

**CYCLOLAB**



*The Cyclodextrin Company*







# **Benefits and Limitations of Using Cyclodextrins in Drug Formulations**

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**BIT's 7<sup>th</sup> Annual International Symposium of Drug Delivery Systems-2017**  
Time: July 12-14, 2017    Venue: Prague, Czech Republic

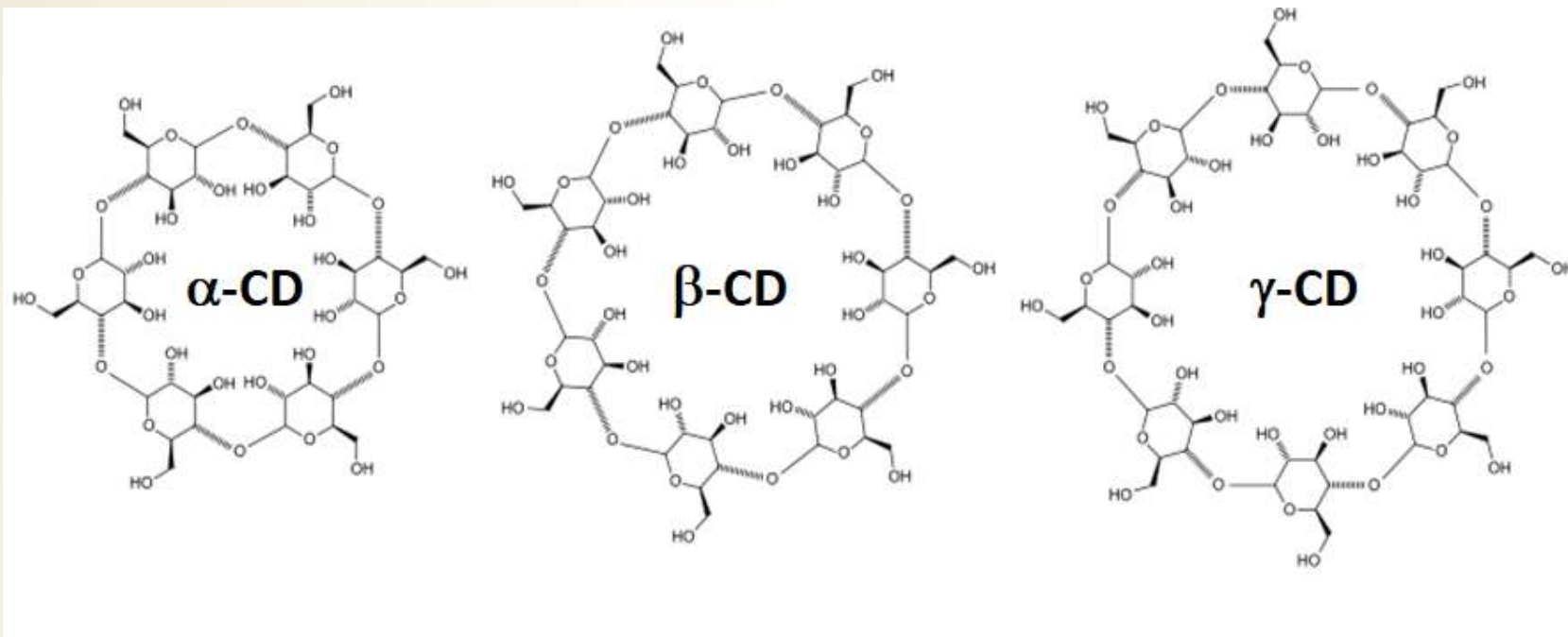
Session 1-2: Enhancing Bioavailability with New Technologies and Strategies

# Outline

-  Cyclodextrins (CDs) as effective solubilizers in drug formulations
-  Cyclodextrins facilitating enhancement of pharmacokinetic properties
-  Cyclodextrins for targeted drug delivery
-  Application in colloidal structures

# Cyclodextrins

## Cyclic glucopyranose oligosaccharides



6-8  $\alpha$ -D-glucose units ( $\alpha$ ,  $\beta$ ,  $\gamma$ -cyclodextrin)

