The Cyclodextrin Company

Cyclodextrin-based formulations

the present and the future

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CycloLab Ltd., Hungary

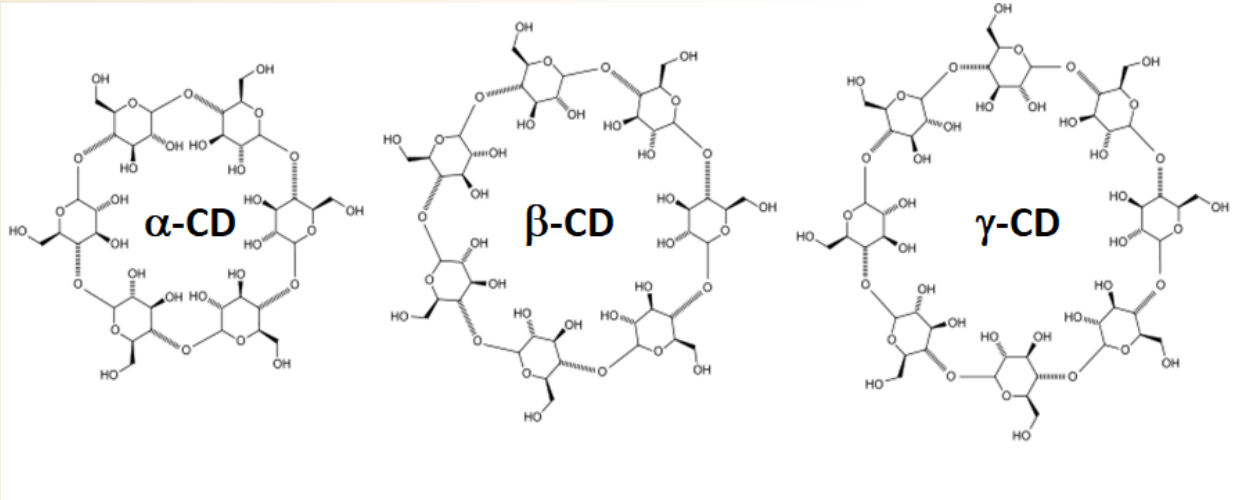
14th International Conference and Exhibition on Pharmaceutical Formulations, 2017

Outline

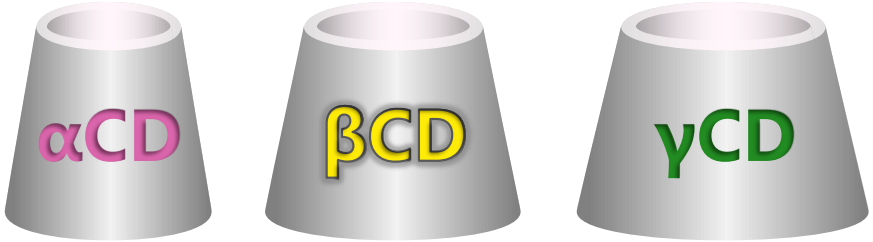
- About Cyclodextrins (CDs)
- Cyclodextrins as effective solubilizers in drug formulations
- Cyclodextrins enhancing pharmacokinetic properties
- Cyclodextrins designed for the target molecule
- Cyclodextrins in complex drug delivery systems
- The future of cyclodextrins: a new family of APIs

Cyclodextrins

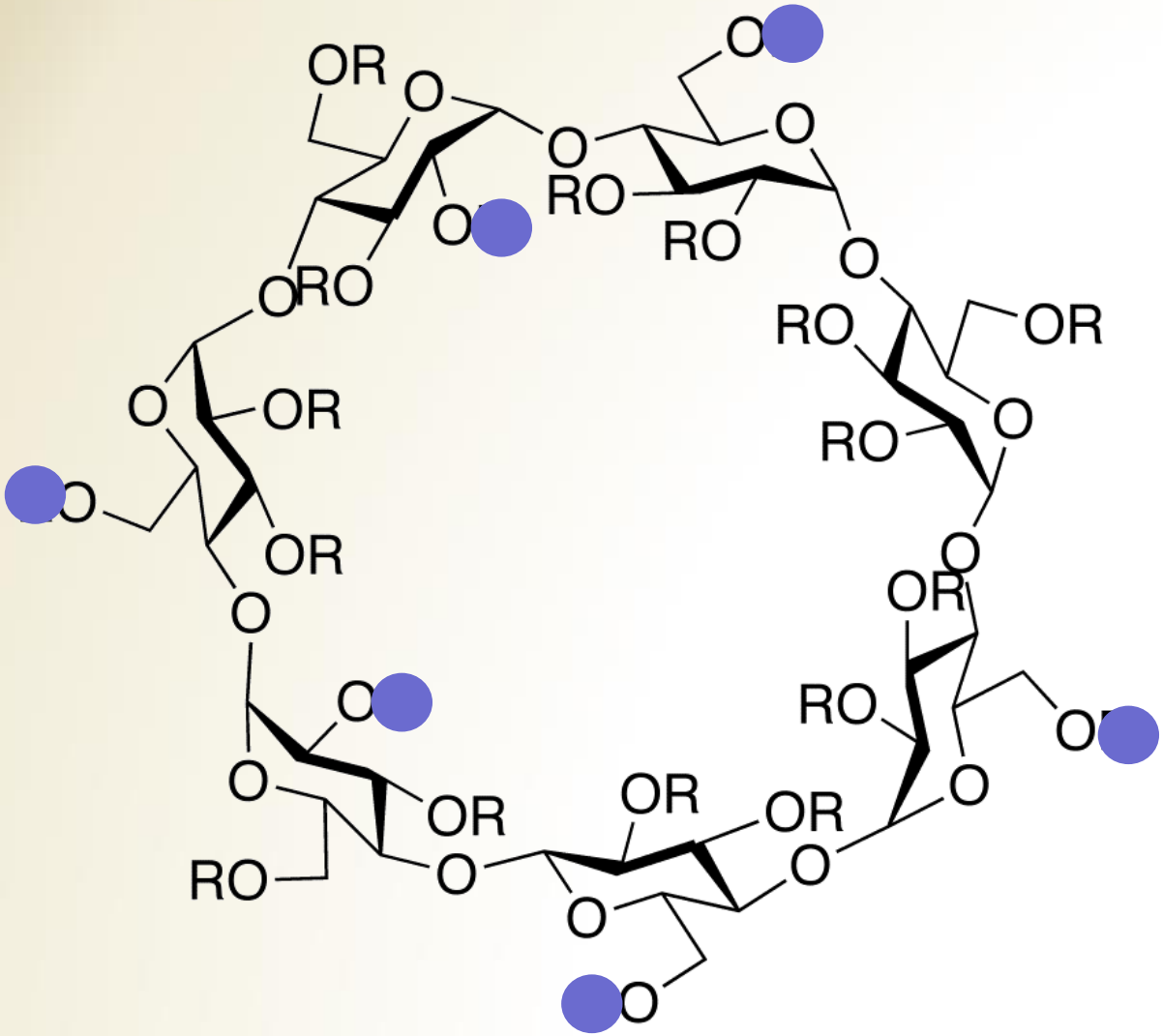
Cyclic glucopyranose oligosaccharides



6-8 α-D-glucose units (α, β, γ-cyclodextrin)



