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:

\( \alpha_{CD} 0.57 \text{ nm}, \beta_{CD} 0.78 \text{ nm}, \gamma_{CD} 0.95 \text{ nm}, (\delta_{CD} 1.3 \text{ nm}) \)
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

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<thead>
<tr>
<th></th>
<th>α-CD</th>
<th>β-CD</th>
<th>γ-CD</th>
<th>HPBCD</th>
<th>SBECRD</th>
<th>RAMEB</th>
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</tbody>
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**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

<table>
<thead>
<tr>
<th></th>
<th>Solubility increase using 10 m/m % SBECD vs purified water</th>
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</thead>
<tbody>
<tr>
<td><strong>Piroxicam</strong></td>
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<tr>
<td><strong>Carbamazepine</strong></td>
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<tr>
<td><strong>Amiodarone</strong></td>
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<td><strong>Voriconazole</strong></td>
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<td><strong>Delafloxacin</strong></td>
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<td><strong>Ziprasidone*HCl</strong></td>
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<tr>
<td><strong>Aripiprazole</strong></td>
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<tr>
<td><strong>Posaconazole pH 6</strong></td>
<td>20X</td>
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<tr>
<td><strong>Posaconazole pH 3</strong></td>
<td>120X</td>
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</tbody>
</table>

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 prediluted-complexed APIs.
  - Ethinyl estradiol stabilizes with βCD
Ulgut (benexate): masking bitter taste

Masking the burning taste

Masking bitter taste

Purposes of using CDs other than solubilizing
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 as stabilizing excipient: molecular encapsulation forms a barrier around API

Alpha-CD(Schwarz Pharma, Ono) encapsulated Alprostadil
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™

A unit dose:
60 mg of carfilzomib + 3 g SBEC
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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