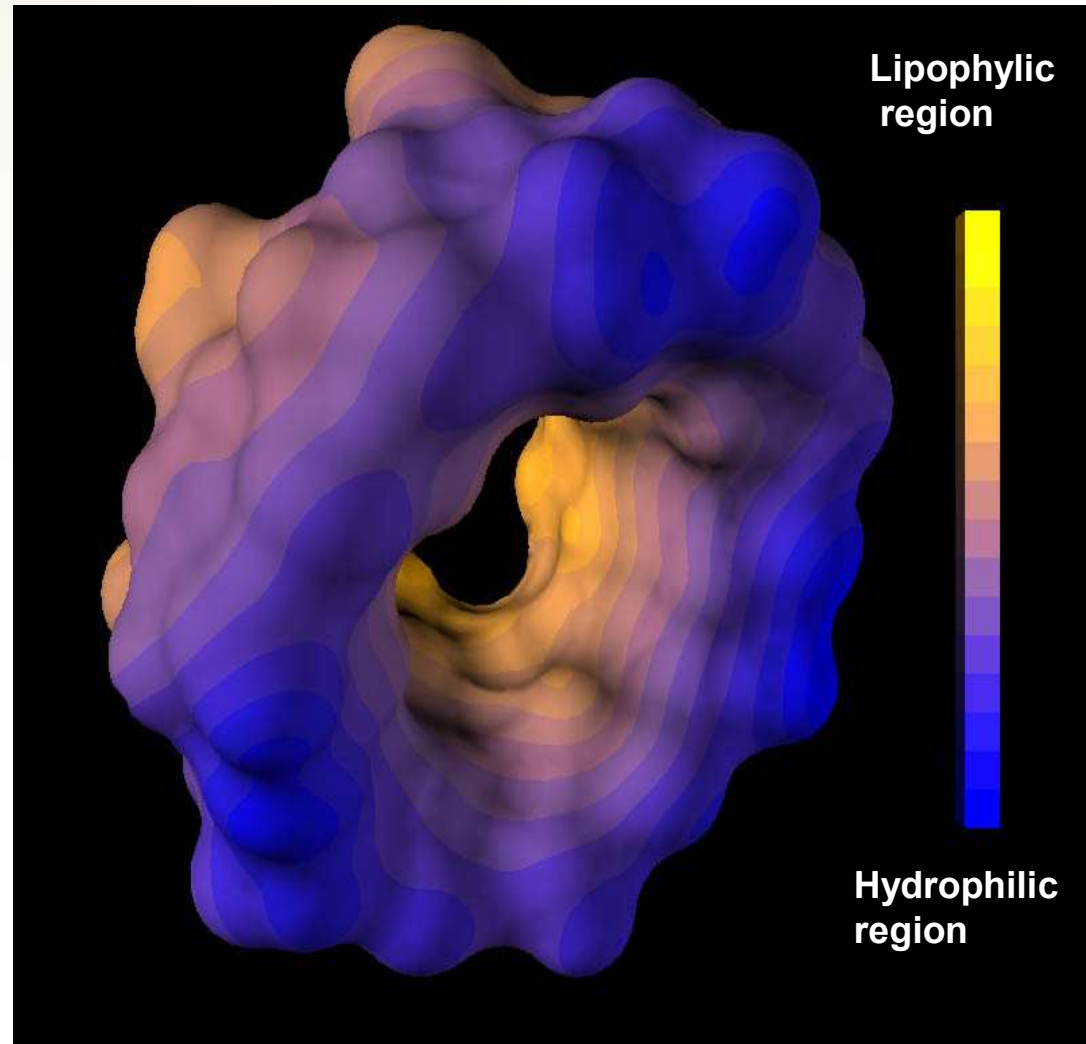


# Cyclodextrins

