



The Cyclodextrin Company



Pharmaceutical Applications of Cyclodextrins

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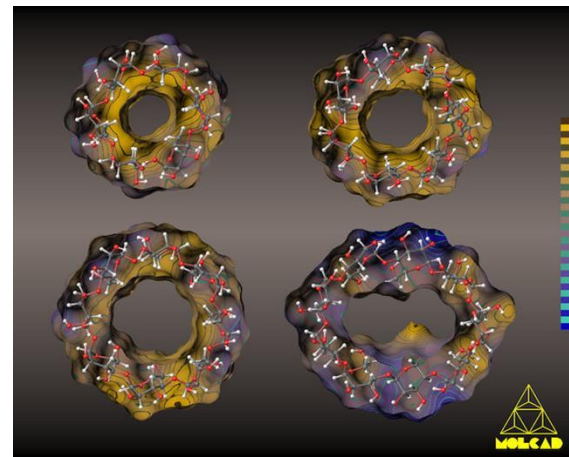
What are cyclodextrins (CDs)?

- Composed of sugars
- Cyclic molecules
- Naturally occurring compounds
- Used in food, pharmaceuticals, drug delivery, chemical industries, agriculture, etc.
- Molecular dimensions of cyclodextrins: **sub-nanometer** sized molecular containers with hydrophilic outer phase and hydrophobic interior properties



Cavity diameters:

α CD 0.57 nm, β CD 0.78 nm, γ CD 0.95 nm, (δ CD 1.3 nm)





History of Pharmaceutical Applications

Traditional Applications

- **CDs as drug complexing agents in drug delivery**
- **Nanosizing, solubilizing, stabilizing, targeting etc.**
- **Summary of results: ~100 marketed products until 2019**

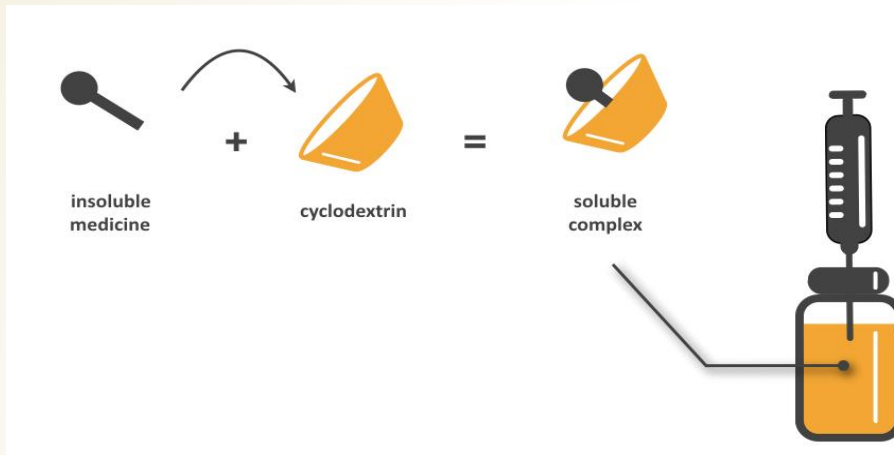
CDs as active ingredients

- **Entrapment of cholesterol : treating Niemann-Pick C disease with HPBCD (FDA Orphan Drug designation 2015)**
- **In clinical anesthesia (Sugammadex/ Bridion®)**



Main functional properties of CDs

- They form **NON-COVALENT** „host-guest” type inclusion complexes in a **reversible** manner (Szejtli,1980)

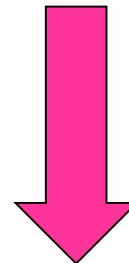


Cyclodextrins may increase:

- *Drug solubility*
- *Wetting, dissolution rate*
- *Drug stability*
- *Absorbed quantity*

Cyclodextrins may decrease:

- *API's dose for same efficacy*
- *Taste*
- *Side effects*
- *Smell*





CDs suitably used in pharmaceuticals

	α -CD	β -CD	γ -CD	HPBCD	SBECD	RAMEB
Oral		X	X	X	X	
Nasal						X
Rectal		X		X		
Dermal		X	X	X		
Ocular		X		X		X
Parenteral	X			X	X	

European Medicinal Agency EMA/CHMP/333892/2013, Committee for Human Medicinal Products (CHMP) Background review for cyclodextrins used as excipients

