CYCLOLAB

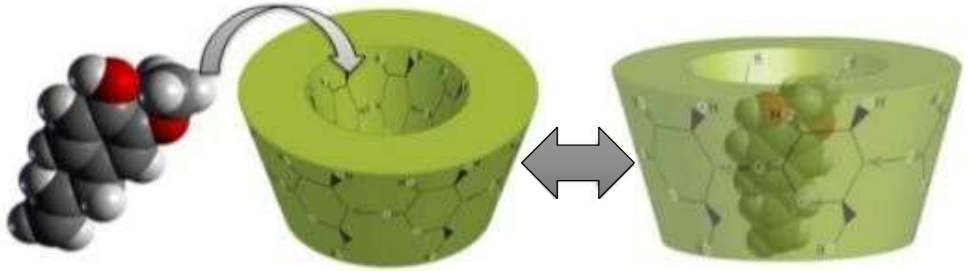
PIONEERS IN CYCLODEXTRIN-BASED INNOVATION

GETTING THE BEST OUT OF CYCLODEXTRINS

Cyclodextrins in ophthalmic drug products

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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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

MARKETED EYE DROPS CONTAINING CDs

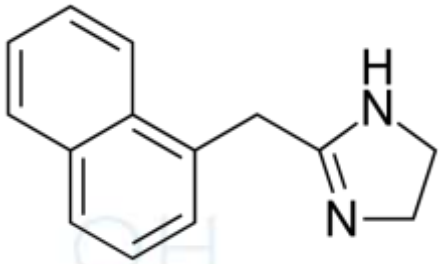
CLEAR EYES

Medted (South Africa)

Active: naphazoline HCl (0.3 mg/ml)

Solubility: 38.1 µg/ml

CD: not specified - less irritation



MARKETED EYE DROPS CONTAINING CDs

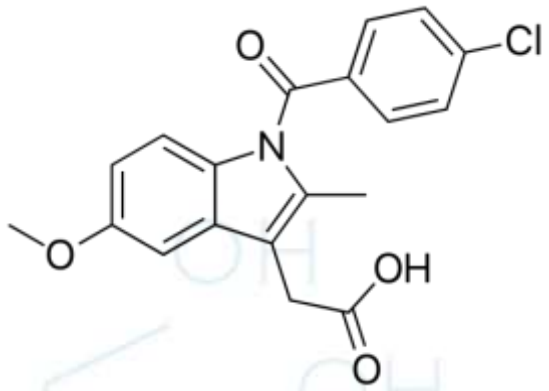
INDOCID / INDOCOLLYRE

Chauvin (Fr.) / Bausch+Lomb (USA)

Active: indomethacin (1 mg/ml)

Solubility: 0.937 µg/ml

HPβCD - 1000x solubility increase



MARKETED EYE DROPS CONTAINING CDs

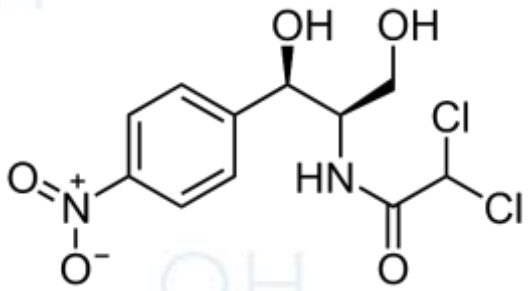
CLOROCIL

Oftalder (Poland) / Edol (Portugal)

Active: chloramphenicol (8 mg/ml)

Solubility: 2.5 mg/ml

RAMEB – solubility increase



MARKETED EYE DROPS CONTAINING CDs

VOLTAREN ophtha CD / VOLTAROL ophtha

Novartis (Switzerland) / Théa (Fr.)

