CYCLOLAB

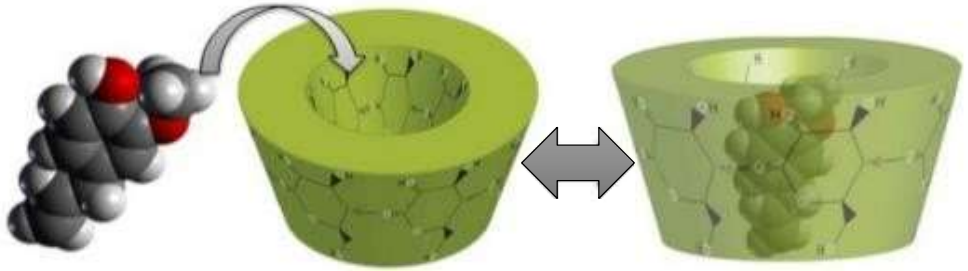
PIONEERS IN CYCLODEXTRIN-BASED INNOVATION

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



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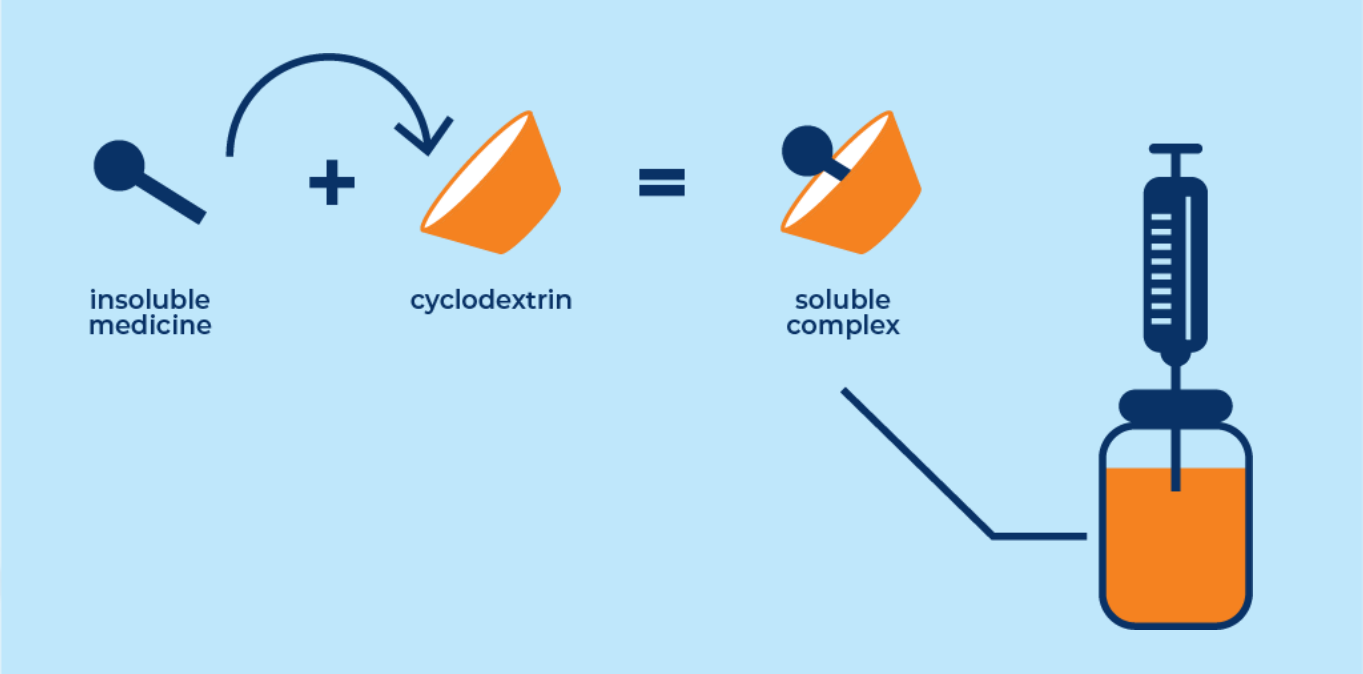
MAIN FUNCTIONAL PROPERTIES OF CDs

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

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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