Cyclodextrin derivatives

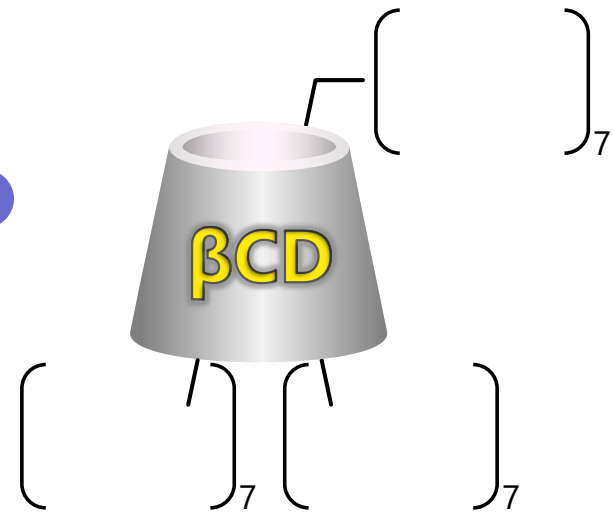


R = H, or

$-CH_3$

$-CH_2CH(OH)CH_3$

$-CH_2CH_2CH_2CH_2SO_3Na$

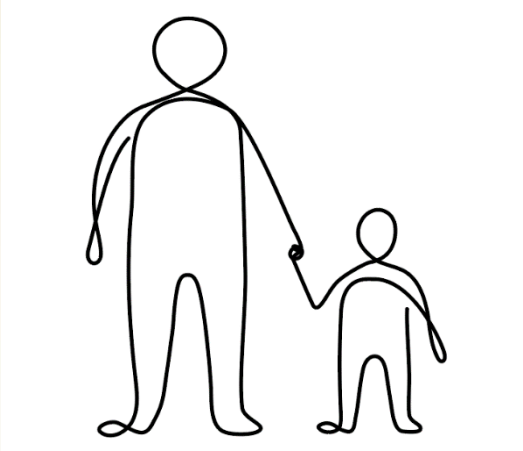


CDs suitably used in pharmaceuticals

Parent

Native

Unsubstituted



Derivatives

Substituted

2-hydroxypropyl β-CD (HP-β-CD)

EP, USP

α-CD (Alfadex)

EP, USP

2-hydroxypropyl γ-CD

β-CD (Betadex)

EP, USP

γ-CD (Gammadex)

USP, JPC

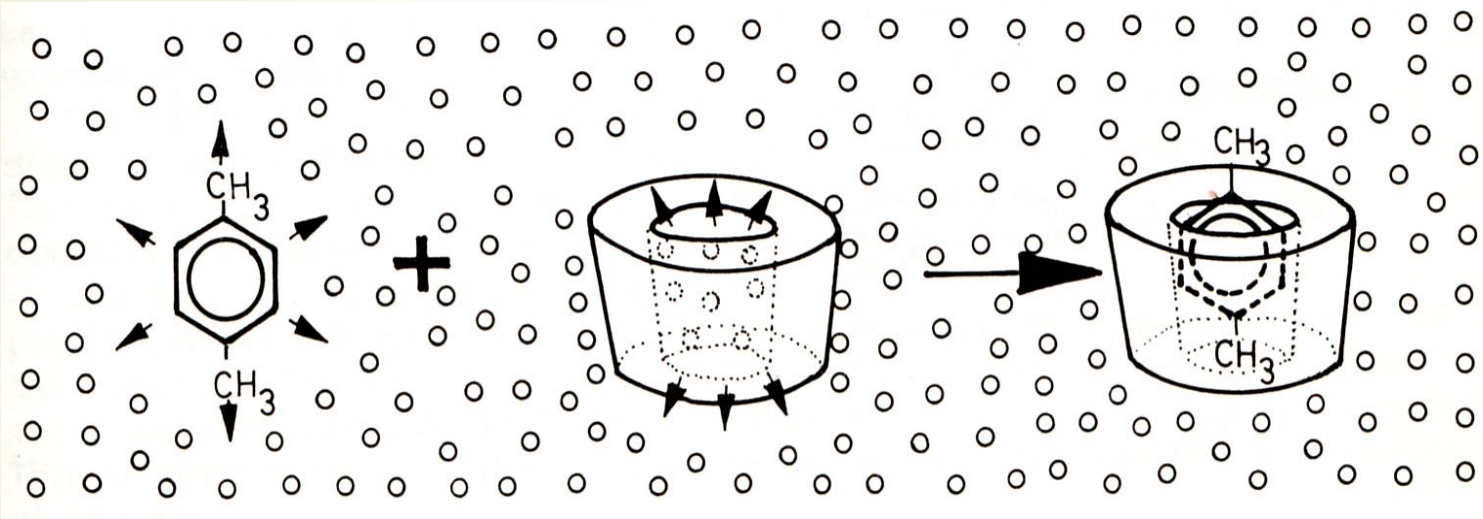
sulfobutylether β-CD (SBE-β-CD)

USP

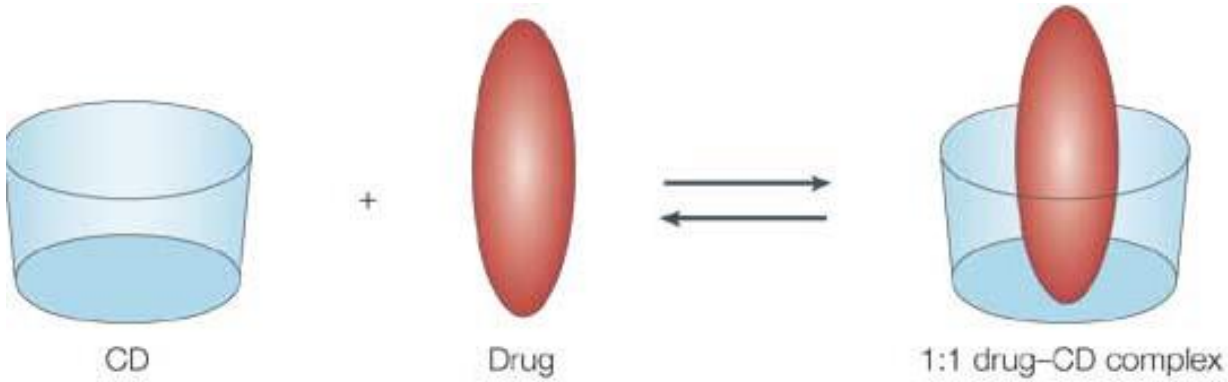
random metylated β-CD (RM-β-CD) (rare: nasal/ocular)