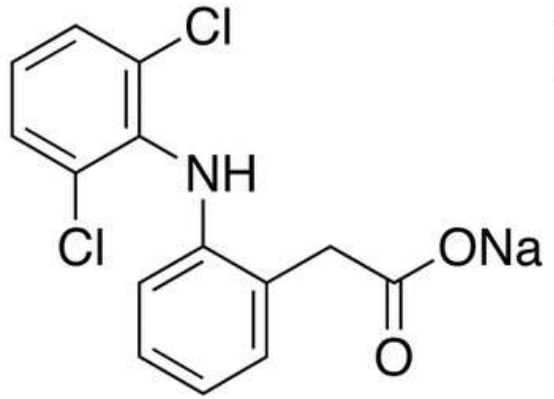
Active: diclofenac (1 mg/ml)

Solubility: 0.8-1.7 mg/ml

HPγCD

On the market since 2005

Preservative is benzalkonium chloride, not thiomersal



MARKETED EYE DROPS CONTAINING CDs

PAZEO

Alcon (Novartis) (Switzerland)

Active: olopatadine hydrochloride (7 mg/ml)

Solubility: (~31 µg/ml, not salt)

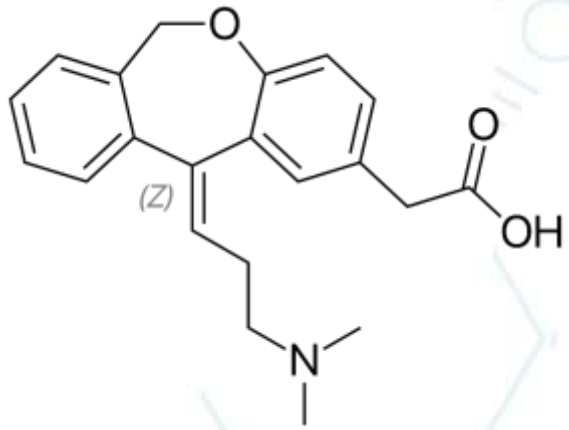
HP-γ-CD

On the market since 2016

Antiallergic (1 drop lasts for 24 hours supposedly)

Solubility increase
(Other marketed products max 1-2 mg/ml)

Preservative benzalkonium chloride (like Voltaren Ophtha)

