Cyclodextrin-based formulations

the present and the future

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CycloLab Ltd., Hungary
Outline

About Cyclodextrins (CDs)

Cyclodextrins as effective solubilizers in drug formulations

Cyclodextrins enhancing pharmacokinetic properties

Cyclodextrins designed for the target molecule

Cyclodextrins in complex drug delivery systems

The future of cyclodextrins: a new family of APIs
Cyclodextrins

Cyclic glucopyranose oligosaccharides

6-8 \(\alpha\)-D-glucose units (\(\alpha\), \(\beta\), \(\gamma\)-cyclodextrin)
Cyclodextrin derivatives

\[ R = H, \text{ or} \]

- \(-\text{CH}_3\)

- \(-\text{CH}_2\text{CH(OH)}\text{CH}_3\)

- \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{Na}\)
CDs suitably used in pharmaceuticals

**Parent**

Native
Unsubstituted

**Derivatives**

Substituted

2-hydroxypropyl β-CD (HP-β-CD)
EP, USP

2-hydroxypropyl γ-CD

sulfobutylether β-CD (SBE-β-CD)
USP

random methylated β-CD (RM-β-CD) (rare: nasal/ocular)

α-CD (Alfadex)
EP, USP

β-CD (Betadex)
EP, USP

γ-CD (Gammadex)
USP, JPC
Cyclodextrin complex formation

\[
CD + G \rightleftharpoons CD\cdot G
\]
The association with cyclodextrin may be versatile.
Chemical stability increases:
- Dihydro prostaglandin E1
- Doxorubicin (γ-CD), daunorubicin (methyl-β-CD)
- Acetylsalicylic acid (β-CD)
- O\textsuperscript{6}-Benzylguanine (SBE-β-CD)

Chemical stability decreases:
Penicillin derivatives are sensitized in the presence of cyclodextrins
Effect of CDs on the bioavailability of drug substances

- **Class III**: Highly soluble, Poorly permeable
- **Class I**: Highly soluble, Highly permeable
- **Class IV**: Poorly soluble, Poorly permeable
- **Class II**: Poorly soluble, Highly permeable

Consequences of CD complexation

Cyclodextrins may increase:

- Drug solubility
  - Wetting, dissolution rate
  - Absorbed quantity

Cyclodextrins may decrease:

- Drug stability
- Irritation
- Taste
- Smell
- Side effects
CDs suitably used in pharmaceuticals

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<tr>
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<th>α-CD</th>
<th>β-CD</th>
<th>γ-CD</th>
<th>HP-β-CD</th>
<th>SBE-β-CD</th>
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European Medicinal Agency EMA/CHMP/333892/2013, Committee for Human Medicinal Products (CHMP) Background review for cyclodextrins used as excipients

> 60 pharma products on the market containing CD
Solubility enhancement of drugs using 10 m/m% SBE-β-CD vs. purified water

<table>
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<tr>
<th>Drug</th>
<th>Solubility x</th>
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<tr>
<td>Piroxicam</td>
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<tr>
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<td>Amiodarone</td>
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<td>Voriconazole</td>
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<td>Delafloxacin</td>
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<td>Ziprasidone.HCl hydrate</td>
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<td>Aripiprazole.HCl hydrate</td>
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<tr>
<td>Posaconazole pH 6</td>
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<td>Posaconazole pH 3</td>
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</table>

Solubility in SBECED solutions: Cyclolab results
Traditional Therapeutic Use of Cyclodextrins: Enabling Pharmaceutical Excipients
(more than 60 approved products)
SBE-β-CD in veterinary formulation

Canine Anti-Nausea
Purpose of using CDs other than solubilizing

- Taste masking
- Fast onset
- Thiomersal free, reduced irritation
Purpose of using CDs other than solubilizing

Ulgut (benexate): masking bitter taste

Chemical stabilization

Masking bitter taste
Folate appended cyclodextrins

Targeting moiety

α, β or γ

„Drug delivery” or „active” moiety


Folate appended cyclodextrins

Host – Guest screening
Interaction confirmation

Folate conjugation

In-vitro study
Cyclodextrins in colloidal drug delivery:

