CYCLOLAB

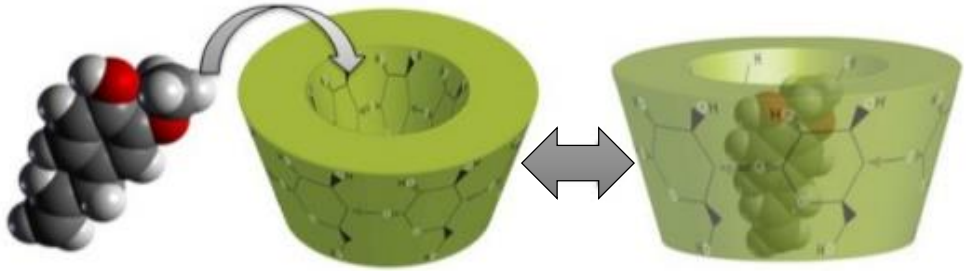
PIONEERS IN CYCLODEXTRIN-BASED INNOVATION

GETTING THE BEST OUT OF CYCLODEXTRINS

Cyclodextrin derivatives as Non-viral RNA/DNA/gene delivery systems

WHAT ARE CYCLODEXTRINS?

- Composed of sugars
- Cyclic molecules
- Naturally occurring compounds
- Used in food, pharmaceuticals, drug delivery, chemical industries, agriculture, etc.
- **Sub-nanometer** sized molecular containers with hydrophilic outer phase and hydrophobic interior properties
- Reversible inclusion complex formation

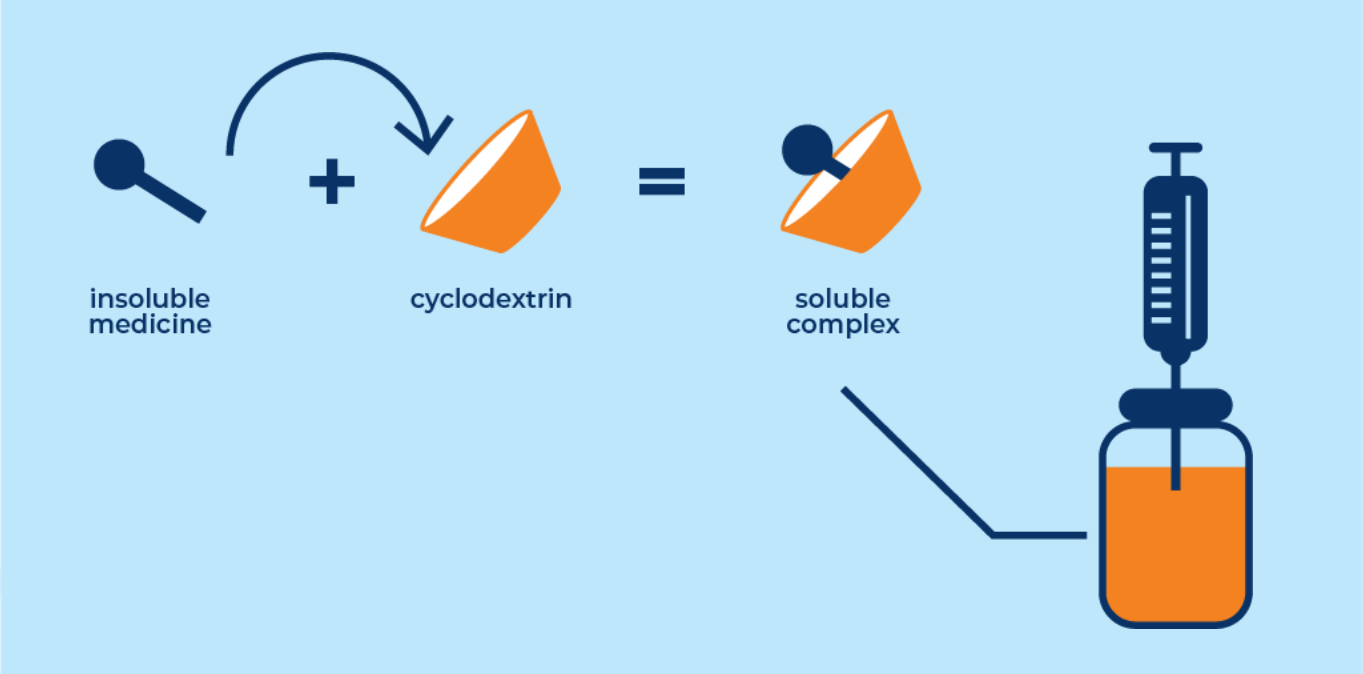


CYCLO AB

DEXOLVE™

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 USED IN PHARMACEUTICALS

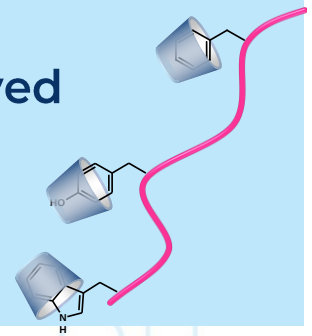
>100 pharma products on the market containing cyclodextrins

