	"GRAS"	Food Additive	Yes	Yes	Yes	Yes
γ CD	"GRAS"	Pending	Yes	In Progress	In Progress	Yes
HP β CD	-	-	-	In Progress	Yes	-

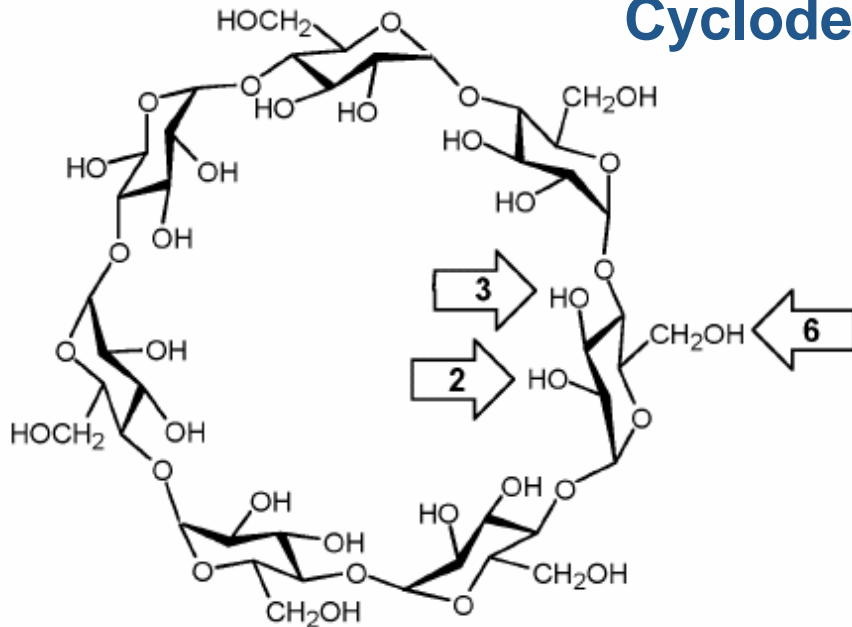
Food additive in Europe: E459 Beta-cyclodextrin (others); ADI 0-5 mg/day/kg bw employed in food as a flavour protecting agent at levels not exceeding 1 g/kg food

WHO: Concerns wrt effects on the absorption of lipid soluble vitamins.
Conclusion that competitive (and preferred) binding to bile salts will ensure that vitamins not be retained in the CD's → implications on oral dosing in prematures and infants with low BS levels?

Characteristics of natural cyclodextrins

	α	β	γ
No of glucose units	6	7	8
Molecular weight	972	1135	1297
Solubility in water (g/100 ml, 25 °C)	14.5	1.85	23.2
Cavity diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
Torus height (Å)	7.9 ± 0.1	7.9 ± 0.1	7.9 ± 0.1
Peripheral diameter (Å)	14.6 ± 0.4	15.4 ± 0.4	17.5 ± 0.4
Appr. volume of cavity (Å ²)	174	262	427
Diffusion constant at 40 °C	3.443	3.223	3.000
pKa (C2 and C3 –OH)	12.33	12.20	12.08
Hydrolysis by α-amylase	negligible	low	rapid

Cyclodextrin derivatives



Aqueous solubility increased by introduction of substituents to OH-groups

Developed to obtain β -cyclodextrins for parenteral delivery with better renal safety profile

Hydroxy propyl β -cyclodextrin (un-ionised)

- average molecular weight 1300-1900, MS = 0.40-1.50

Sulfobutyl ether β -cyclodextrin (ionised) (as Na⁺ -salt)

- average molecular weight 2163, MS = 0.9 (DS ~7 → 7 Na⁺-ions!)

Physiological effects of cyclodextrins

Due to capacity of cyclodextrins to solubilize endogenous lipophilic components

- phospholipids / α -CD
- cholesterol / β -CD and derivatives (parenterals!)
- bile salts / β -CD and derivatives (oral!)

Strong complex formation between cholesterol and β -CD (also 1:2 complexes)

- low solubility of cholesterol : β -CD complexes
- complexes precipitate in kidney during excretion phase of β -CD
→ cause of nephrotoxicity

HP β CD and SBE β CD high aqueous solubility

- low haemolytic effects
- low(er) nephrotoxicity compared to parent β -CD

Reduced renal elimination in infants below 6 – 12 months

- higher sensitivity to renal toxicity
- higher potential for CD-drug interaction with other drugs (in the kidney)

Excipient justification – benefit - risk analysis

EMA/CHMP/SWP/146166/2007 CHMP Scientific Article 5(3) Opinion on the potential of carcinogens, mutagens and substances toxic to reproduction (CMR) when these substances are used as excipients of medicinal products for human use

In addition to CMR toxicity, also a summary on the general justification on the use of excipients and risk-benefit analysis

“Overall, the use of **any excipient** with a **known potential toxicity**, and which **could not be avoided or replaced**, would only be authorised if the safety profile was considered to be clinically acceptable in the conditions of use, taking into account the **duration of treatment**, the **sensitivity of the target population** and the **benefit-risk ratio for the particular therapeutic indication**.”