

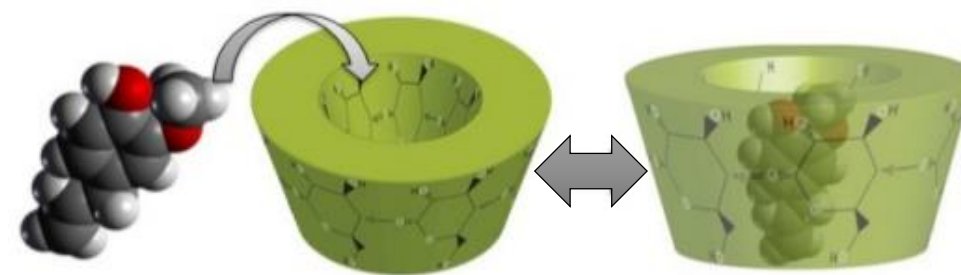
GETTING THE BEST OUT OF CYCLODEXTRINS

Cyclodextrins in
drug delivery systems



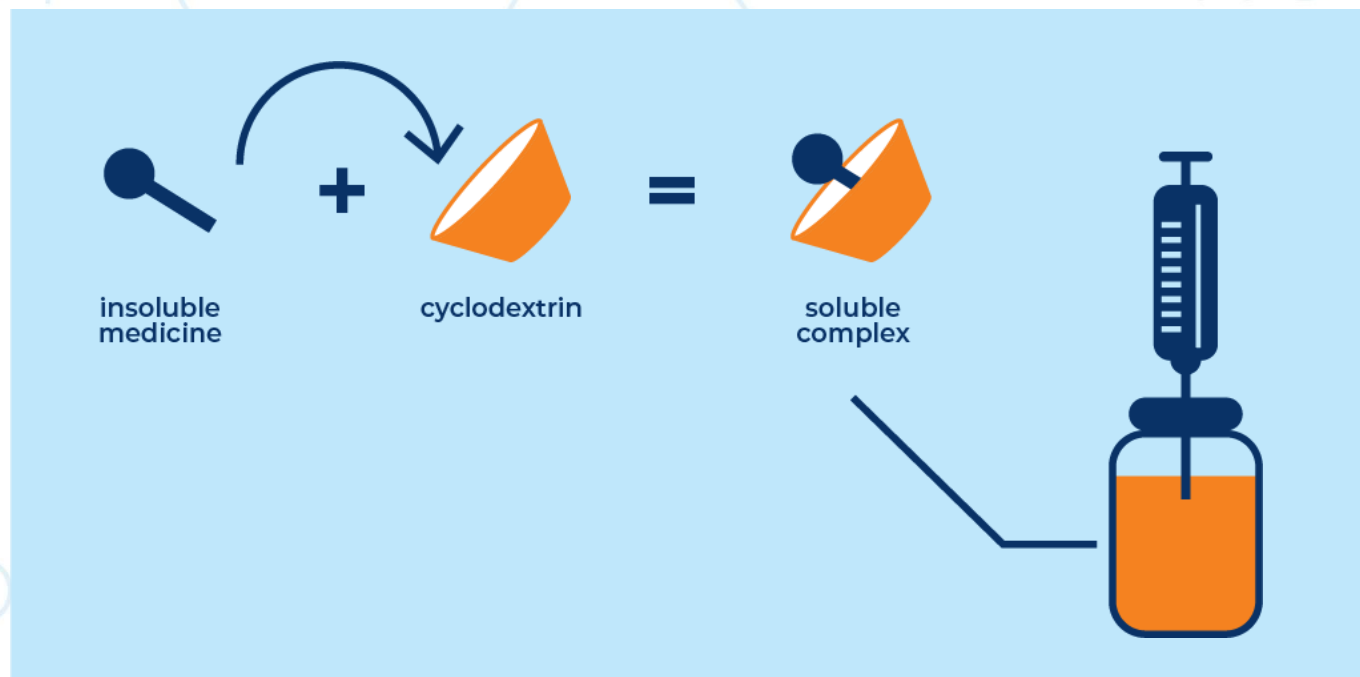
WHAT ARE CYCLODEXTRINS?