Loftsson J. Incl. Phenom. Macrocycl. Chem. 2014, 80,1–7

Challa et al. AAPS PharmSciTech 2005, 6(2), E329–E357

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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

ORODISPERSIBLE FORMULATIONS

Orally disintegrating tablets (ODT)

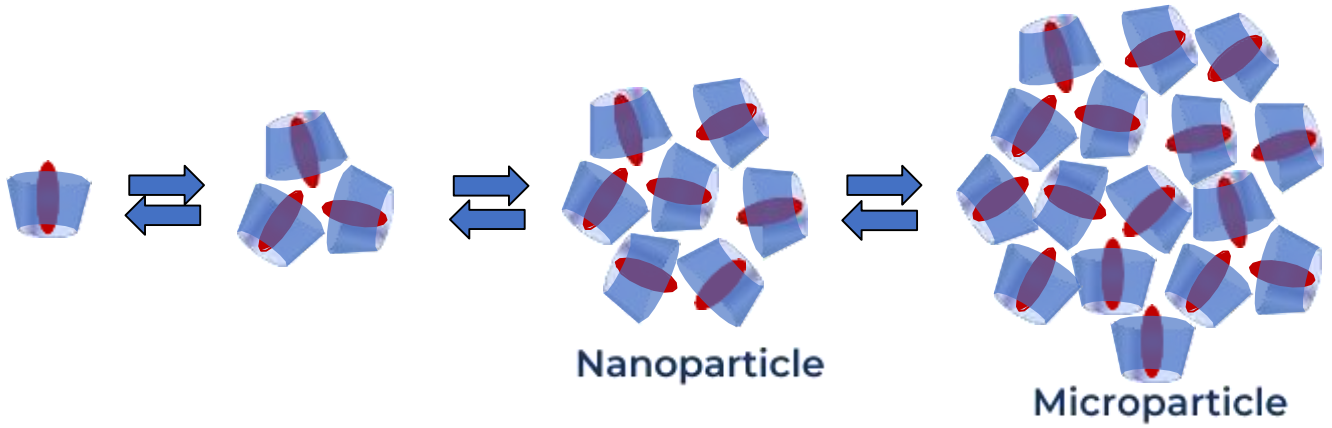
- Fast dispersion, dissolution
- Reduced bitter taste

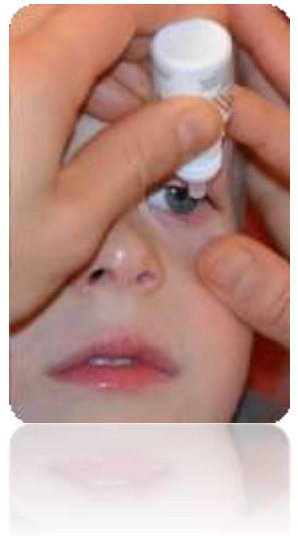
Piroxicam in beta-cyclodextrin dispersible tablets

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

Loftsson & Stefansson: Int. J. Pharm. 2017, 531, 413 -423

DRUGS IN CDs IN LIPOSOMES

Drug

Complex

Phospholipid

Cholesterol

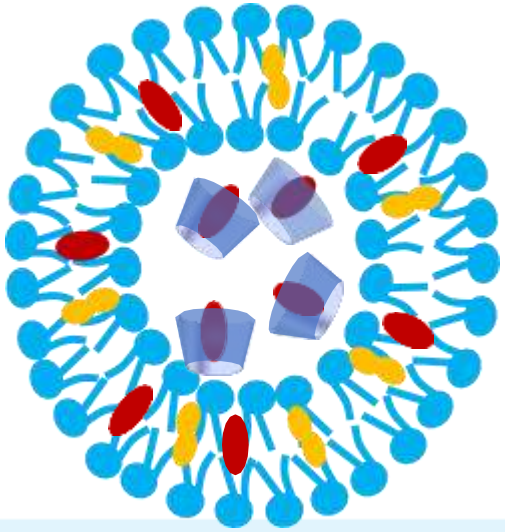
Small unilamellar vesicles (SUV)

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)