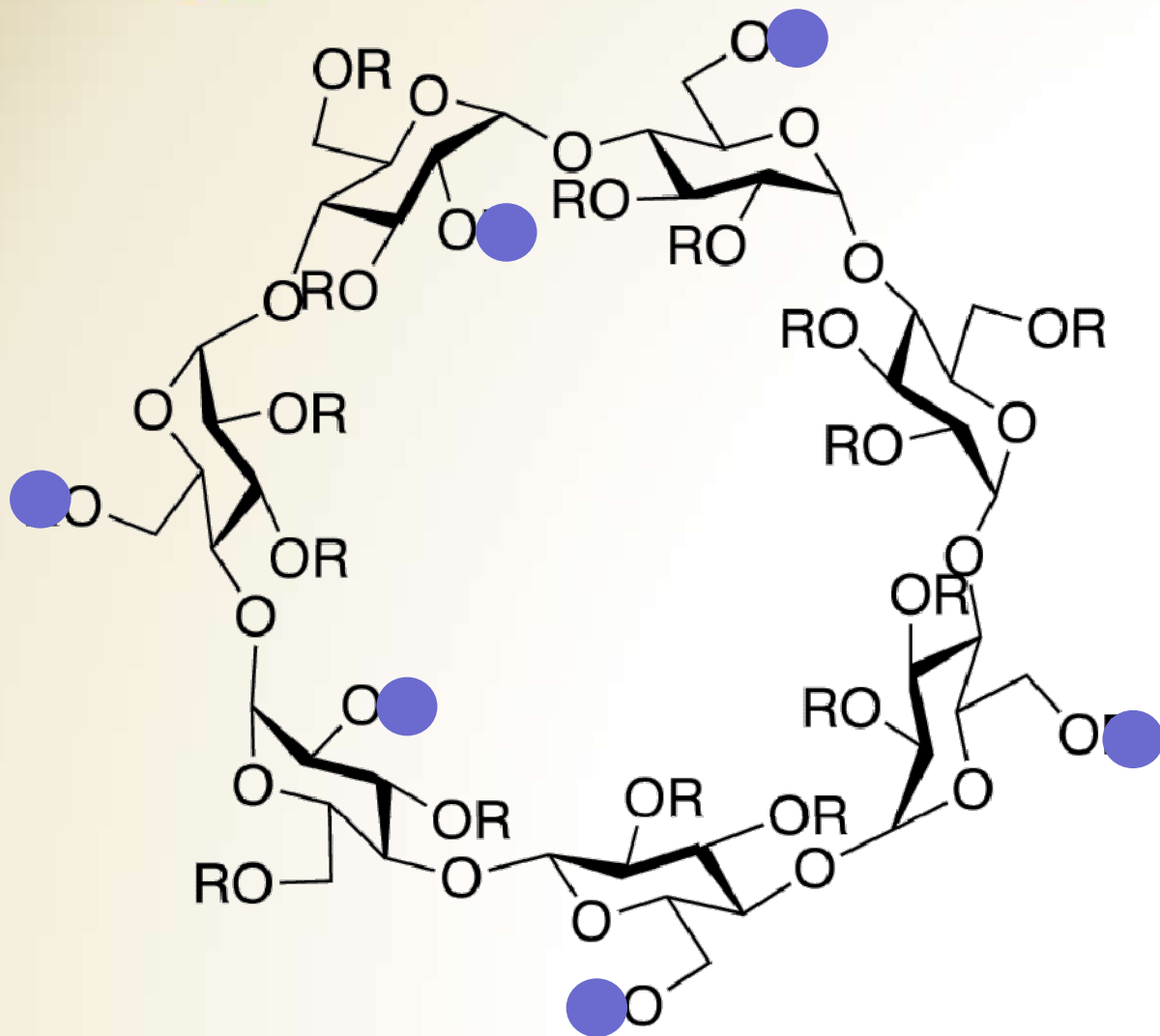
**Doughnut  
or truncated cone  
shape molecules**

