Pharmaceutical Applications of Cyclodextrins

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Budapest, Hungary
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:

\[ \alpha\text{CD} \ 0.57 \text{ nm}, \ \beta\text{CD} \ 0.78 \text{ nm}, \ \gamma\text{CD} \ 0.95 \text{ nm}, \ (\delta\text{CD} \ 1.3 \text{ nm}) \]
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

<table>
<thead>
<tr>
<th></th>
<th>α-CD</th>
<th>β-CD</th>
<th>γ-CD</th>
<th>HPBCD</th>
<th>SBEC</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>Drug</th>
<th>Solubility increase using 10 m/m % SBECID vs purified water</th>
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<tbody>
<tr>
<td>Piroxicam</td>
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<tr>
<td>Carbamazipine</td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Voriconazole</td>
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<td>Delafloxacin</td>
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<td>Ziprasidone*HCl</td>
<td>470X</td>
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<tr>
<td>Aripiprazole</td>
<td>3350X</td>
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<tr>
<td>Posaconazole pH 6</td>
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<tr>
<td>Posaconazole pH 3</td>
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</tbody>
</table>

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 βCD

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

Purpose of using CDs other than solubilizing
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 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 SBEC
against lymphoma marketed as Kyprolis™

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