Gharib et al. Carbohydr. Polym. 2015, 129, 175-186

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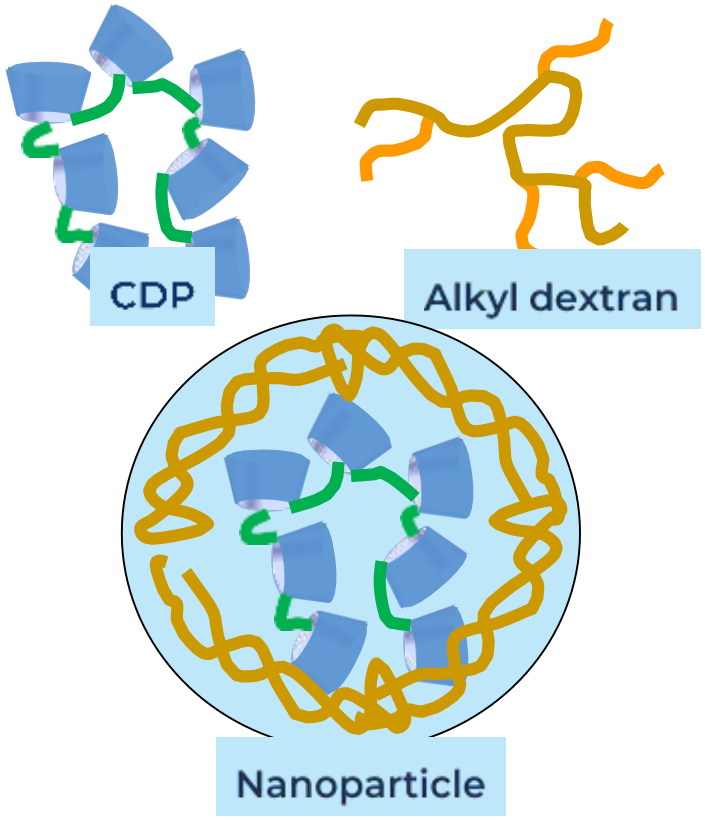
SELF-ASSEMBLED NANOPARTICLES



Ø = 200 nm

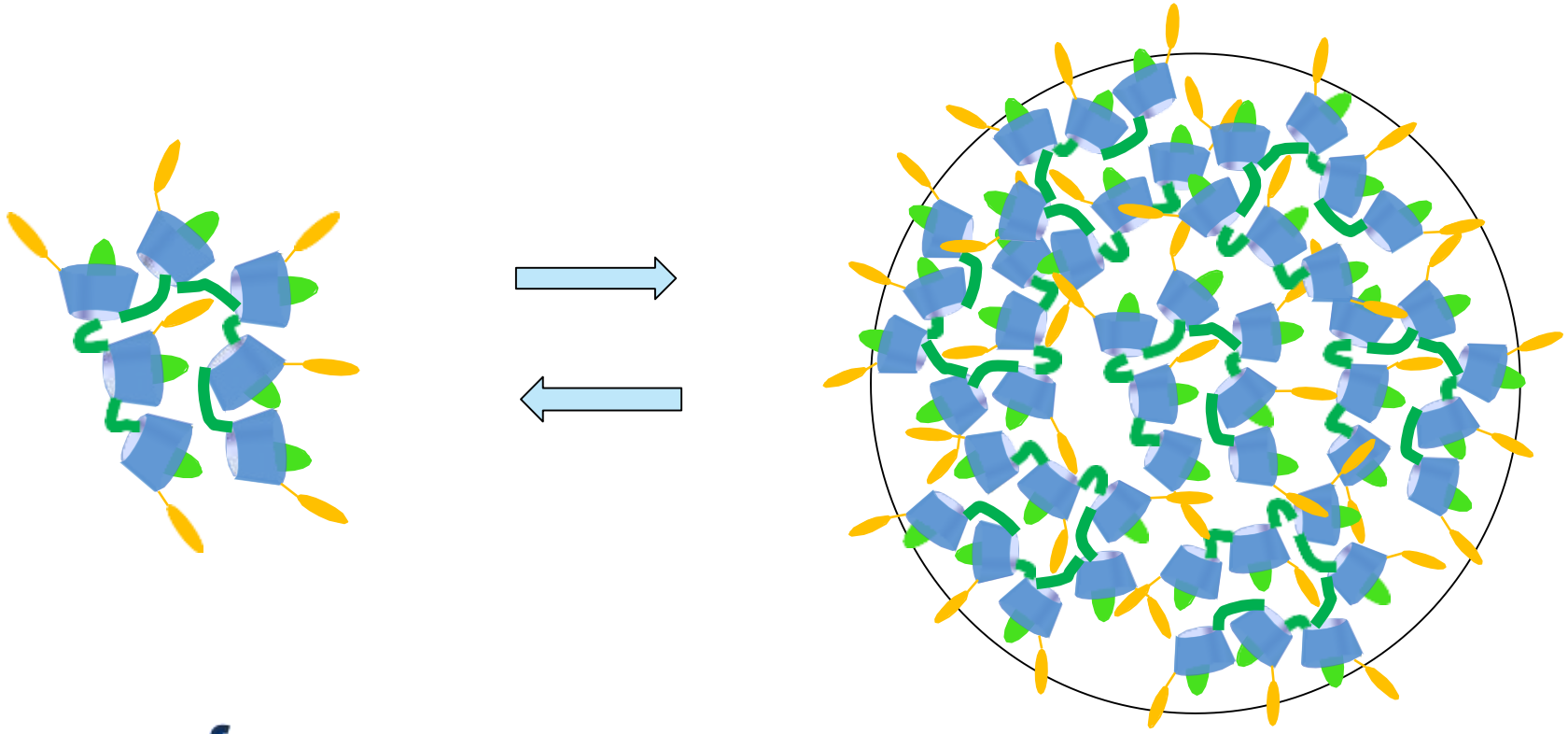
Some of the CD units in a CD polymer (CDP) form complexes with the alkyl chains on dextran, others with a drug