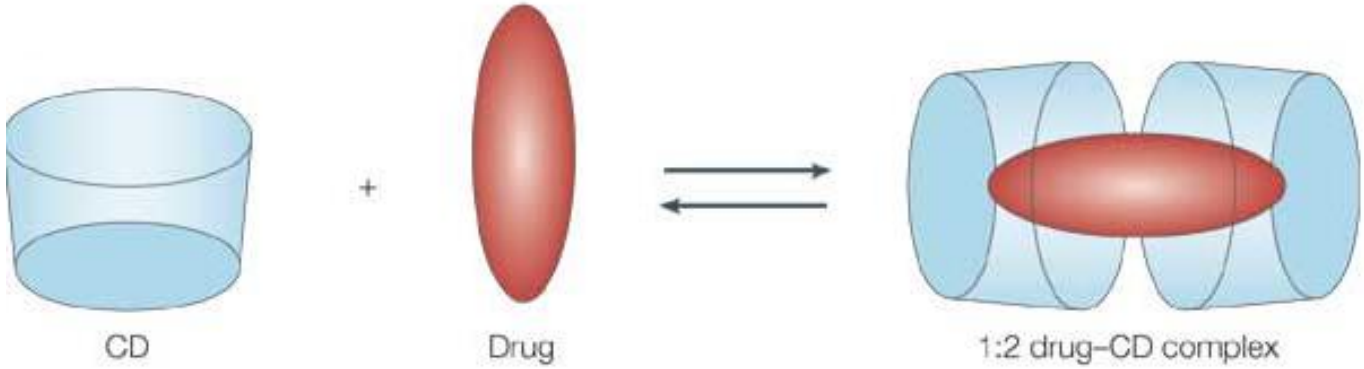
Cyclodextrin complex formation

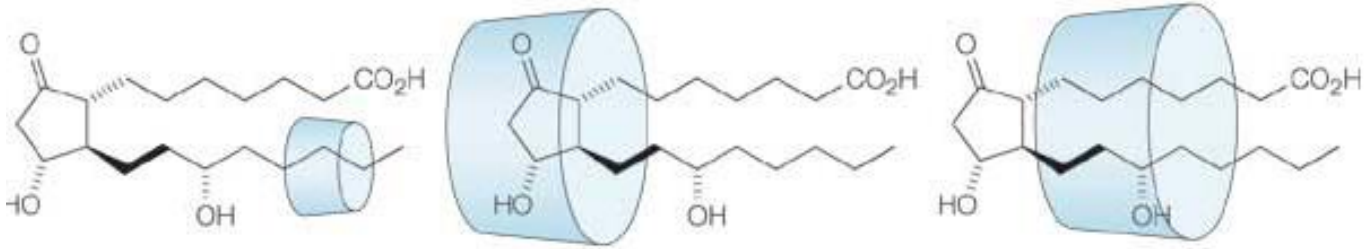
$$CD + G \rightleftharpoons CD{\cdot}G$$



The association with cyclodextrin may be versatile

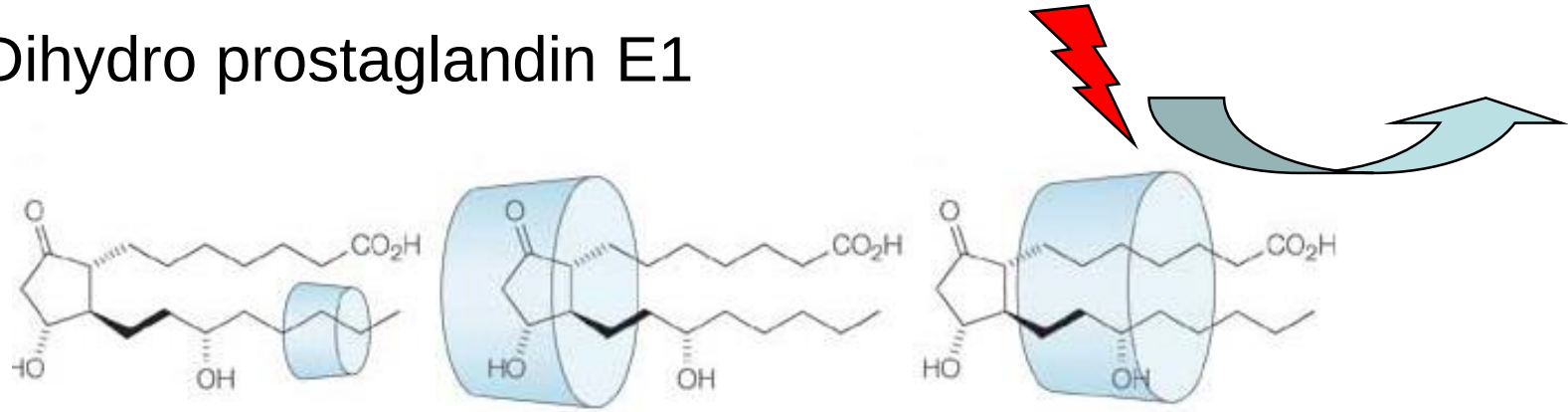






Chemical stability increases: $h\nu$, O_2, OH^-, H^+

- Dihydro prostaglandin E1

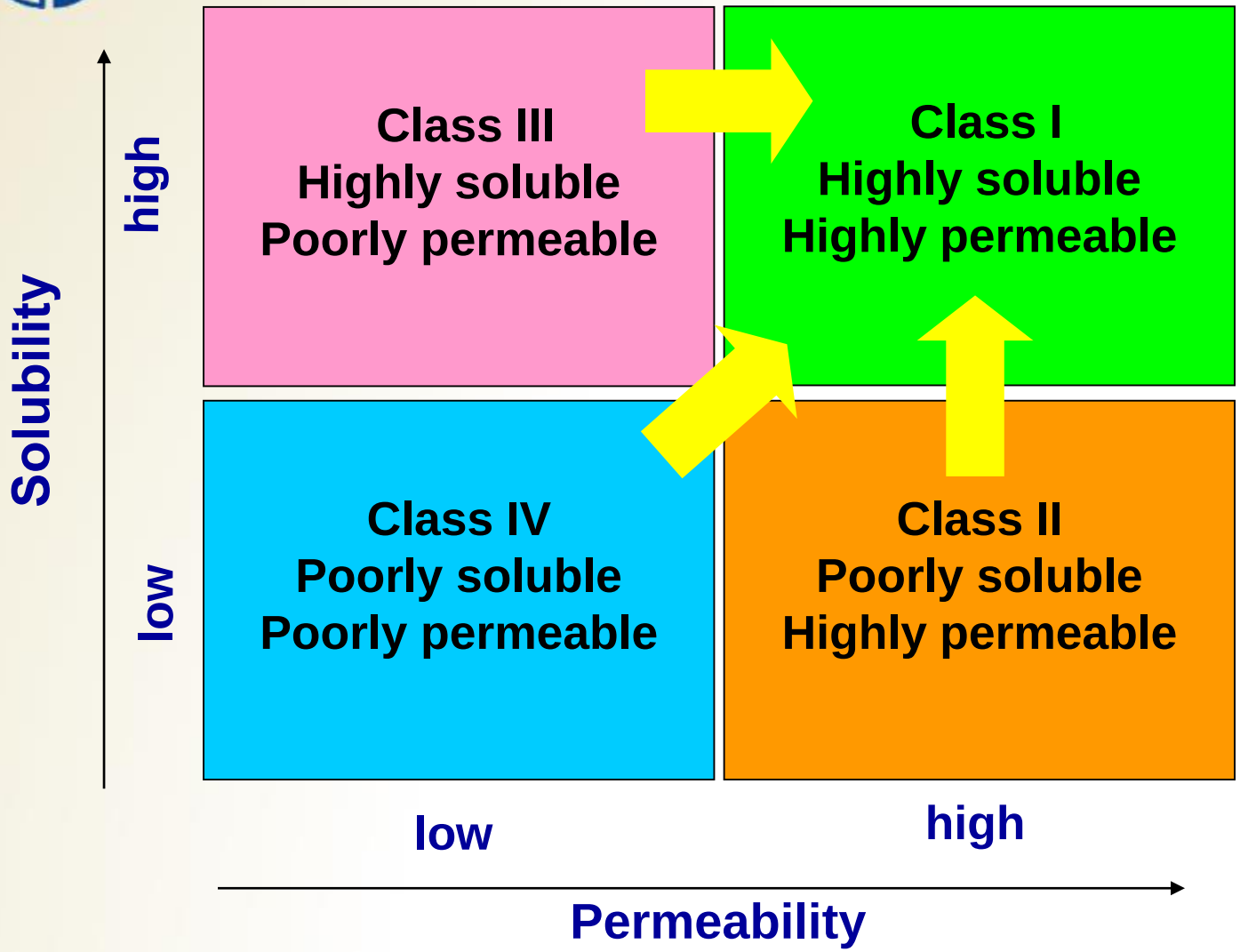


- Doxorubicin (γ-CD), daunorubicin (methyl-β-CD)
- Acetylsalicylic acid (β-CD)
- O^6-Benzylguanine (SBE-β-CD)

Chemical stabiliy decreases:

Penicillin derivatives are sensitized in the presence of cyclodextrins

Effect of CDs on the bioavailability of drug substances



Amidon et al 1995, Pharm. Res. 12:413-420; T. Loftsson 2002, J.Incl.Phenom. 44:63-67