	α-CD	β-CD	γ-CD	HP-β-CD	SBE-β-CD	RM-β-CD	HP-γ-CD
ORAL		X	X	X	X		
NASAL						X	
RECTAL		X		X			
DERMAL		X	X	X			
OCULAR		X		X	X	X	X
PARENTERAL	X			X	X		X

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

Why use CDs in protein and biological formulations?

- Safer than 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
- Life-cycle management

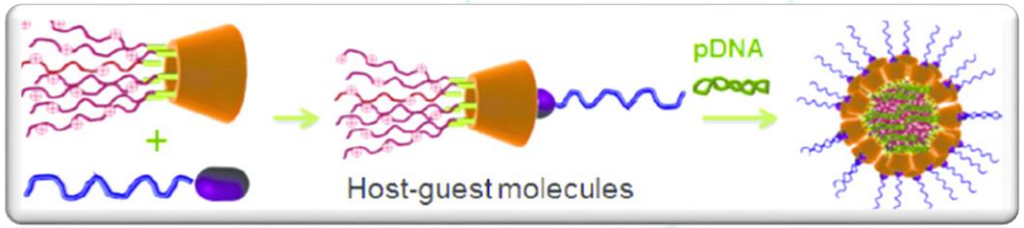


Protein without CD | Protein + CD1 | Protein + CD2 | Protein + CD3

Cyclodextrins' effect on insulin aggregation after stirring

FORMULATING siRNA

Why use CDs in non-viral gene delivery?



- Novel approach with a lot of promise and potential to protect intellectual property
- The systems offer delivery of synthetic siRNA to target cells
- Act as gene delivery vectors by condensing DNA and forming liquid crystalline complexes with oligonucleotides
- Ability to self-assemble in aqueous solvent forming micelles or vesicles and can be used as hosts for the solubilization and/or stabilization of various compounds
- Nanoparticle system based on CD complexed siRNA has been effective in phase I clinical trials for the treatment of solid tumors

Cyclodextrins as Non-viral gene delivery systems

Why use CDs in non-viral gene delivery:

- **Novel approach with lot of promise and potential to protect intellectual property**
- **The systems offer delivery to target cells**
- **Act as gene delivery vectors by condensing DNA and forming liquid crystalline complexes with oligonucleotides**
- **Ability to self-assemble in aqueous solvent forming micelles or vesicles and can be used as hosts for the solubilization and/or stabilization of various compounds**
- **targeted delivery of synthetic siRNA**

Cyclodextrins as Non-viral gene delivery systems

Amphiphilic cyclodextrins represent a new generation of CDs capable of forming all the assemblies expected of amphiphiles, but showing additional supramolecular properties

Self-assembling nanoparticle systems based on CD complexed siRNA has been effective in phase I clinical trials for the treatment of solid tumors

WF Lai: Cyclodextrins in non-viral gene delivery, Biomaterials, 2014

Cyclodextrins as Non-viral gene delivery systems

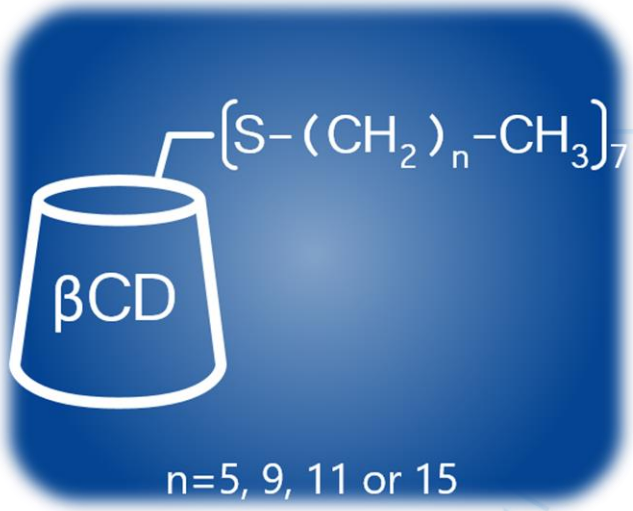
CDs are compatible in co-formulations: two amphiphilic cyclodextrins (CDs), one cationic and the other PEGylated or others including human transferrin (Tf) as a targeting ligand as possible.