Controlled release

Gref, R et al. J. Contr. Rel. 2006, 111(3), 316-324

SELF-ASSEMBLED NANOPARTICLES

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



Combination therapy for cancer

Davis: Adv. Drug Deliv. Rev. 2009, 61(13), 1189-1192

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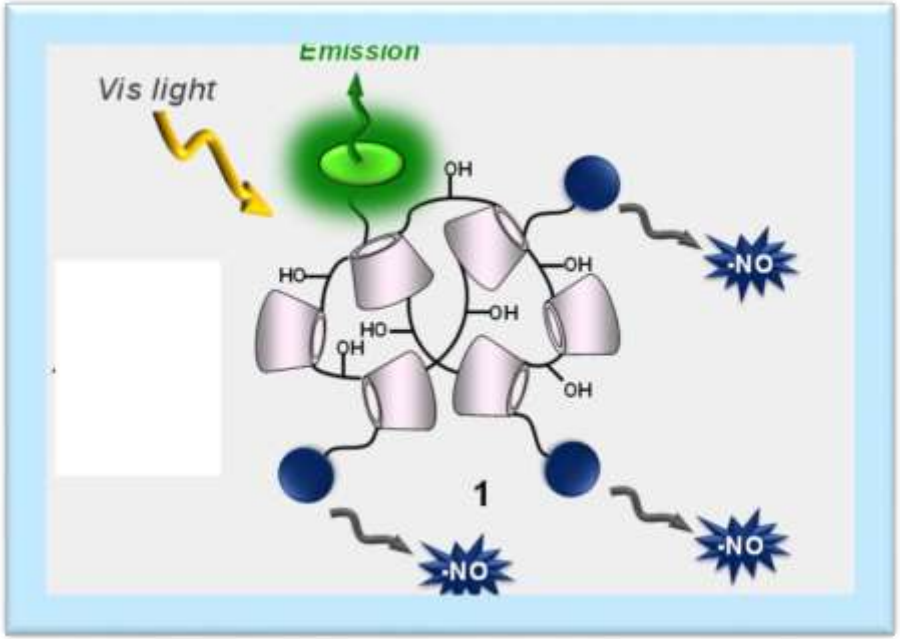
TARGETING BY LIGHT

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

Malanga et al.: Biomater. Sci. 2019, 7, 2272
Benkovics et al.: Int. J. Pharm. 2017, 531(2), 614-620