**Inclusion complexation**

**Molecular self-assembly**



# Cyclodextrin derivatives



R = H, or

-CH<sub>3</sub>

-CH<sub>2</sub>CH(OH)CH<sub>3</sub>

-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SO<sub>3</sub>Na



## CDs suitably used in pharmaceuticals

### Parent

*Native*

*Unsubstituted*

**$\alpha$ -CD (Alfadex)**

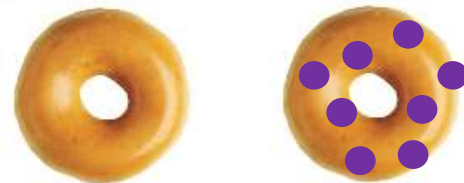
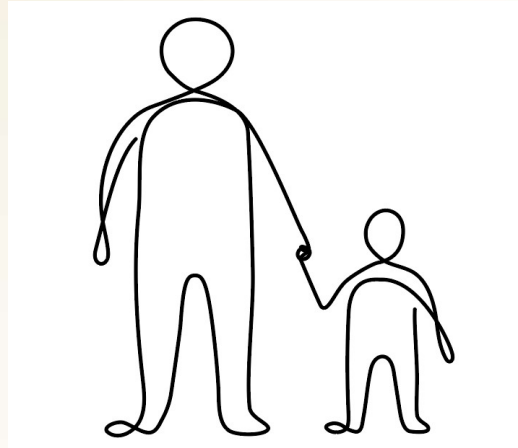
*EP, USP*

**$\beta$ -CD (Betadex)**

*EP, USP*

**$\gamma$ -CD**

*USP, JPC*



### Derivatives

*Substituted*

**2-hydroxypropyl  $\beta$ -CD  
(HP- $\beta$ -CD)**

*EP, USP*

2-hydroxypropyl  $\gamma$ -CD

**sulfobutylether  $\beta$ -CD  
(SBE- $\beta$ -CD)**

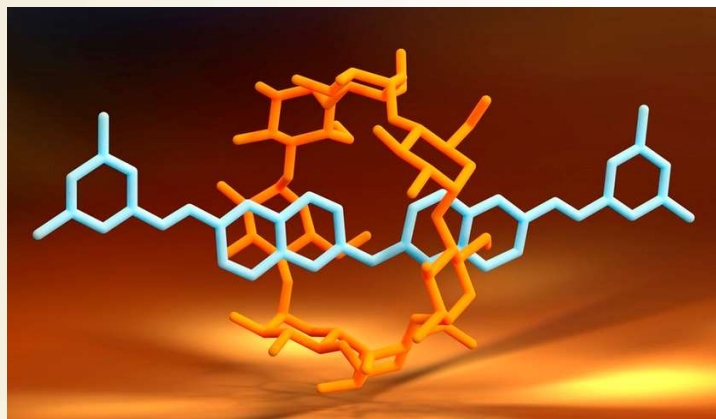
*USP*

random methylated  $\beta$ -CD  
(RM- $\beta$ -CD) (rare: nasal/ocular)





**"för design och syntes av molekylära maskiner"**

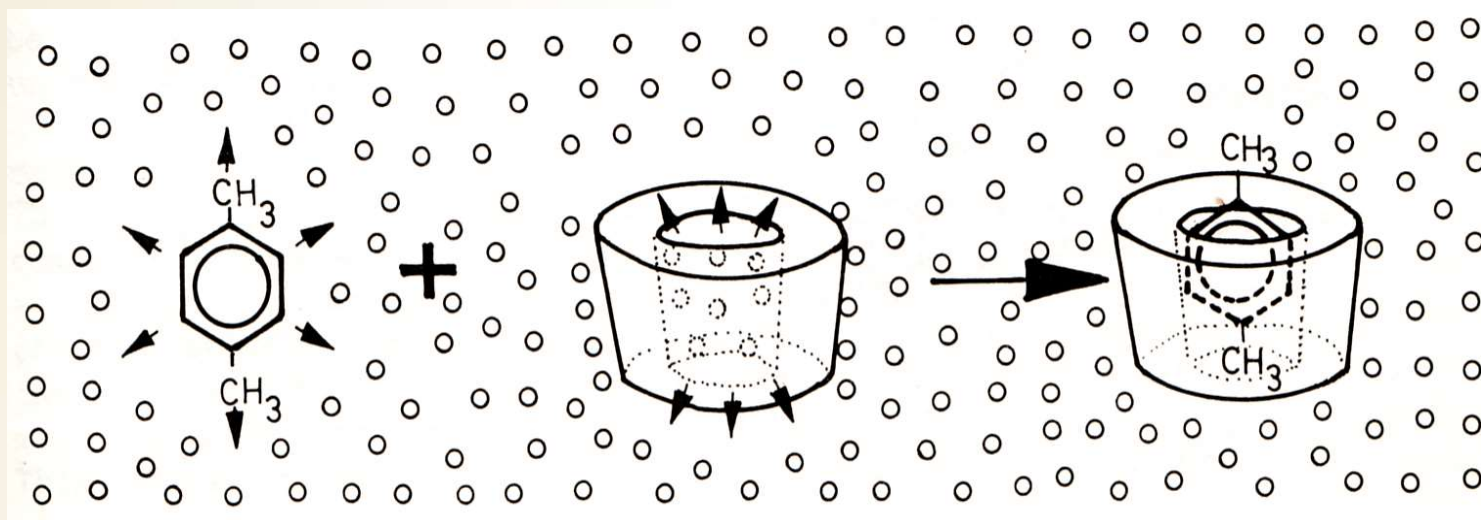
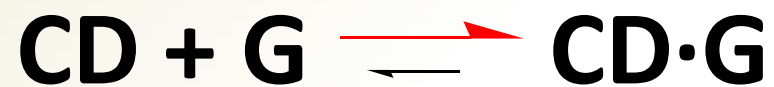


