CYCLOLAB

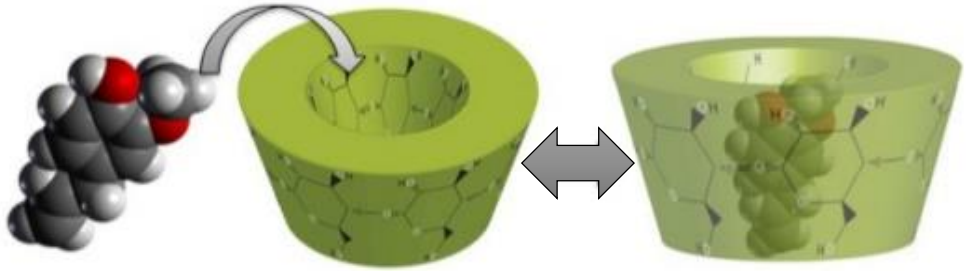
PIONEERS IN CYCLODEXTRIN-BASED INNOVATION

GETTING THE BEST OUT OF CYCLODEXTRINS

Pharmaceutical Applications of Cyclodextrins

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™

HISTORY OF PHARMACEUTICAL APPLICATIONS

Traditional Applications

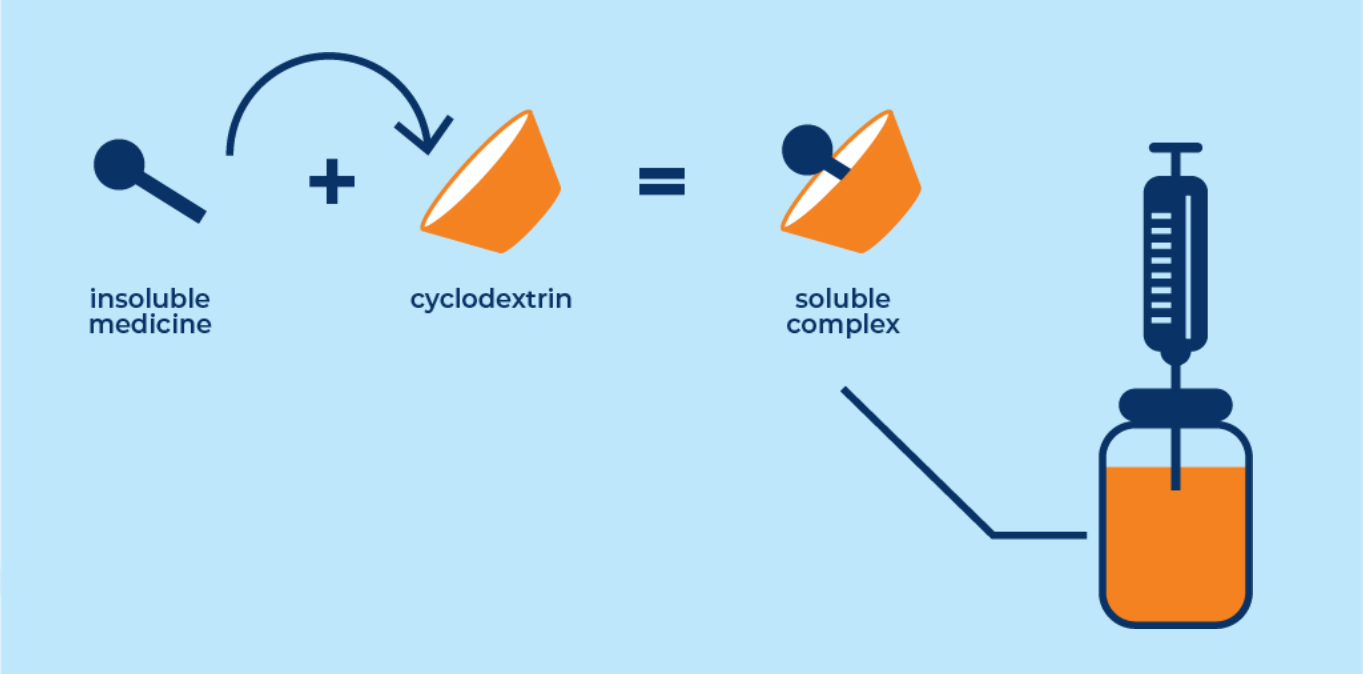
- CDs as drug complexing agents in drug delivery
- Nanosizing, solubilizing, stabilizing, targeting etc.
- Summmary of results: >100 marketed products in 2021