>84 pharma products on the market containing cyclodextrins



Solubility enhancement of poorly soluble drugs

	<i>Solubility increase using 10 m/m % SBECD vs purified water</i>
Piroxicam	20X
Carbamazepine	36X
Amiodarone	50X
Voriconazole	85X
Delafloxacin	340X
Ziprasidone*HCl	470X
Aripiprazole	3350X
Posaconazole pH 6	20X
Posaconazole pH 3	120X



**Aqueous solubilities: Pubmed database (<https://pubchem.ncbi.nlm.nih.gov>)
solubility in SBECD solutions: Cyclolab results**



Purposes of using CDs other than solubilizing



**Fast onset and IP issues
Omeprazole/BCD/arginine
ternary complex**



**Thiomersal-free,
reduced irritation in
diclofenac stabilized
eye drops**



**Use of CDs to ensure
content uniformity:
low dose units with pre-
diluted-complexed APIs.
Ethinyl estradiol
stabilizes with β CD**

Purposes of using CDs other than solubilizing



**Ulgut (benexate):
masking bitter
taste**



**Masking the
burning taste**



**Masking
bitter taste**



Particle size engineering by Cyclodextrins: A simple way to molecular dispersity (to sub-nanometer size)

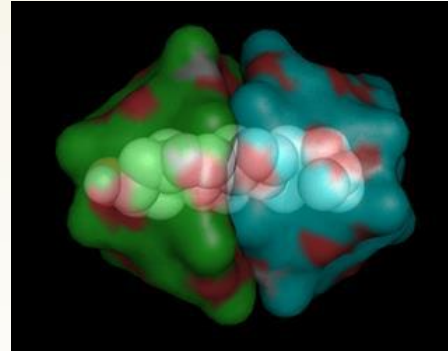
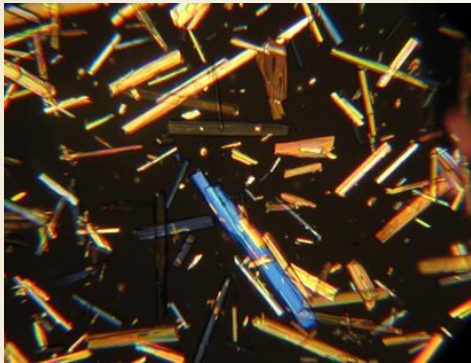
Molecular encapsulation of drugs by CDs results in:

- **Molecular dispersity** (each drug is surrounded by a CD ring)
- **No original crystalline lattice of drug remains (X-ray diffraction and DSC evidences)**
- **Novel solid phase (but **No** New Chemical Entity)**
- **No need to “destroy” crystalline lattice of drug on dissolution**
- **Molecular scale hydrophilic packing around lipophilic drug**
- **Improved wetting and dissolution properties in water**

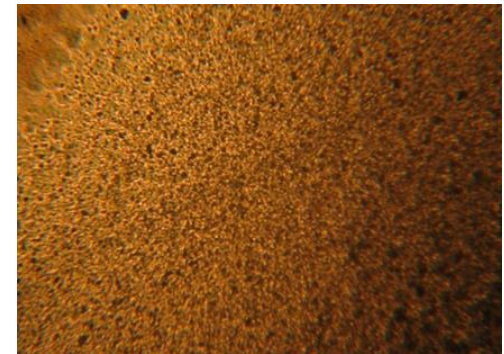


Solid-phase engineering, nanosizing via molecular entrapment

API before cyclodextrin inclusion



API after cyclodextrin inclusion

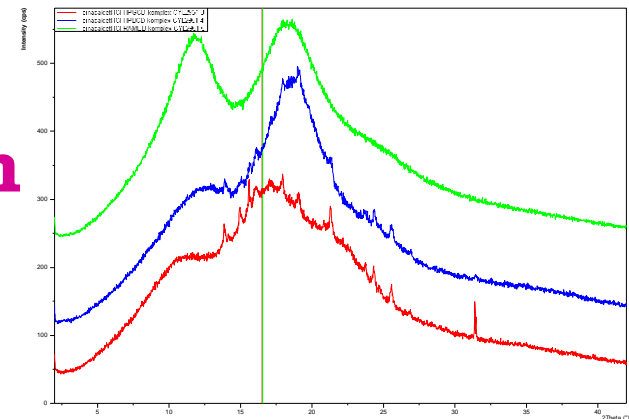
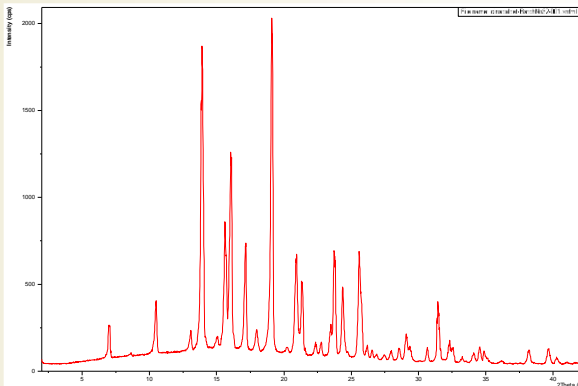