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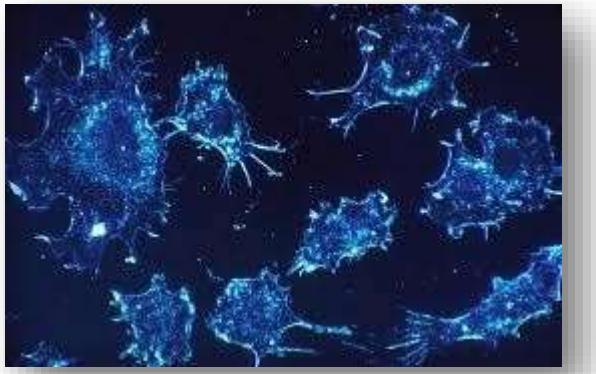
TARGETING BY MAGNETIC FIELD

CD-coating of magnetic nanoparticles

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



Tumor targeted drug delivery by using magnetic field

Cutrone et al.: Int. J. Pharm. 2017, 531(2), 621-639

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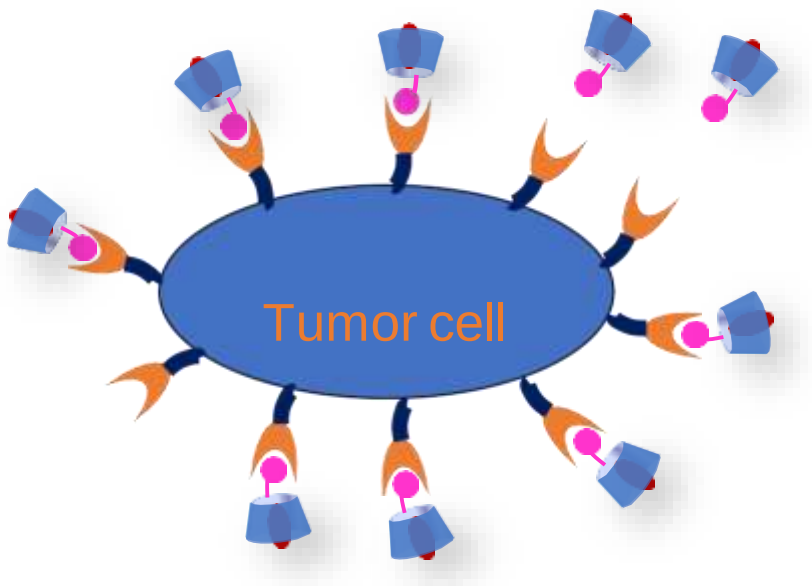
CELL TARGETING

Tumor targeting by folate and/or mannoside moieties

Cell-penetrating peptide-conjugated CD

Cationic CDs

Multivalency



Drug

Complex

Targeting group

Receptor

Salmaso et al. Journal of Drug Targeting 2007, 15(6), 379-390
Cutrone et al. Carbohydrate Polymers 2018, 199, 649-660

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ANTIBODY-CONJUGATED CD FOR TUMOR DRUG DELIVERY

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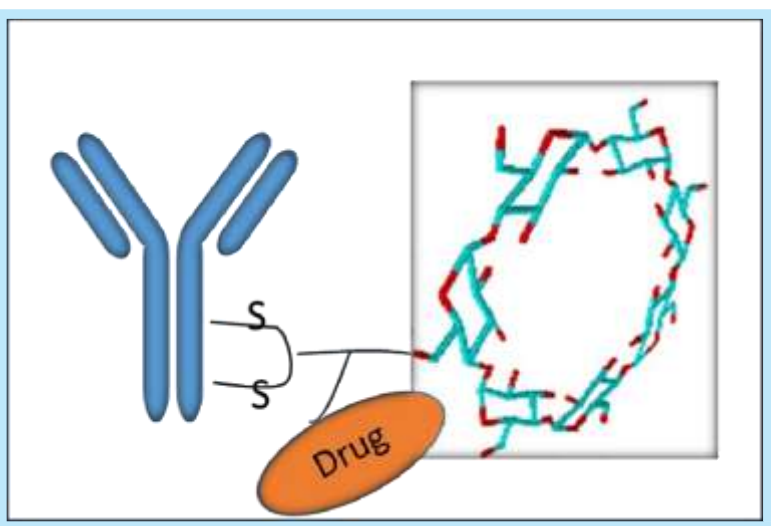
Both the drug and antibody covalently bound to CD
Stable and site-specific delivery systems for drugs and genes