Consequences of CD complexation

Cyclodextrins may increase:

Drug solubility

Wetting, dissolution rate

Absorbed quantity

Drug stability

Cyclodextrins may decrease:

Irritation

Taste

Smell

Side effects

CDs suitably used in pharmaceuticals

	α-CD	β-CD	γ-CD	HP-β-CD	SBE-β-CD	RM-β-CD
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

> 60 pharma products on the market containing CD

Solubility enhancement of drugs using 10 m/m% SBE-β-CD vs. purified water

Piroxicam	20 x
Carbamazepine	36 x
Amiodarone	50 x
Voriconazole	85 x
Delafloxacin	340 x
Ziprasidone.HCl hydrate	470 x
Aripiprazole	3350 x
Posaconazole pH 6	20 x
Posaconazole pH 3	120 x

Aqueous solubilities: Pubmed database (https://pubchem.ncbi.nlm.nih.gov)
Solubility in SBECD 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

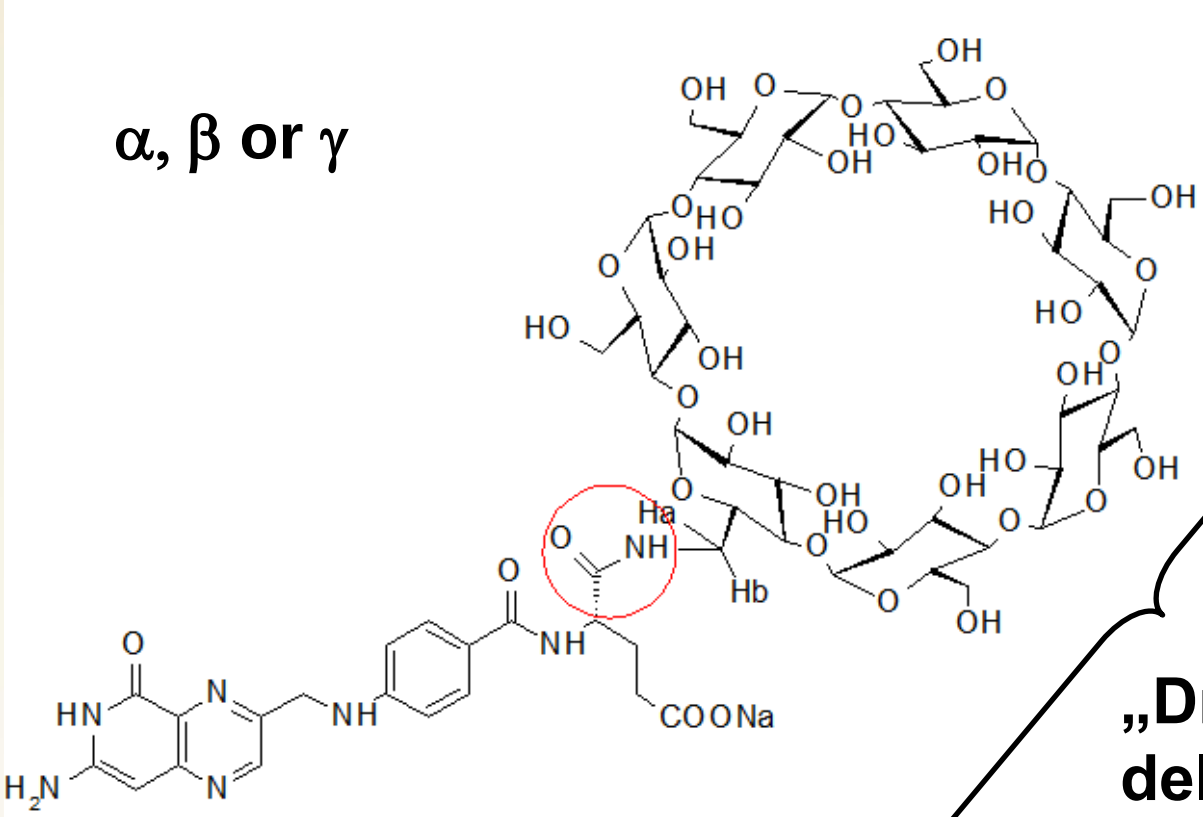