1:2 mol/mol

API-BCD

Inclusion complex

Solid phase transformation





Cyclodextrin protein interactions

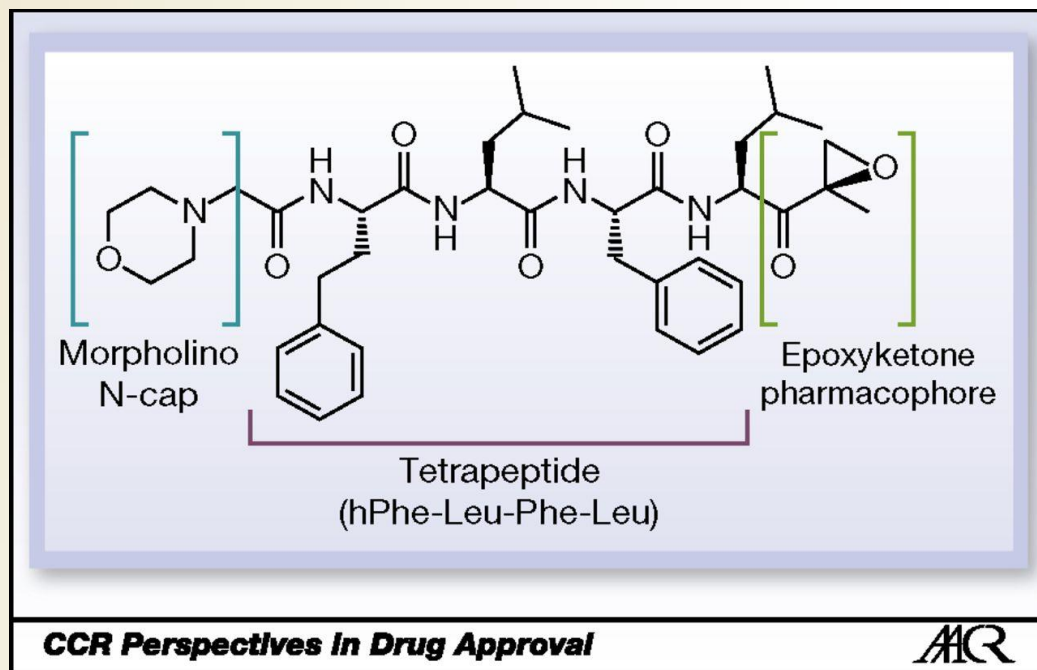
Why use CDs in protein and biological formulations:

- **Safer** than most current excipients (e.g. Tween®) – **no peroxide formation**, no corresponding immunogenicity and degradation
- Prevention of **aggregation**, delayed **folding**
- **Less protein adsorption** onto container surface
- Reduce/maintain **viscosity**
- Improved **injectability/syringeability**
- Physical and chemical **stabilization** of proteins
- **Life-cycle management (IP)**



First approved peptide/cyclodextrin-containing product Carfilzomib-SBECd (by AMGEN)

A synthetic **tetrapeptide** – complexed with **SBECd** against lymphoma marketed as **Kyprolis™**



Carfilzomib

**A unit dose:
60 mg of carfilzomib + 3 g SBECd
1:16 guest-host molar ratio**



Summary

In 2019

- parent alpha-, beta- and gamma cyclodextrins,
- Hydroxypropyl-beta-cyclodextrin
- Sulfobutylether-beta-cyclodextrin-Na as **excipients are in Pharmacopoeias**

In 2019

>84 pharmaceutical products are in the market containing a cyclodextrin excipient

In 2019

2 Cyclodextrins as APIs are approved:

- **Sugammadex/Bridion (MSD)** used in anesthesiology
- **2-Hydroxyl-propyl- β -cyclodextrin** has **Orphan Drug** designation for treatment of a rare fatal disease (Niemann Pick-C)



Pharmaceutical Applications of Cyclodextrins

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