„Switchable rotaxanes may act as drug-release nanovalves in an attempt to develop controllable drug delivery systems for use in the fight against cancer.”

**Chemistry  
Nobel Prize  
2016:  
Sir Fraser  
Stoddart (UK)**

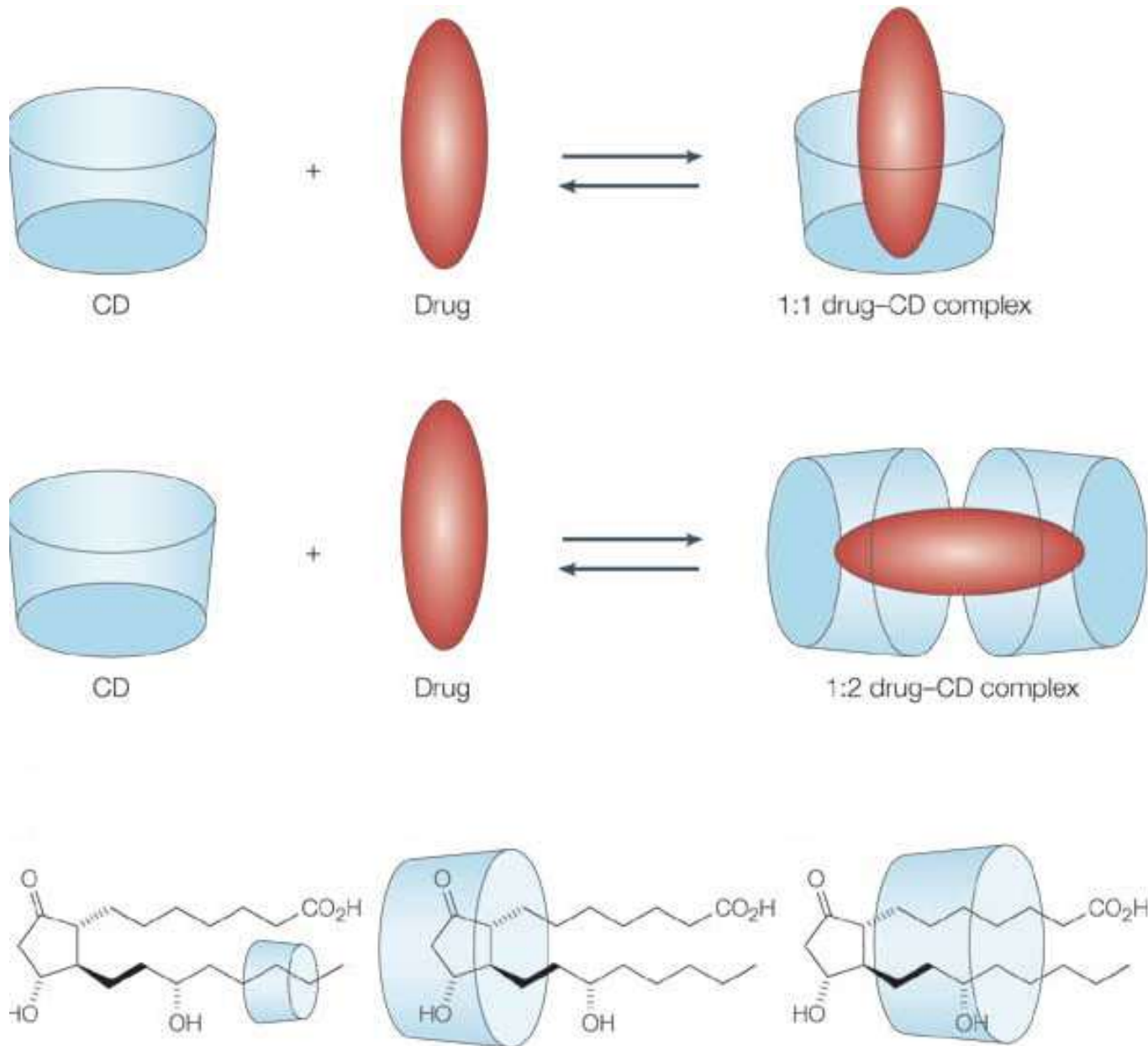


# Cyclodextrin complex formation



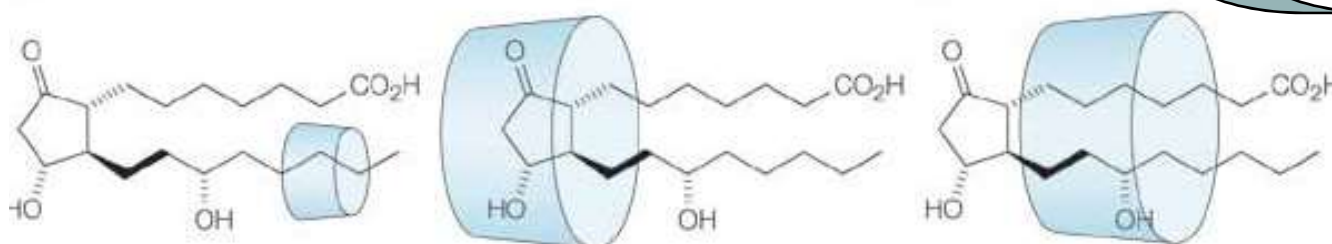