Ulgut (benexate): masking bitter taste

Chemical stabilization

Masking bitter taste

16

Folate appended cyclodextrins



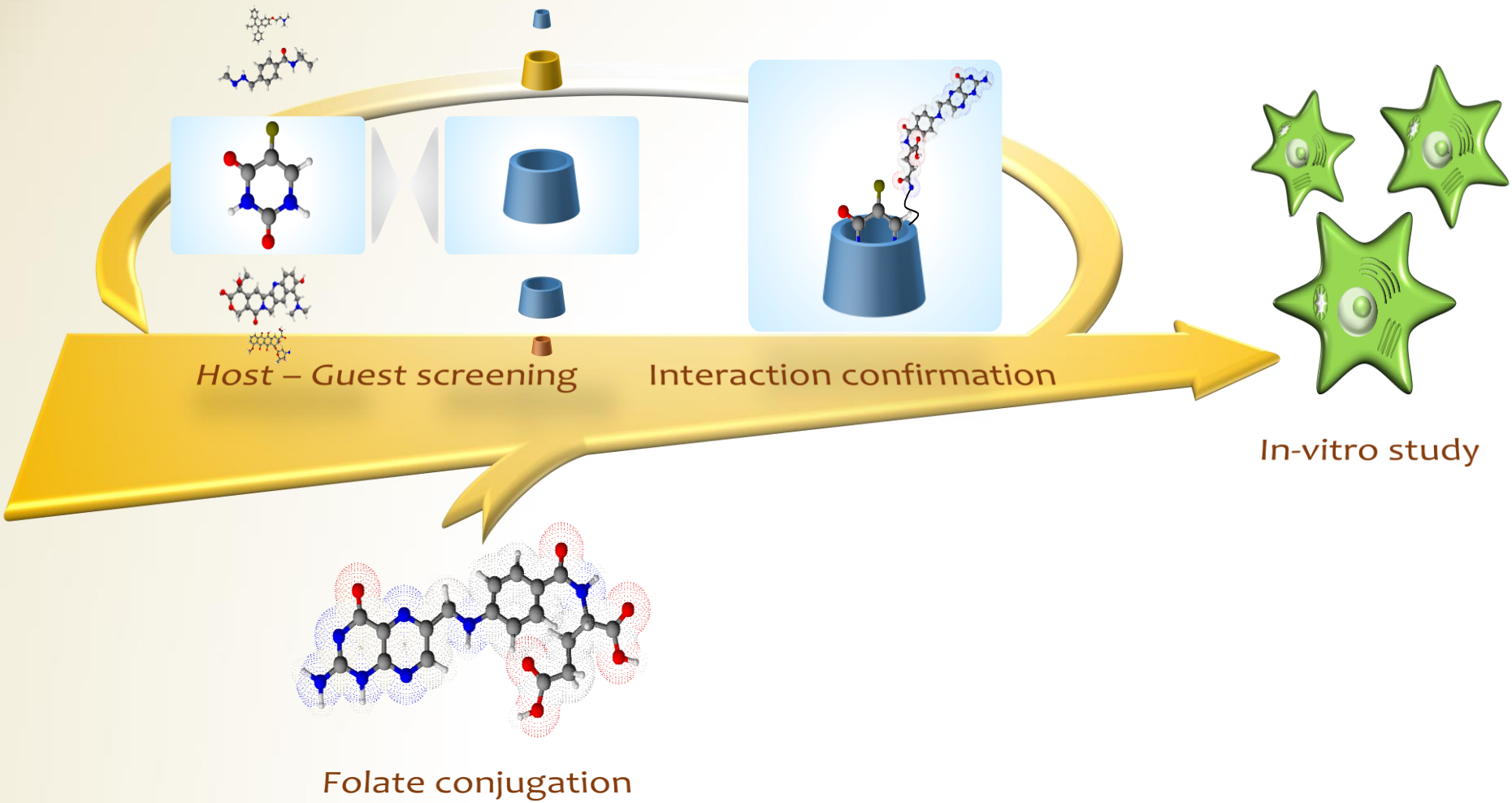
Targeting moiety

„Drug delivery" or „active" moiety

R. Onodera, K. Motoyama, A. Okamatsu, T. Higashi, H. Arima, Scientific Reports, 2013, 3, 1104.

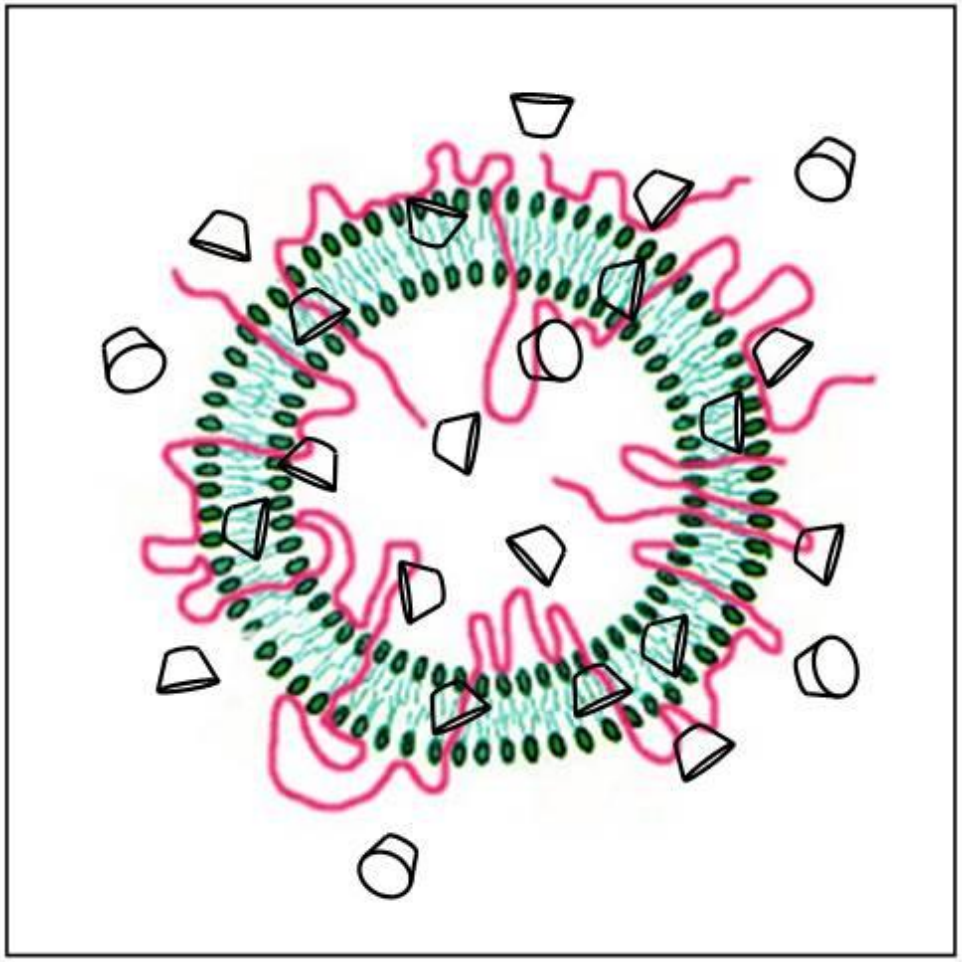
J. Szemán, K. Csabai, E. Varga, M. Malanga, K. Ludányi, L. Szente:
HPLC Analysis of Folate Appended Cyclodextrins, HPLC 2017, Prague, 18-22 June, 2017

Folate appended cyclodextrins



Cyclodextrins in colloidal drug delivery:

Liposomes in combination with host-guest chemistry

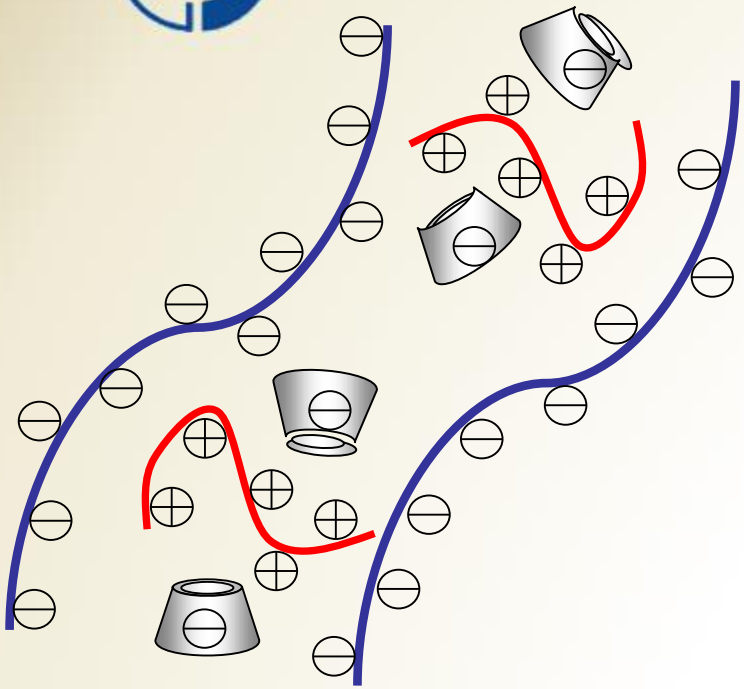


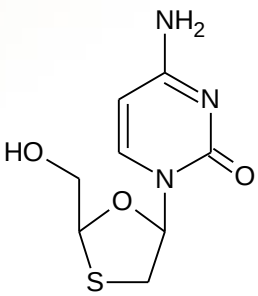
Cyclodextrin

Polymer

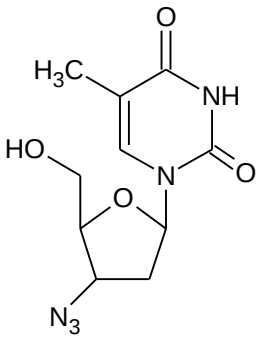
I. Puskás, F. Csempesz:
Colloids and Surfaces B: Biointerfaces 58(2), 218-224 (2007)