CDs as active ingredients

- Lowering lysosomal 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

WHY USE CYCLODEXTRINS? POSSIBILITIES

- Significant solubility enhancement (10 to 100,000 fold)
- Improvement of chemical stability
- Increased bioavailability, facilitated delivery
- Reduced aggregation
- Moderate irritation or reduced side-effects
- Maximized patient safety, complete renal elimination
- Enables formulation of water-insoluble APIs in all dosage forms
- Lower API doses can be achieved

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CDs USED IN PHARMACEUTICALS

Parent

Native

Unsubstituted

α-CD (Alfadex)
EP, USP

β-CD (Betadex)
EP, USP

γ-CD (Gammadex)
EP, USP, JPC

Derivatives

Substituted

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

Sulfobutylether β-CD (SBE-β-CD, betadex sulfobutyl ether sodium)
EP, USP

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

2-hydroxypropyl γ-CD (HP-γ-CD)

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

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FOR IMPROVED PHARMACEUTICAL FORMULATIONS

	Solubility increase using 10 m/m % SBECD vs purified water
Piroxicam	20X
Carbamazipine	36X
Amiodarone	50X
Voriconazole	85X
Delafloxacin	340X
Ziprasidone*HCl	470X
Aripiprazole	3350X
Posaconazole pH 6	20X
Posaconazole pH 3	120X

FDA REGISTERED — DMF No. 21922

GMP — OGYÉI/577 92-7/2018

CANADA HEALTH — DMF No. 2009-080

CFDA — DMF No. F20180001741

MFDS KOREA — In progress

EudraGMDP — OGYÉI/3039 1-2/2018

Aqueous solubilities: Pubmed database
(https://pubchem.ncbi.nlm.nih.gov)
solubility in SBECD solutions: CycloLab results

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PURPOSES OF USING CDs OTHER THAN SOLUBILIZING

Thiomersal-free, reduced
irritation in diclofenac stabilized eye drops

Fast onset and life-cycle management
Omeprazole/BCD/arginine ternary complex

Use of CDs to ensure content uniformity:
low dose units with pre-diluted-complexed APIs.
Ethinyl estradiol stabilizes with βCD

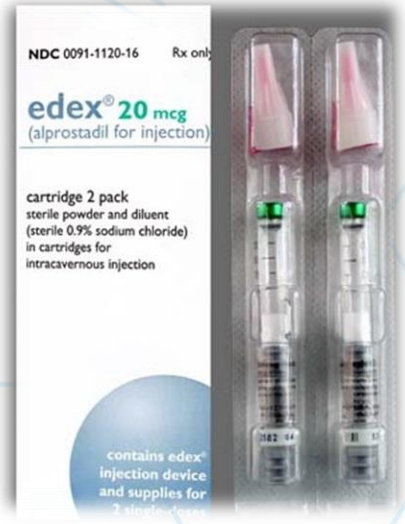
PURPOSES OF USING CDs OTHER THAN SOLUBILIZING