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/

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ELECTROSPUN NANOFIBERS TO CONTROL DRUG RELEASE

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Polymer-Free Cyclodextrin Nanofibers

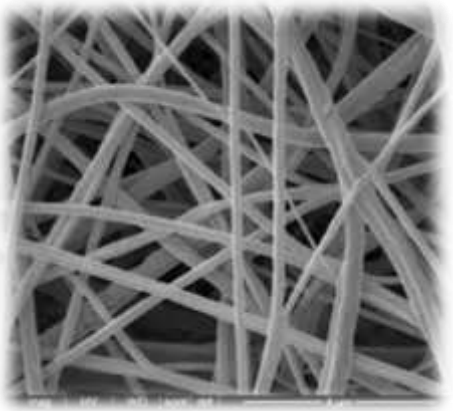
Rapid dissolution
Fast drug release

Poly-Cyclodextrin Functional Nanofibers

Crosslinking with citric acid

CD-Drug Blended Polymeric Nanofibers

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



Thopuz & Uyar Pharmaceutics. 2019, 11{1}, 6

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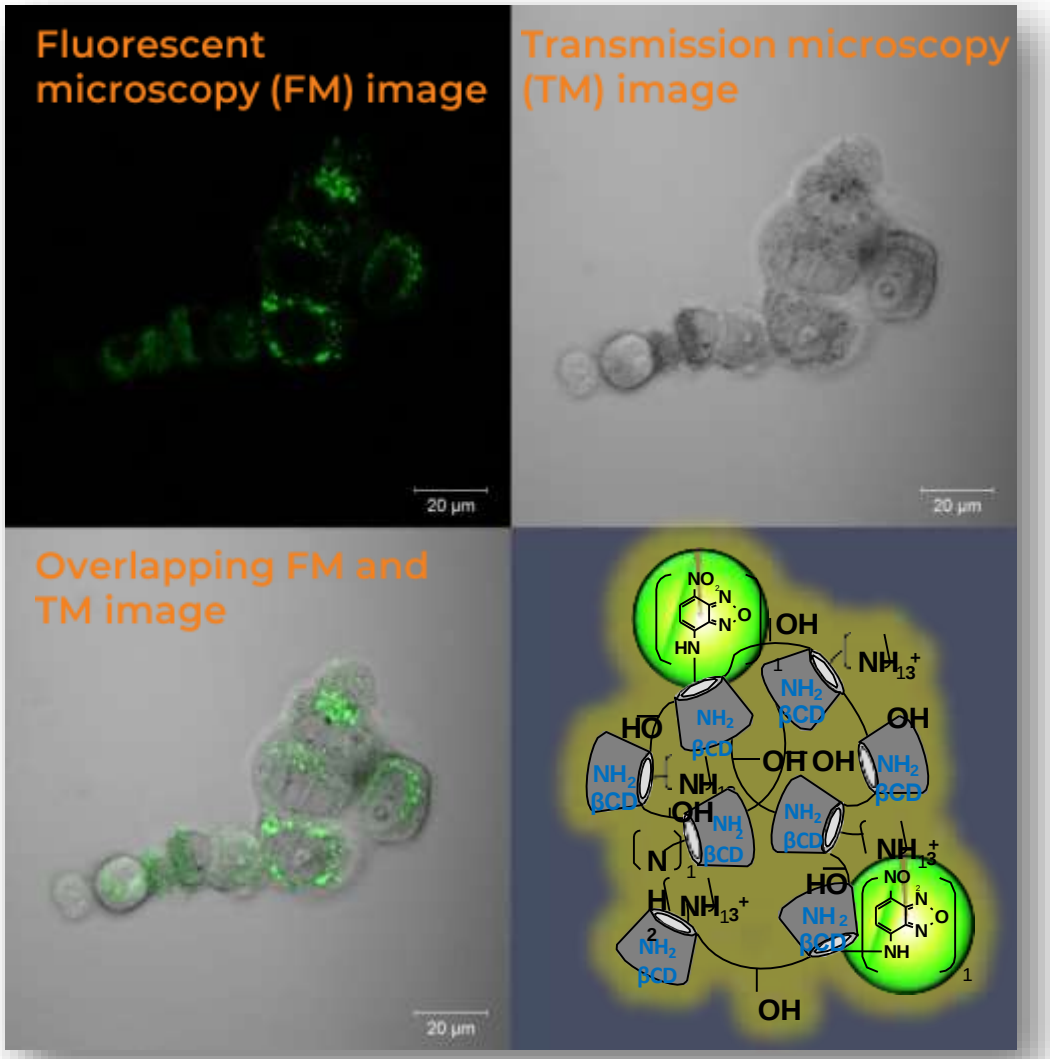
ENHANCED CELL PENETRATION WITH FLUORESCENTLY-LABELLED CD-POLYMERS