Supra-colloidal assembly for sustained release of antiretroviral drugs





lamivudine



zidovudine

Polylysine

Hyaluronic acid

SBE-β-CD

B. Song, I. Puskás, L. Szente, J. E. K. Hildreth: J. Pharm. Sci. 105(9), 2760, 2016

SPOILER ALERT

Small molecules vs big guys

- **Cyclodextrins in protein formulations**

- **CDs in DNA/RNA/siRNA delivery**

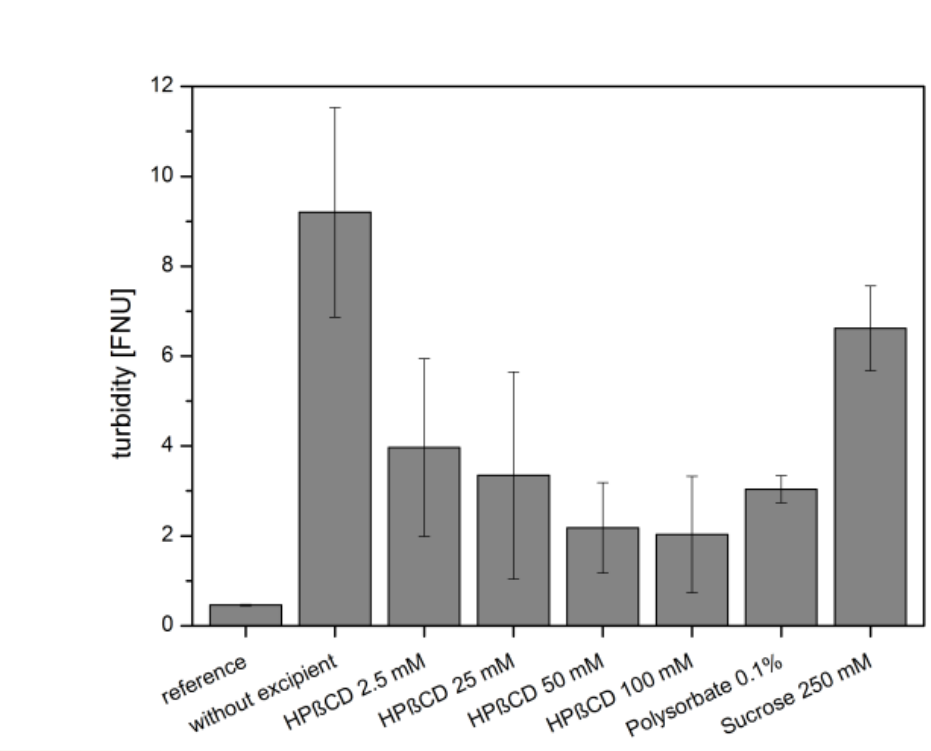
Cyclodextrin protein interactions

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

Cyclodextrin protein interactions

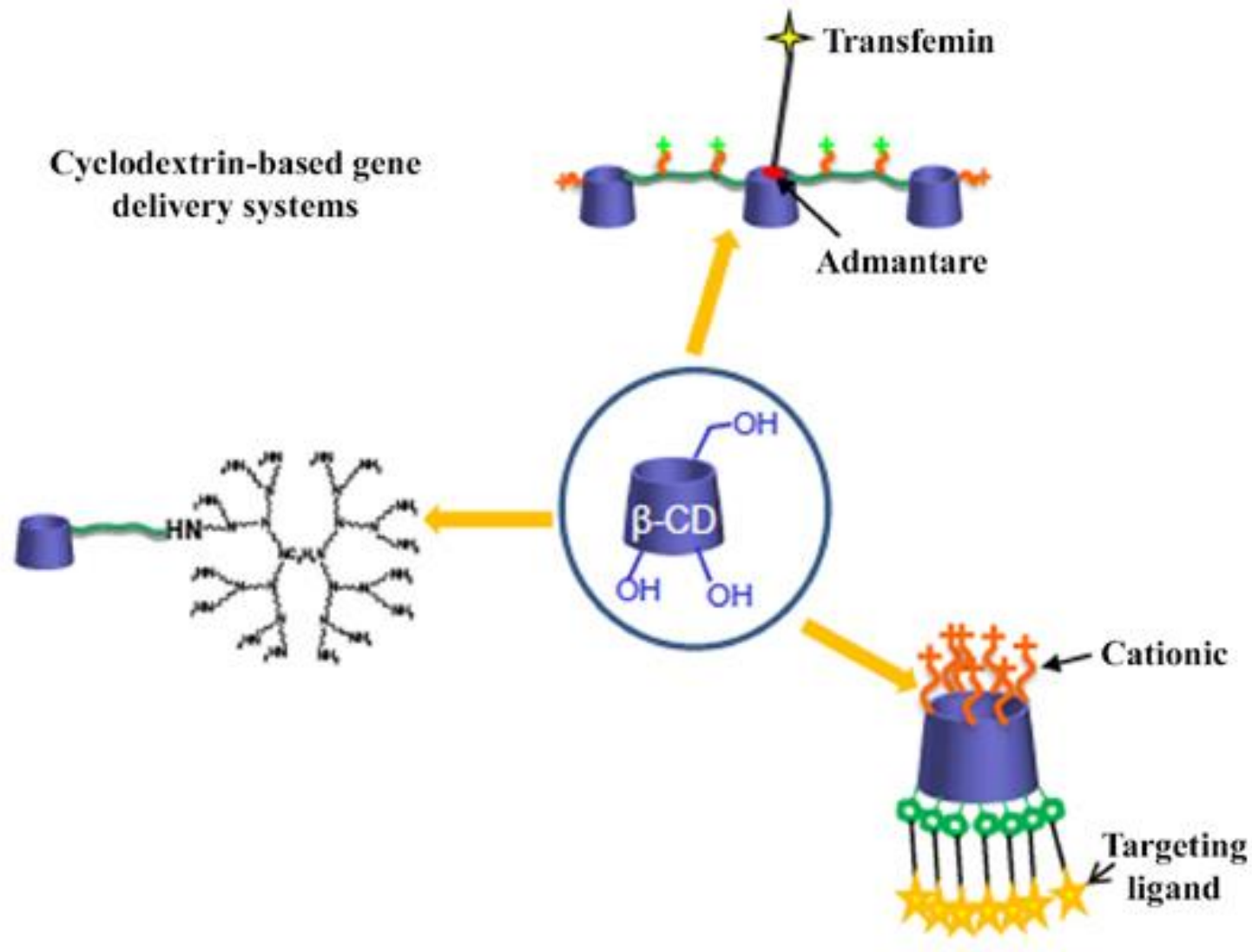
Cyclodextrin's effect on Ig B aggregation



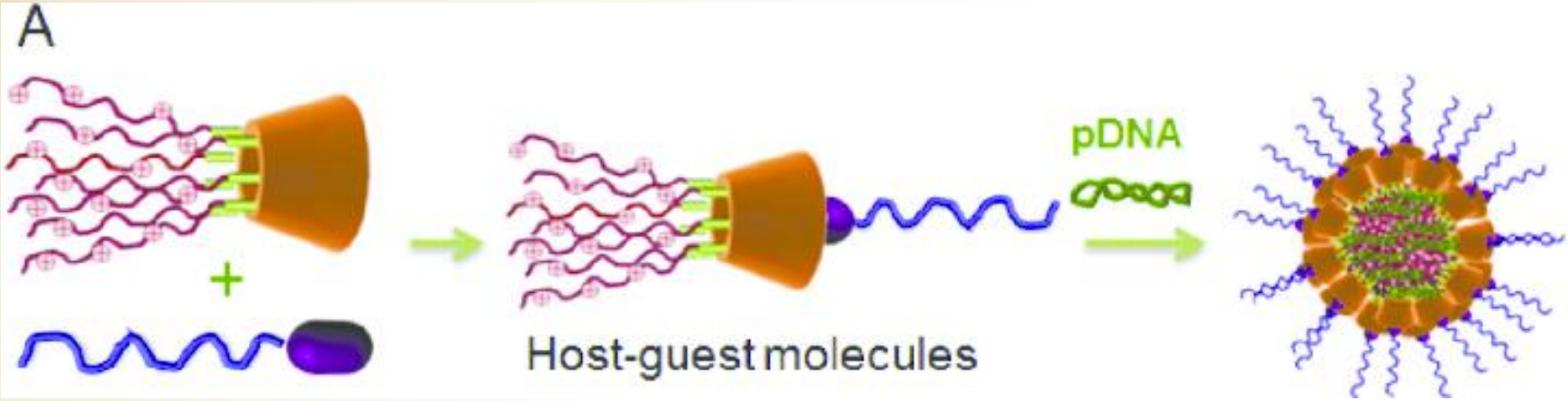
Turbidity of 1.8 mg/mL Ig B aqueous solution after 1 h stirring

Hartl, E., Dixit, N., Besheer, A., Kalonia, D., Winter, G: Eur J Pharm Biopharm 85, 2013, 781-789