- 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



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

DRUG DELIVERY

By „traditional” complexation with CDs

Improved release rate of lipophilic drugs from hydrophilic aqueous vehicles

Improved oral and dermal delivery

Improved delivery of drug into the back (posterior segment) of eye

Deeper delivery of complexed drug into hair follicles



Novel possibilities with modified CDs

CDs with moieties **targeting** cancer cells e.g. folate, maltosyl

CDs with **photosensitizer** moieties for photodynamic therapy (PDT)

Ethylated, acetylated CDs for **sustained delivery**

Drug-CD **conjugates** for targeted colon delivery

Self-assembled **nanoparticles** of CD polymers for cancer therapy

Stimuli responsive nanoparticles

Antibody-targeted nanoparticles for **siRNA delivery**

CD immobilized on polymer for controlled release of anesthetics

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



Orally disintegrating tablets (ODT)

- Fast dispersion, dissolution
- Reduced bitter taste

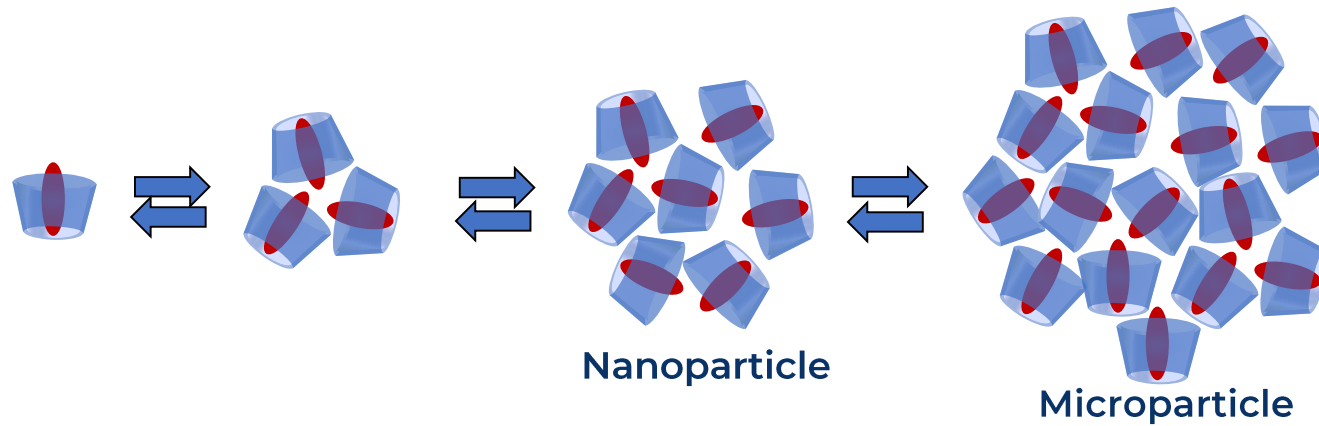


Piroxicam in beta-cyclodextrin dispersible tablets

Oral flexible tablets (OFTs) for pediatrics and geriatrics

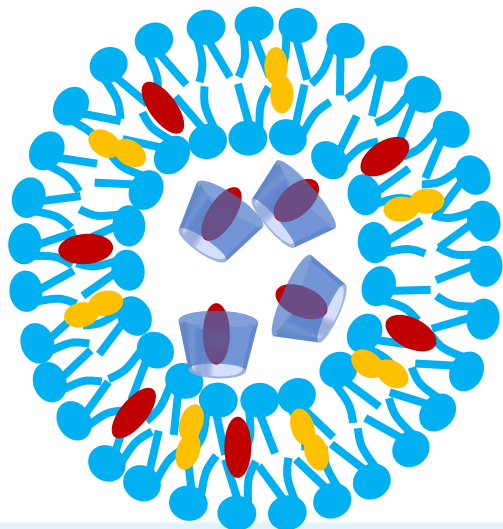
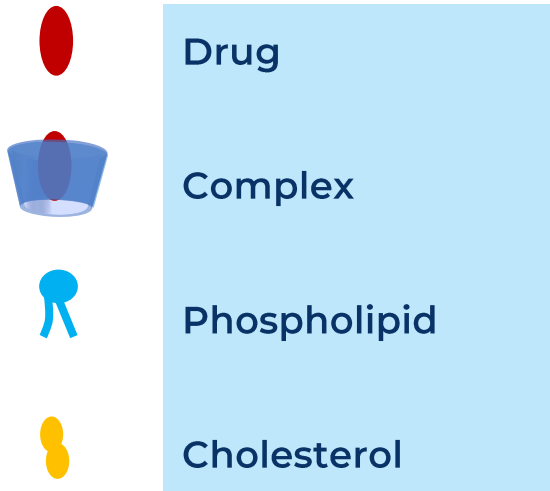
- Flexibility in dose administration
- Fast dissolving films/strips

CD AGGREGATES FOR TARGETING POSTERIOR SEGMENT OF EYE



- Aggregates of γ -CD complexes
- Enhanced drug concentration in the retina
- Eye drops can replace intravitreal injections and implants

DRUGS IN CDs IN LIPOSOMES

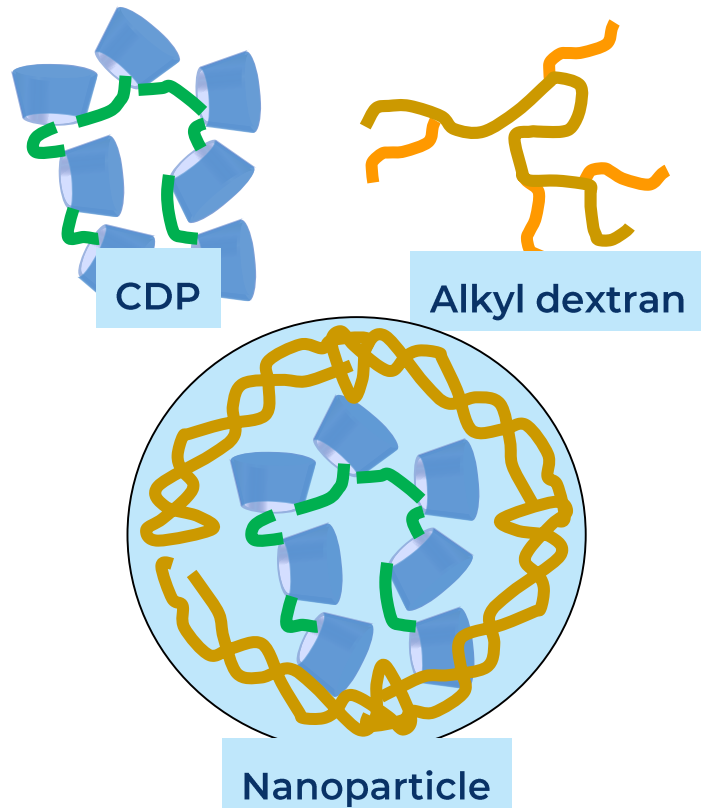


Small unilamellar vesicles (SUV)
 Large unilamellar vesicles (LUV)
 Multilamellar vesicles (MLV)

Double loading:

- drug in the bilayer
- drug in CD

Enhanced bioavailability of drug in CD in liposome compared to binary systems (drug in CD and drug in liposome)