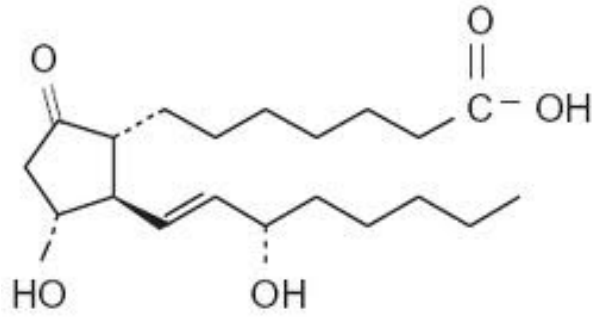
Ulgut (benexate): masking bitter taste

Masking the burning taste

Masking bitter taste

CYCLODEXTRIN AS STABILIZING EXCIPIENT: MOLECULAR ENCAPSULATION FORMS A BARRIER AROUND API





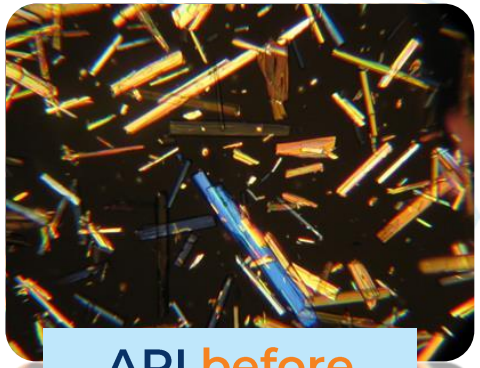
Alpha-CD (Schwarz Pharma, Ono)
encapsulated Alprostadil

PARTICLE SIZE ENGINEERING BY CYCLODEXTRINS: A SIMPLE WAY TO MOLECULAR DISPERSITY (TO SUB-NANOMETER SIZE)

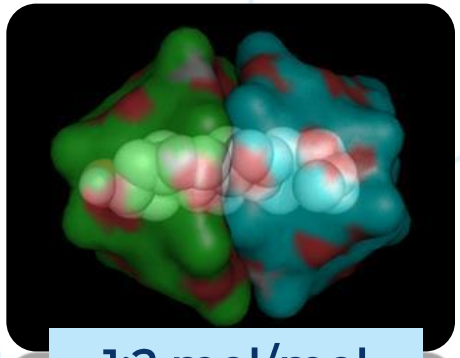
Molecular encapsulation of drugs by CDs results in

- 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

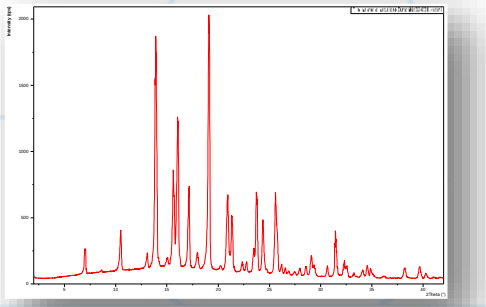


API before cyclodextrin inclusion



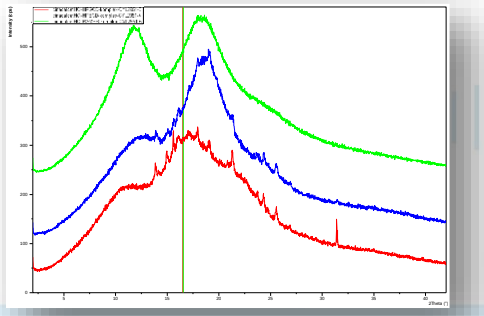
1:2 mol/mol API-BCD Inclusion complex

API after cyclodextrin inclusion



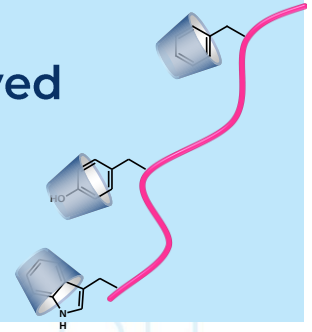
Solid phase transformation

(solid state also depends on the type of CD)