Successful gene delivery to a variety of cell types (liver, intestinal epithelial in in vivo tumor models)

Up to 4000-fold increase in transfection level recorded (O'Driscoll, Eur J Pharm Sci, 2004)

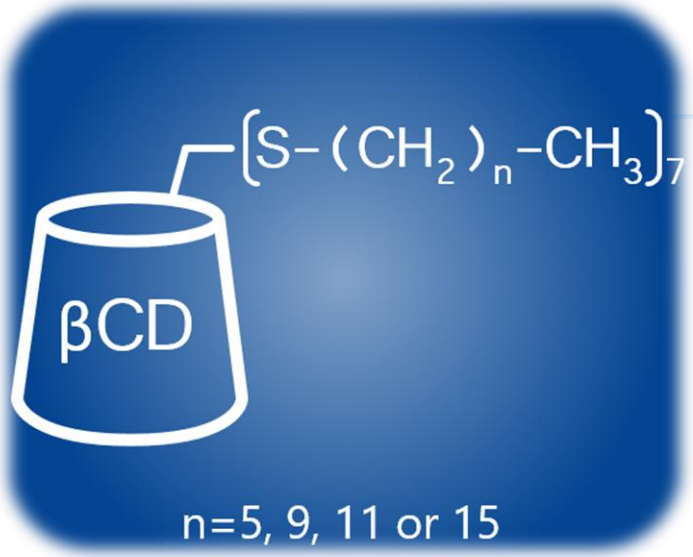
Cyclodextrins as Non-viral gene delivery systems

The per-(6-alkylthio)-CDs are compounds homogeneously substituted on the primary side with apolar chains of various length (C6/C10/C12/C16). The preparation of these compounds is performed through a standard and well established procedure at CycloLab.



Cyclodextrins as Non-viral gene delivery systems

These compounds are the ideal substrates for the preparation of amphiphilic cyclodextrins. The secondary side can be modified with polar groups such as oligo(ethylene glycol) units thus generating an amphiphilic structure and further modification can lead to the introduction of ionic groups.



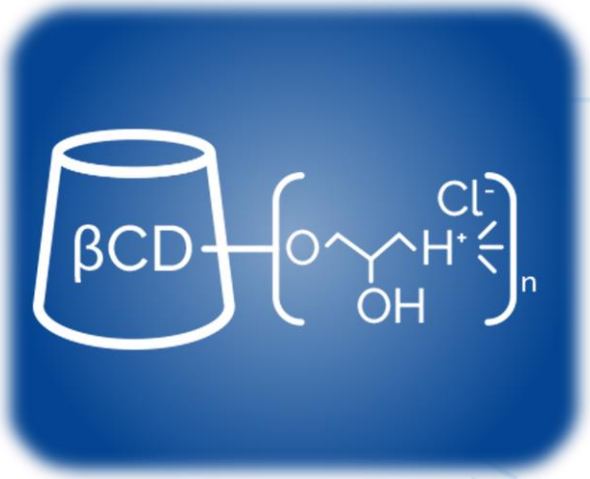
A. Mazzaglia et al.: Novel Amphiphilic Cyclodextrins: Graft-Synthesis of Heptakis(6-alkylthio-6-deoxy)-â-cyclodextrin 2-Oligo(ethylene glycol) Conjugates and Their-Halo Derivatives.

C.M O'Driscoll et al.: Cationic and PEGylated Amphiphilic Cyclodextrins: Co-Formulation Opportunities for Neuronal Sirna Delivery

C.M O'Driscoll et al.: Cell transfection with polycationic cyclodextrin vectors

Cyclodextrins as Non-viral gene delivery systems

Cyclolab offers a wide range of cationic cyclodextrins that are ideal host molecules to interact with RNA and DNA fragments. These may be available as permanently charged (quaternary amines), pH dependently charged (primary amines) and even as polymers of these products.



COMPANY CONTACTS

CYCLOLAB CYCLODEXTRIN RESEARCH & DEVELOPMENT LABORATORY LTD.

Budapest, P.O. Box 435, H-1525 Hungary

Location: Illatos út 7., Budapest, H-1097- Hungary

Tel: (+36) 1-347-60-70

E-mail: info@cyclolab.hu

Web: http://www.cyclolab.hu

CONTACT PERSON

Mihály Bálint

R&D Director - Chemistry

E-mail: balint@cyclolab.hu

Tel: (+36) 1-347-60-78

Tamás Sohajda

CEO

E-mail: sohajda@cyclolab.hu

Tel: (+36) 30-315-7038

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