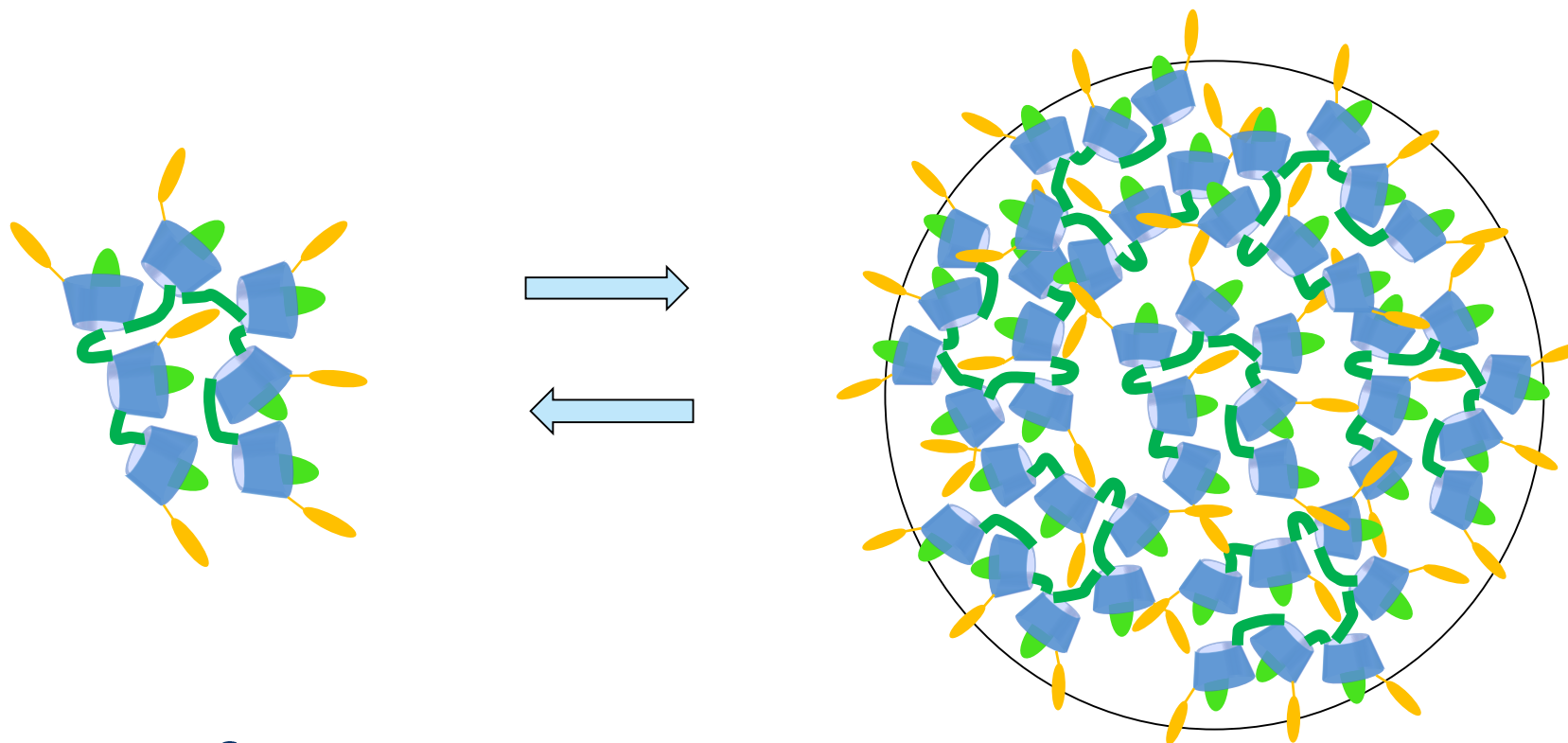
$\varnothing = 200 \text{ nm}$

Some of the CD units in a CD polymer (CDP) form complexes with the alkyl chains on dextran, others with a drug