Cell targeting with NH2

human squamos carcinoma cells (A 431)

Useful for

Imaging
Anticancer drugs delivery

Malanga et al. Biomater. Sci. 2019, 7, 2272-2276

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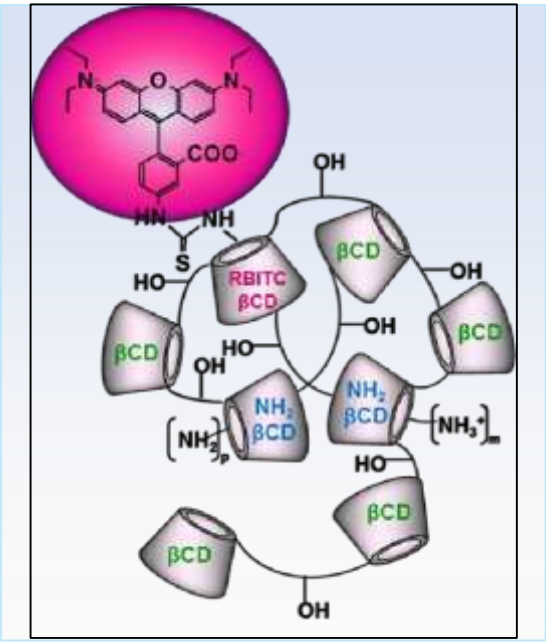
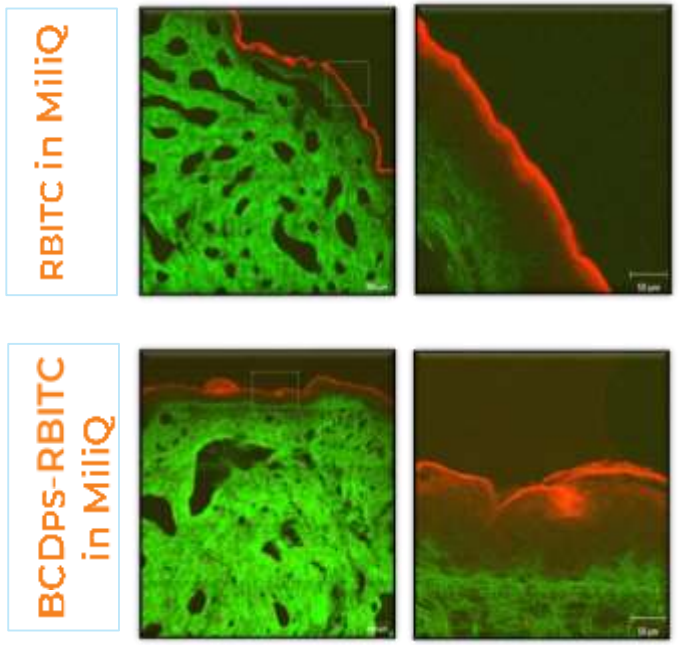
ENHANCED TRANSDERMAL DELIVERY WITH FLUORESCENTLY-LABELLED CD-POLYMERS

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



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



Confocal microscopy of cryosections of human skin

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WHO ARE WE AT CYCLOLAB?

The world's only all-round CYCLODEXTRIN company with experience in CD-technology since 1991

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

Experience

Over 540 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

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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

Life cycle management

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

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