# The association with cyclodextrin may be versatile



**Chemical stability increases:**

- Dihydro prostaglandin E1



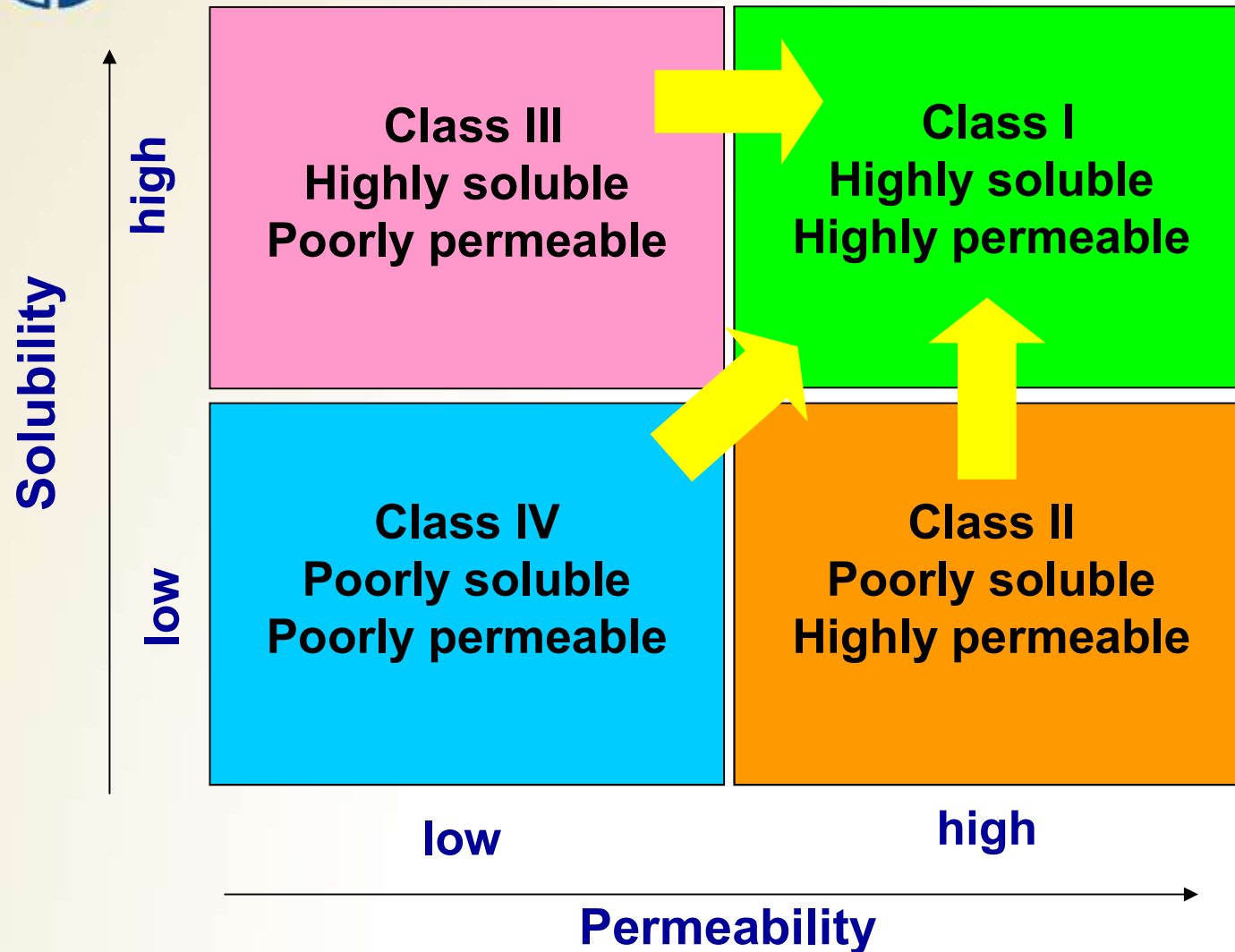
- Doxorubicin ( $\gamma$ -CD), daunorubicin (methyl- $\beta$ -CD)
- Acetylsalicylic acid ( $\beta$ -CD)
- O<sup>6</sup>-Benzylguanine (SBE- $\beta$ -CD)