Cyclodextrins in gene delivery



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

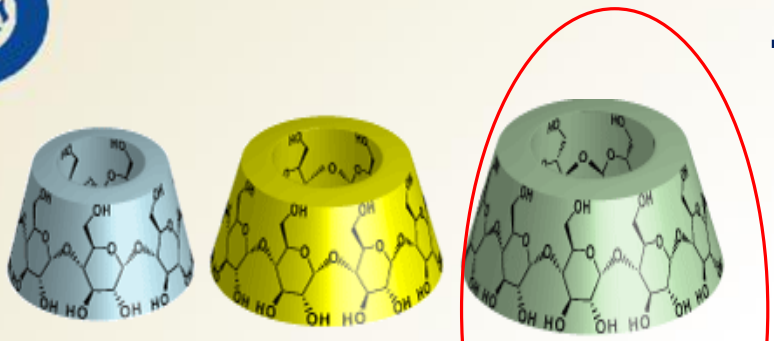
Pioneering role of an eminent NIH scientist: Josef Pitha

(***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***)

Proof of his concept: first clinical life saving action: rescue from retinoid intoxication in 1987*(J. Pitha and Carpenter T. Hypervitaminosis A in Siblings J. of Pediatrics 111 507, **1987**.)*

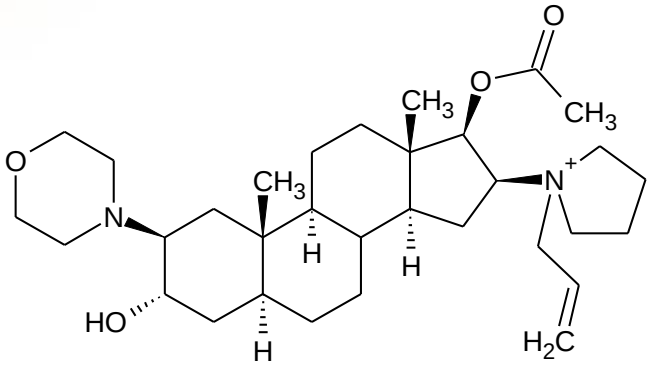
Father of CD-based clinical detoxication

The design of Sugammadex: Cavity size matters!



	α-CD	β-CD	γ-CD
No. of Glucose Units	6	7	8
Cavity Diameter (nm)	0.47	0.60	0.75
Height of Torus (nm)	0.79	0.79	0.79

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:

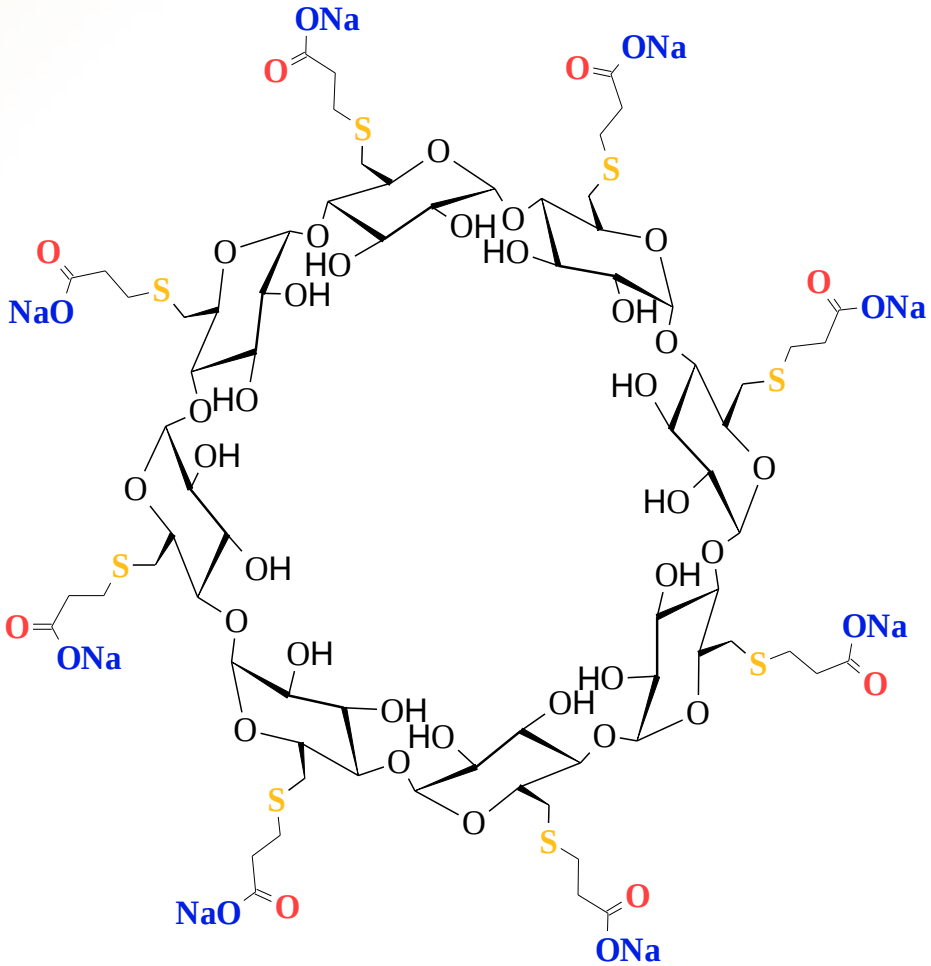
- **The gamma-CD cavity size is OK, nice fit**
- **Cavity height is not enough→ should be extended**
- **Need a negative charge on the CD surface to have electrostatic interaction besides inclusion**