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



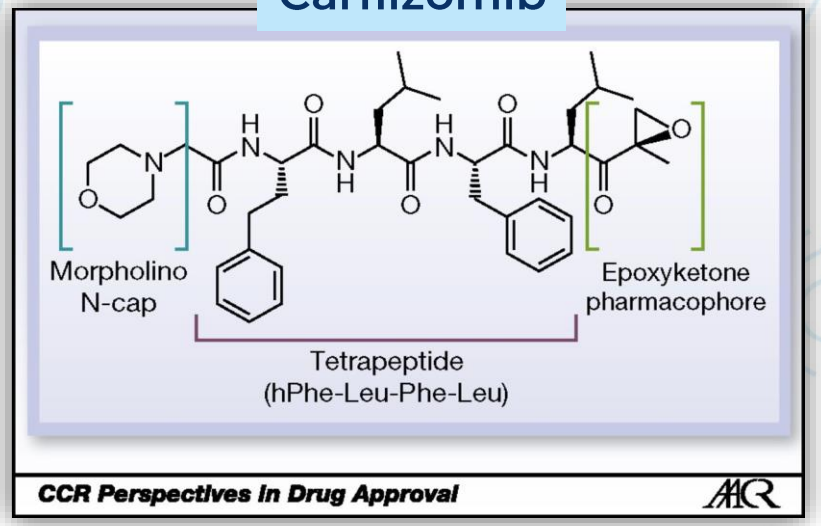
Protein without CD | Protein + CD1 | Protein + CD2 | Protein + CD3

Cyclodextrins' effect on insulin aggregation after stirring

FIRST APPROVED PEPTIDE/CYCLODEXTRIN-CONTAINING PRODUCT CARFILZOMIB-SBECD (BY AMGEN)

A synthetic tetrapeptide – complexed with SBECD against lymphoma marketed as Kyprolis™

Carfilzomib



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

AMGEN

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CYCLOLAB SERVICE PORTFOLIO AND PIPELINE PROGRAMS RELATED TO FORMULATION

Early phase drug development

Customization of CD enabled formulations

Investigation of changes in physico-chemical properties

In vitro bioequivalence studies

Design in vitro studies to support bioequivalence of a CD enabled formulation.