**Chemical stability decreases:**

Penicillin derivatives are sensitized in the presence of cyclodextrins



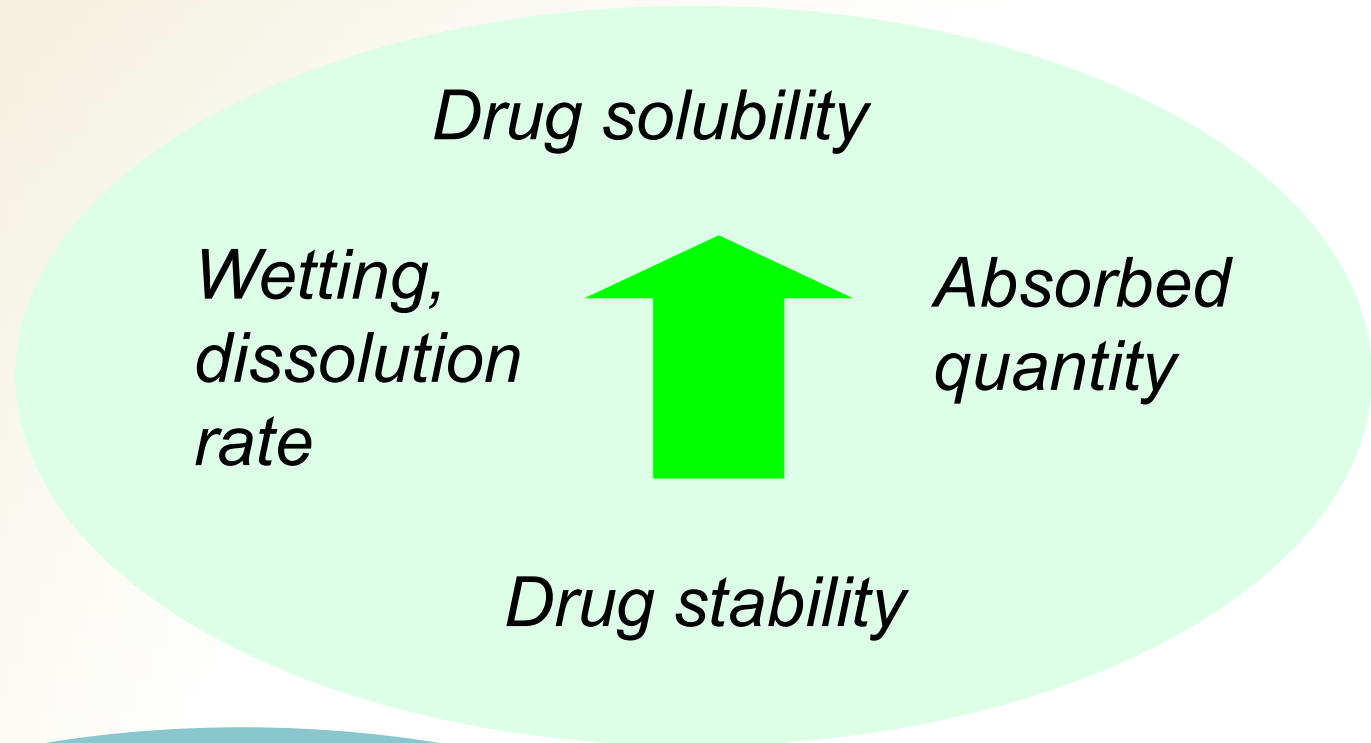
# Effect of CDs on the bioavailability of drug substances