Controlled release

SELF-ASSEMBLED NANOPARTICLES

Drug 1  covalently bound to CDP
Drug 2  non-covalently bound



Combination therapy for cancer

TARGETING BY LIGHT

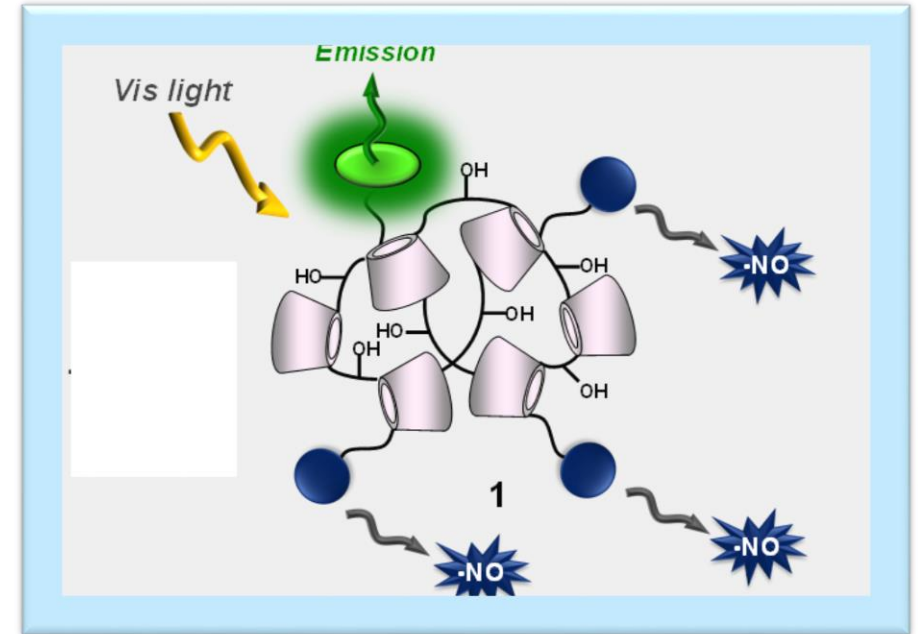
Conjugation of photosensitizer/ fluorescent moiety/NO-releasing agent

Photoexcitation

- Fluorescence emission for imaging
- Nitric oxide radical release for therapy
- Anticancer and antibacterial effects

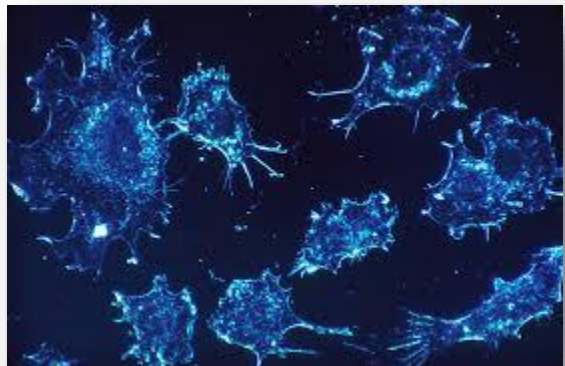
Multifunctional drug delivery

- Drug 1: NO-releasing agent
- Drug 2: anticancer, antibacterial drug complexed by CD



CD-coating of magnetic nanoparticles

- Enhanced drug load
- Improved biocompatibility
- Reduced cytotoxicity
- Improved cell internalization