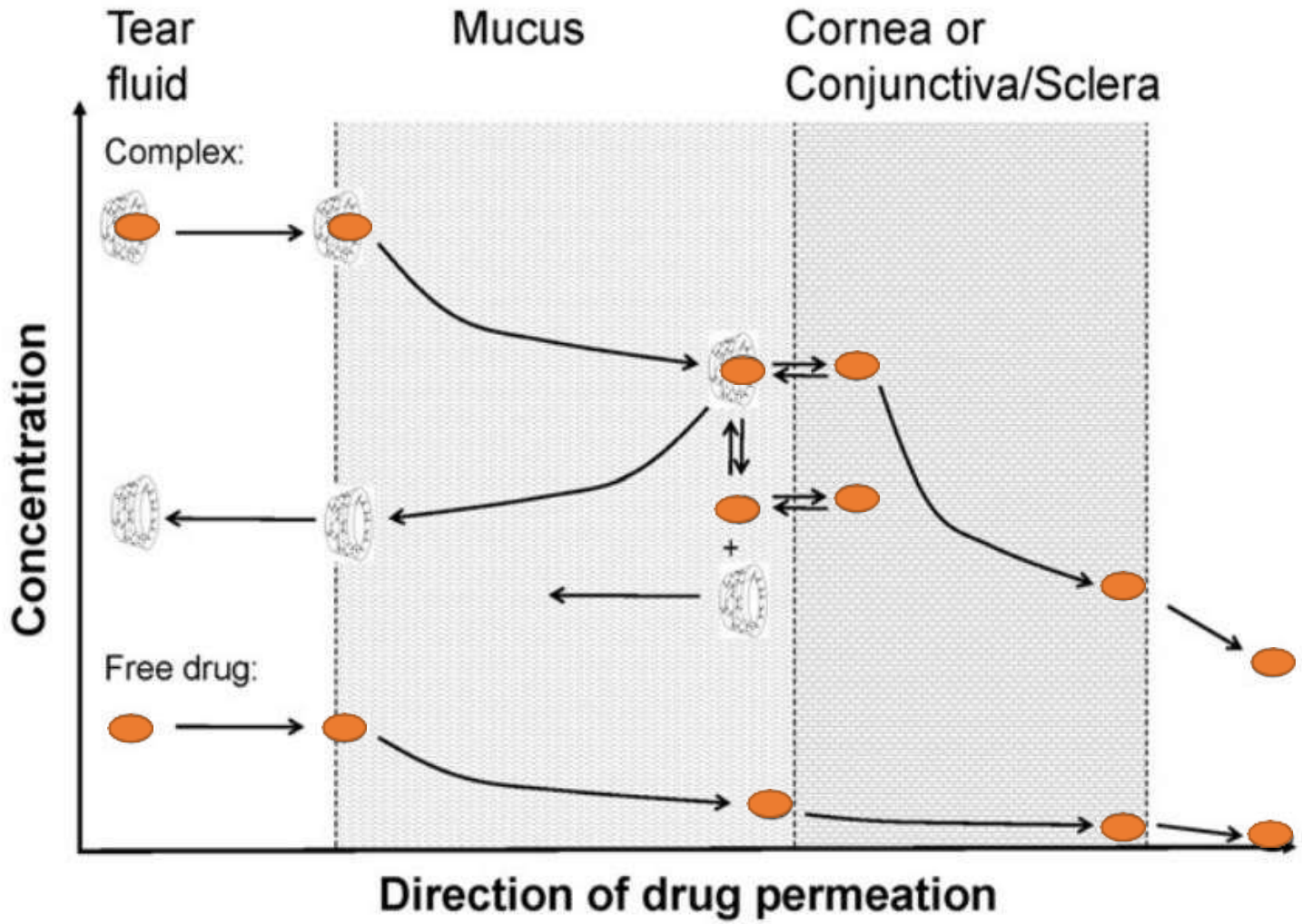


EMA STANDPOINT FOR OCULAR USE OF CDs

CD/route	α-CD	β-CD	γ-CD	RM-β-CD	HP-β-CD/SBE-β-CD[1]
Ocular					
Safe solution, %	<4	±1	N	<5	10
TH adult	1	1	-	1	10
TH neonate	0.1	0.1	-	0.1	1

- Cyclodextrins improve solubility, stability, membrane permeation and reduce the irritation
- αCD might be able to mediate the drug transport through the layer of the cornea
- Cyclodextrins are usually safe
- SBEβCD and HPβCD found not to be toxic or irritating even at high concentrations (10 and 12.5% tested respectively)
- αCD and RAMEB can be toxic at high concentrations to the corneal epithelium of rabbits (max. safe concentration 4 and 5% respectively)

HOW CDs CAN HELP IN PERMEATION



Ref: Jansook et al. (2015). Pharm Dev and Tech

CONCLUSION

- The administered quantity of an eye drop is low (40-50 µl per drop), relatively high API concentration is needed
- CDs have the potential of improving eye drops in several ways
- Irritation and pharmacokinetics studies can be necessary during the development of a supergeneric drug formulation containing CDs
- There are no γCD containing ophthalmic products currently on the market, but there are some in clinical trials
- (Oculis – Iceland – several formulations in the clinical/pre-clinical pipeline)

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

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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CYCLOLAB SERVICE PORTFOLIO

Feasibility study

Running a short feasibility study with your molecule free of charge

Proof of concept to consider CD based formulations

Go/no go milestone to consider CD based formulations

CycloLab Grant

CycloLab offers a unique possibility to collaborate on creating novel and interesting cyclodextrins under the terms of the CycloLab Grant

The proposal after application is thoroughly evaluated by CycloLab

If the application is approved, the cyclodextrin is provided free of charge for the beneficiary

DEXOLVE™

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