Liposomes in combination with host-guest chemistry

I. Puskás, F. Csempesz:
Colloids and Surfaces B: Biointerfaces 58(2), 218-224 (2007)
Supra-colloidal assembly for sustained release of antiretroviral drugs


lamivudine

zidovudine

Polylysine
Hyaluronic acid
SBE-β-CD
Small molecules vs big guys

• Cyclodextrins in protein formulations

• CDs in DNA/RNA/siRNA delivery
Cyclodextrin protein interactions

Why to use CDs in protein and biological formulations:

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

Cycloextrin’s effect on Ig B aggregation

Turbidity of 1.8 mg/mL Ig B aqueous solution after 1 h stirring

Cyclodextrins in gene delivery
„nanoparticles system based on CD complexed siRNA has been effective in phase I clinical trials for the treatment of solid tumors”

„successful gene delivery by modified β-CDs to a variety of cell types including liver cells and intestinal epithelial cells and to in vitro and in vivo tumour models,“

„heptakispyridylamino CD, produced a 4000-fold increase in transfection level over DNA alone“
Non-excipient type
Therapeutic Utility

Therapeutic applications based on
selective molecular recognition/complex
formation of cyclodextrins (CDs)
Cyclodextrins as Antidotes
Cyclodextrin-assisted Detoxication

Pioneering role of an eminent NIH scientist: Josef Pitha
(J. Pitha and L. Szente: Rescue from hypervitaminosis A or potentiation of retinoid toxicity by different modes of cyclodextrin administration, Life Sci., 32 (7), 719-23, 1983)

The design of Sugammadex: **Cavity size matters!**

Target API: **rocuronium**

**API is a cationic aminosteroid, with approx. 1.6 nm x 0.9 nm size**

To form a highly stable non-covalent complex:

- **The gamma-CD cavity size is OK, nice fit**
- **Cavity height is not enough → should be extended**
- **Need a negative charge on the CD surface to have electrostatic interaction besides inclusion**
Sugammadex: the first CD derivative approved as API

6A,6B,6C,6D,6E,6F,6G,6H-Octakis-S-(2-carboxyethyl)-
6A,6B,6C,6D,6E,6F,6G,6H-octathio-Gamma-cyclodextrin-Na
Molecular mass: 2178.01

CD „Octopus”
Sugammadex follow-ups

Time elapsed until the reversal of neuromuscular blockade induced with pipecuronium

Normalized contraction

Time (s)

CMGCD DS-4

Bridion
Cyclodextrin overcomes deficient lysosome-to-endoplasmic reticulum transport of cholesterol in Niemann-Pick type C cells

Lina Abi-Mosleh, Rodney E. Infante, Arun Radhakrishnan¹, Joseph L. Goldstein², and Michael S. Brown²

Department of Molecular Genetics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8046

Contributed by Joseph L. Goldstein, September 23, 2009 (sent for review September 15, 2009)

,,The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein "for their discoveries concerning the regulation of cholesterol metabolism”
In this therapy the therapeutic target is **CHOLESTEROL**

Aqueous solubility of Cholesterol in the presence of 10% HPBCD of different DS

Malanga, M., Szemán, J., Fenyvesi, É., Puskás, I., Csabai K., Gyémánt Gy., Fenyvesi, F., Szente, L.
“BACK TO THE FUTURE”: A NEW LOOK AT HYDROXYPROPYL BETA-CYCLODEXTRINS
Next targets?

- CDs as LMWH and heparin antidotes
- CDs as a new concept to fight multiresistant bacteria
- CDs as APIs for rare lysosomal diseases
Conclusions

• **Major benefits of using CDs in drug formulations:**
  - Enhancing bioavailability
  - Successful injectable formulations of poorly soluble drugs
  - Stabilization (physical / chemical)

• **Limitations:**
  - Administration routes of some CDs are limited
  - Supergeneric strategy was not a success

• **Opportunities:**
  - Designed (smart) CD-derivatives for drug delivery
  - CDs in protein formulations and gene delivery
  - Cyclodextrins as APIs
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