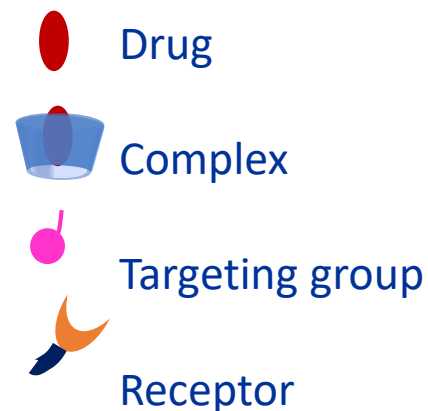
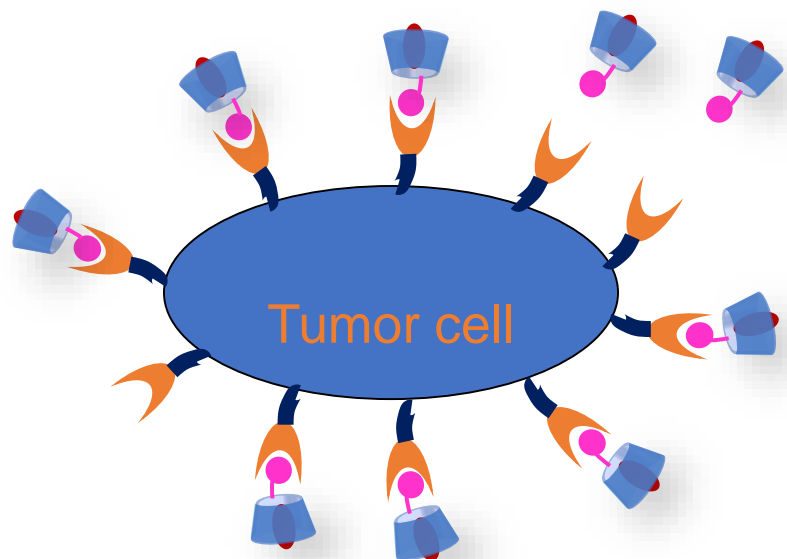
Tumor targeted drug delivery
by using magnetic field

Tumor targeting by folate and/or mannoside moieties

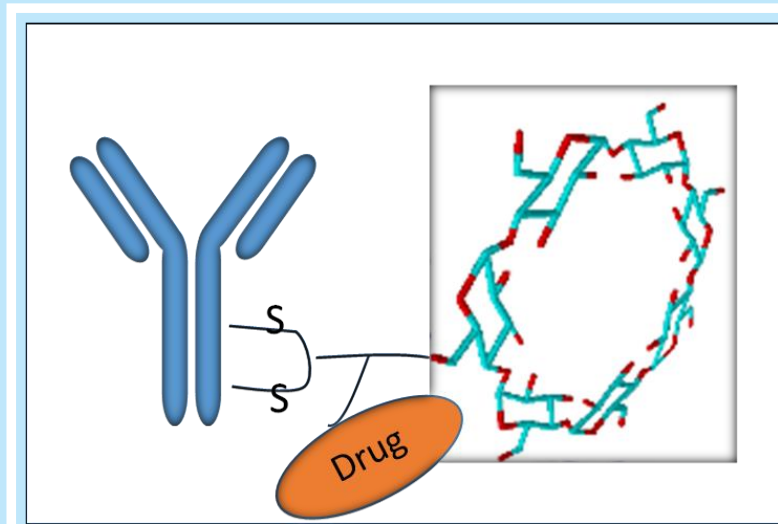
Cell-penetrating peptide-conjugated CD

Cationic CDs

Multivalency



Both the drug and antibody covalently bound to CD Stable and site-specific delivery systems for drugs and genes



Antibody-targeted cyclodextrin-based nanoparticles for siRNA delivery in the treatment of acute myeloid leukemia

Guo et al. Mol. Pharm. 2017, 14(3), 940-952
<https://cyclodextrinnews.com/2018/10/10/antibody-conjugated-cyclodextrin-for-tumor-drug-delivery/>