IP services and consultation

Analytical services

Method development, validation

HPLC, GC, CE, UV, MS, NMR, IR

Stability studies

CD-guest interaction studies

Assay, impurity tests

PIPELINE FOR PARTNERING

Pediatric and geriatric reformulation

Injectable panobinostat – various types of cancer

Injectable lonafarnib – progeria

Injectable repurposing: oral drugs reformulated as injectables

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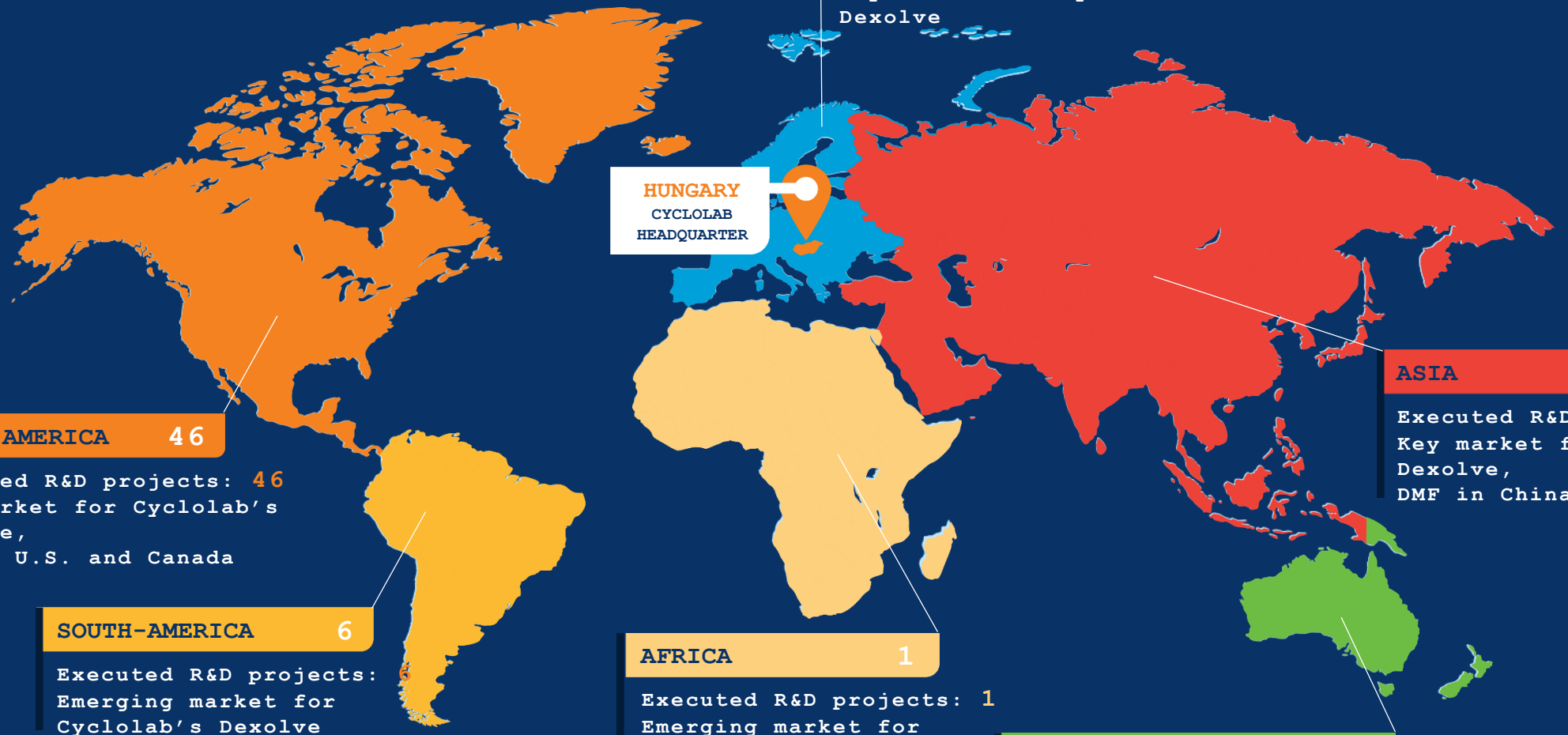
GLOBAL FOOTPRINT OF CYCLOLAB



EUROPE 95

Executed R&D projects: 95
Key market for Cyclolab's Dexolve

NORTH AMERICA 46

Executed R&D projects: 46
Key market for Cyclolab's Dexolve,
DMF in U.S. and Canada

SOUTH-AMERICA 6

Executed R&D projects:
Emerging market for Cyclolab's Dexolve

AFRICA 1

Executed R&D projects: 1
Emerging market for Cyclolab's Dexolve

ASIA 35

Executed R&D projects: 35
Key market for Cyclolab's Dexolve,
DMF in China, South Korea

AUSTRALIA 2

Executed R&D projects: 2
Emerging market for Cyclolab's Dexolve

DEXOLVE™: BETADEX SULFOBUTYL ETHER SODIUM (SBECD)
2016 - 2021 NUMBER OF EXECUTED R&D PROJECTS: 184

SUMMARY

In 2021

- parent alpha-, beta- and gamma cyclodextrins, Hydroxypropyl-beta-cyclodextrin, Sulfobutylether-beta-cyclodextrin Na as excipients are in Pharmacopoeias (USP, EP, JP)
- 3 other cyclodextrins not listed in Ph yet present in apporved products

>100 pharmaceutical products are in the market containing a cyclodextrin excipient

2 Cyclodextrins as APIs are approved:

- Sugammadex/Bridion (MSD) used in anesthesiology
- 2-Hydroxypropyl-β-cyclodextrin has Orphan Drug designation for treatment of a rare fatal disease (Niemann Pick-C)
- Sulfobutyl-ether- β-cyclodextrin has Orphan Drug designation for treatment of a rare disease (Stargardt)

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