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

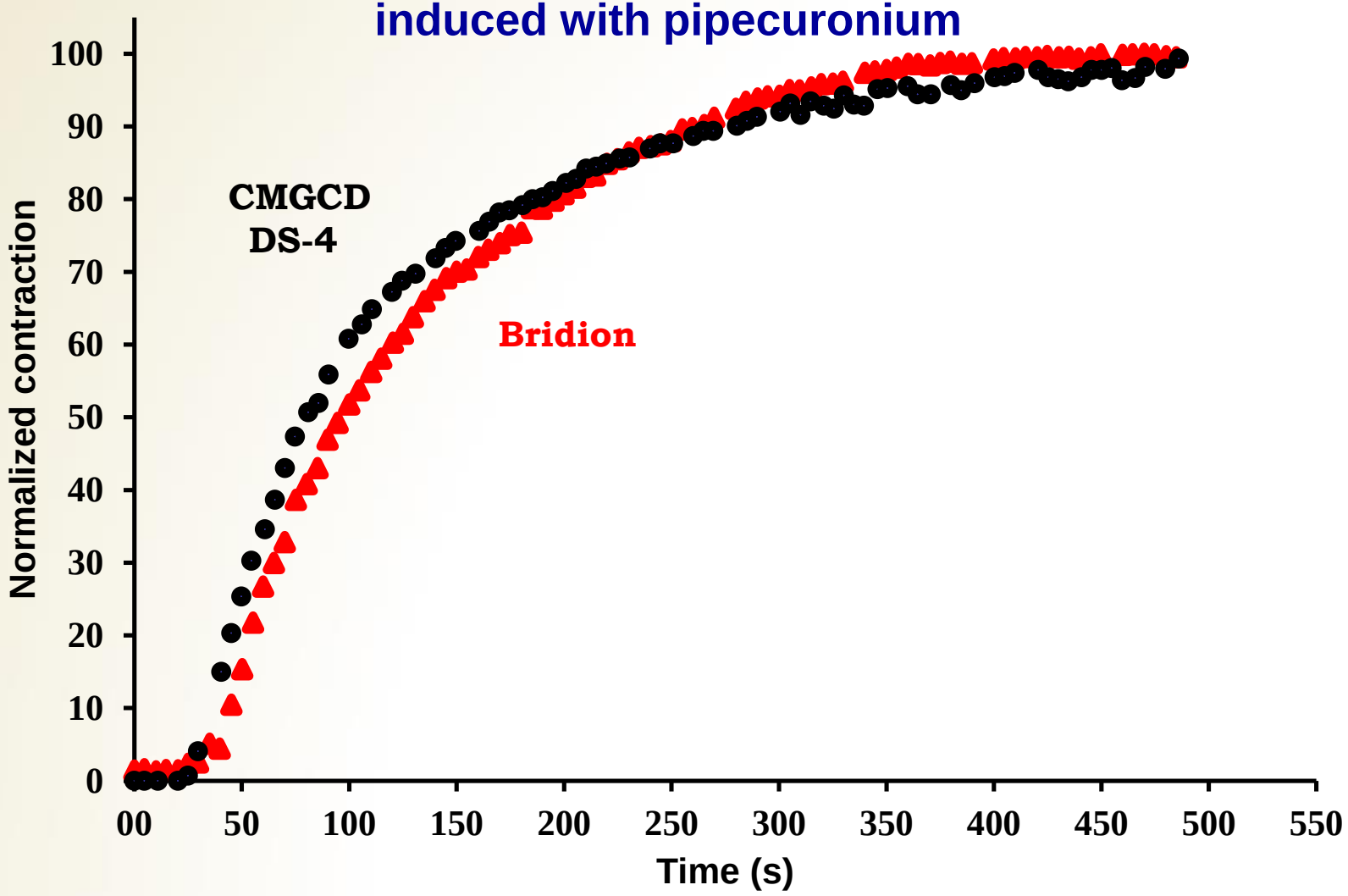
Molecular mass: 2178.01

CD „Octopus"



Sugammadex follow-ups

Time elapsed until the reversal of neuromuscular blockade induced with pipecuronium



Old cholesterol Masters, Brown and Goldstein joined to the early studies

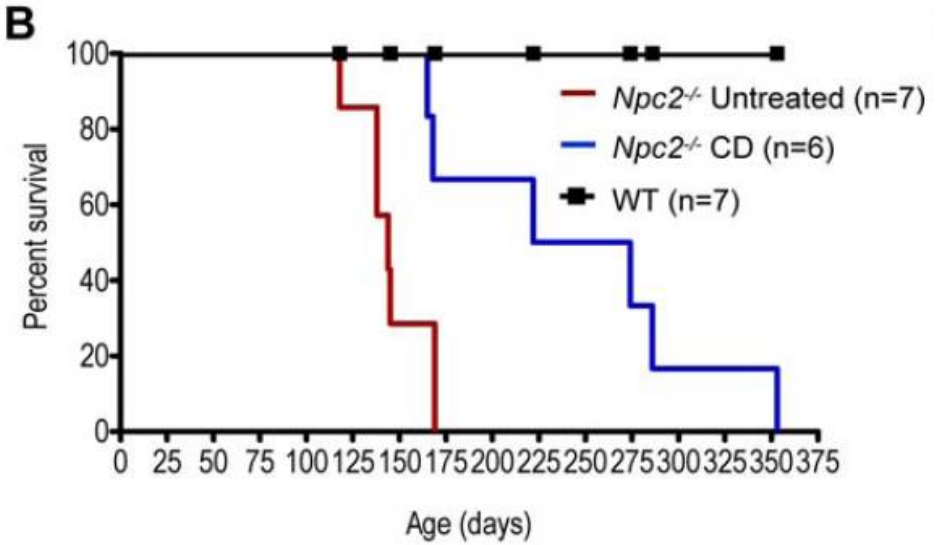
PNAS

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

Lina Abi-Mosleh, Rodney E. Infante, Arun Radhakrishnan[1], Joseph L. Goldstein[2], and Michael S. Brown[2]

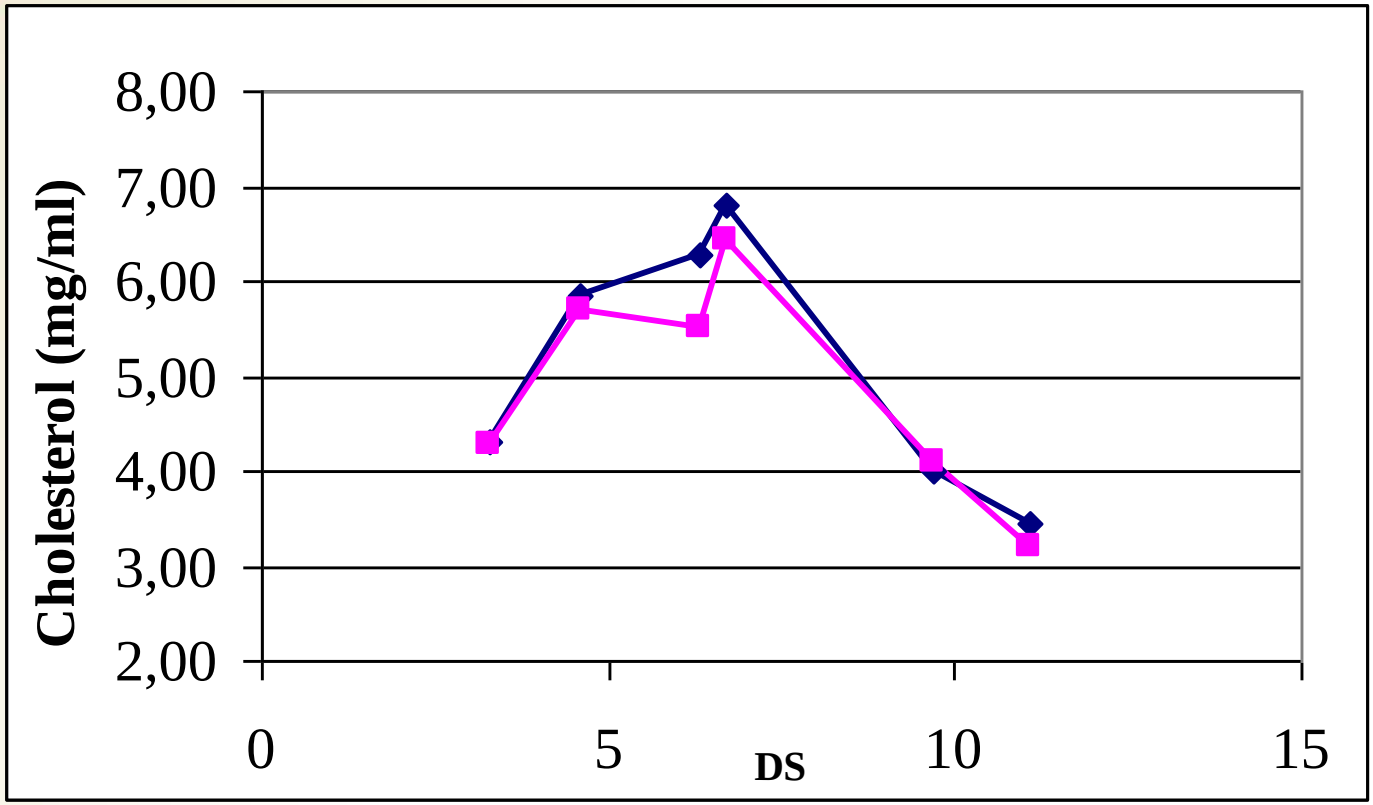
Department of Molecular Genetics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9046

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
Journal of Pharmaceutical Sciences, Volume 105, Issue 9, 2921–2931 (2016)

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
- Succesful 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

Acknowledgements

István Puskás (Cyclolab Ltd)

Milo Malanga (Cyclolab Ltd)

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