ELECTROSPUN NANOFIBERS TO CONTROL DRUG RELEASE

Polymer-Free Cyclodextrin Nanofibers

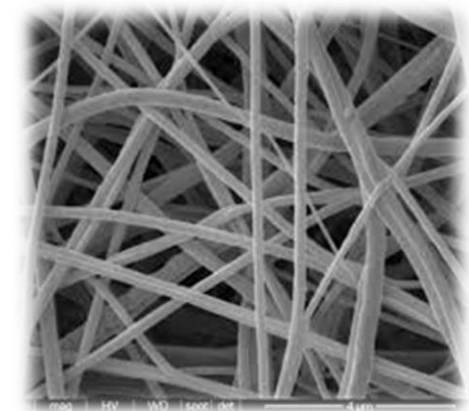
Rapid dissolution
Fast drug release

Poly-Cyclodextrin Functional Nanofibers

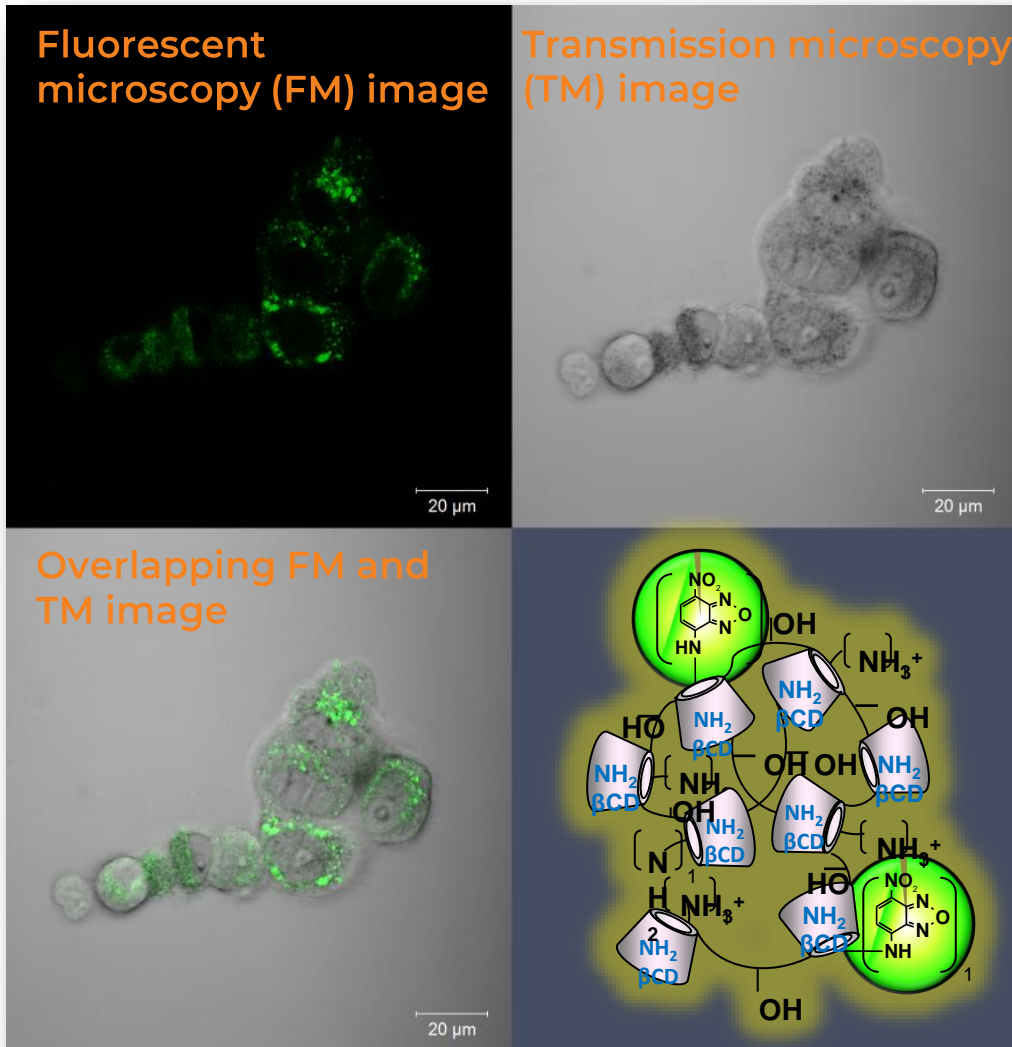
Crosslinking with citric acid

CD-Drug Blended Polymeric Nanofibers

Polycaprolactame, hydroxypropyl cellulose,
polyvinylpyrrolidone, etc.
Slower dissolution
Sustained drug release



ENHANCED CELL PENETRATION WITH FLUORESCENTLY-LABELLED CD-POLYMERS



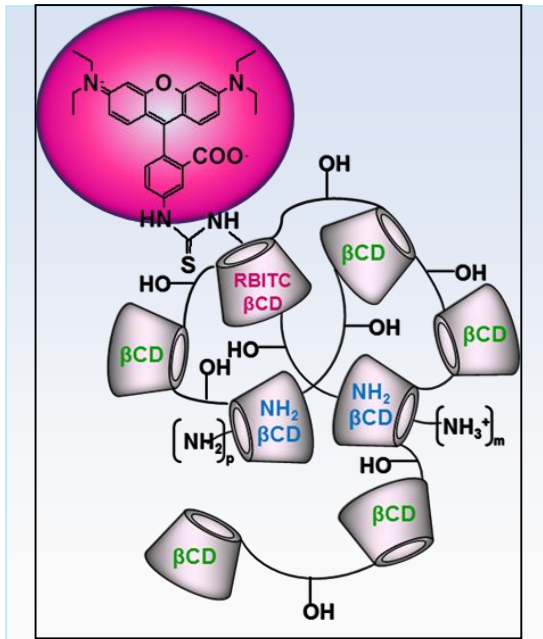
Cell targeting with NH_2

human squamos carcinoma cells (A 431)

Useful for

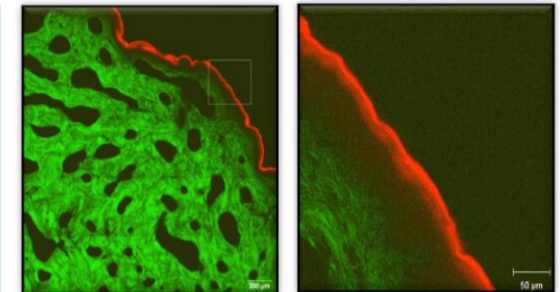
Imaging
Anticancer drugs delivery

Targeting with NH₂ function Imaging through fluorescent substituents (rhodamine-B, RBITC)

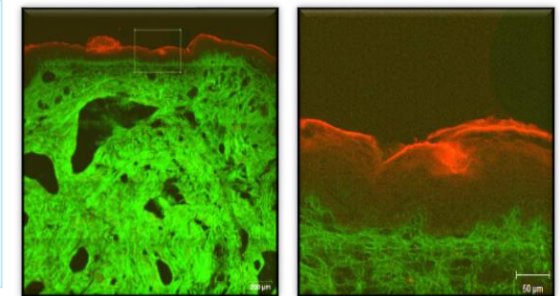


Topical delivery with
β-cyclodextrin polymer labeled RBITC
(in cooperation with group of M. Ericson)

RBITC in MiliIQ



BCDps-RBITC
in MiliIQ



Confocal microscopy of
cryosections of human skin  DEXOLVE™

WHO ARE WE AT CYCLOLAB?



The world's only all-round **CYCLODEXTRIN** company with over

40-year experience of CD-technology

in pharmaceutical-, cosmetics-, food-, environmental- and analytical applications

Experience

Over 490 technical/scientific papers and 950 technical reports to customers

200 different cyclodextrin derivatives
130 patents/applications
40 products on the market

Drug Master Files (USA type IV) and eCTD

Over 20,000 citations to CYCLOLAB's papers

Expertise & Technology

Custom synthesis

Drug solubilization and stabilization

Further industrial applications

Cyclodextrin-related analytics

Stability testing

GMP-conform manufacturing

Feasibility studies



CYCLOLAB SERVICE PORTFOLIO AND PIPELINE PROGRAMS RELATED TO DRUG DELIVERY



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

Platform for selective and targeted anticancer therapy with unmodified APIs

Platform for improving BBB penetration



CDs in DRUG DELIVERY

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