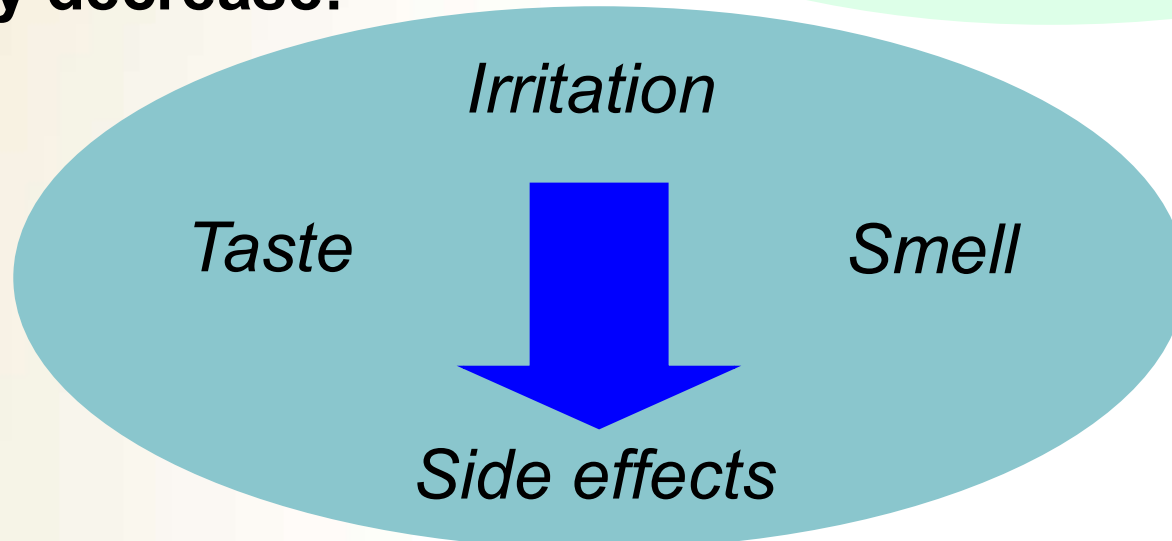


## Consequences of CD complexation

**Cyclodextrins may increase:**



**Cyclodextrins may decrease:**





## CDs suitably used in pharmaceuticals

	$\alpha$ -CD	$\beta$ -CD	$\gamma$ -CD	HP- $\beta$ -CD	SBE- $\beta$ -CD	RM- $\beta$ -CD
<b>Oral</b>		X	X	X	X	
<b>Nasal</b>						X
<b>Rectal</b>		X		X		
<b>Dermal</b>		X	X	X		
<b>Ocular</b>		X		X		X
<b>Parenteral</b>	X			X	X	

*European Medicinal Agency EMA/CHMP/333892/2013, Committee for Human Medicinal Products (CHMP) Background review for cyclodextrins used as excipients*

**~49 pharma products on the market containing CD**



## Solubility enhancement of drugs using 10 m/m% SBE- $\beta$ -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*







## SBE- $\beta$ -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**



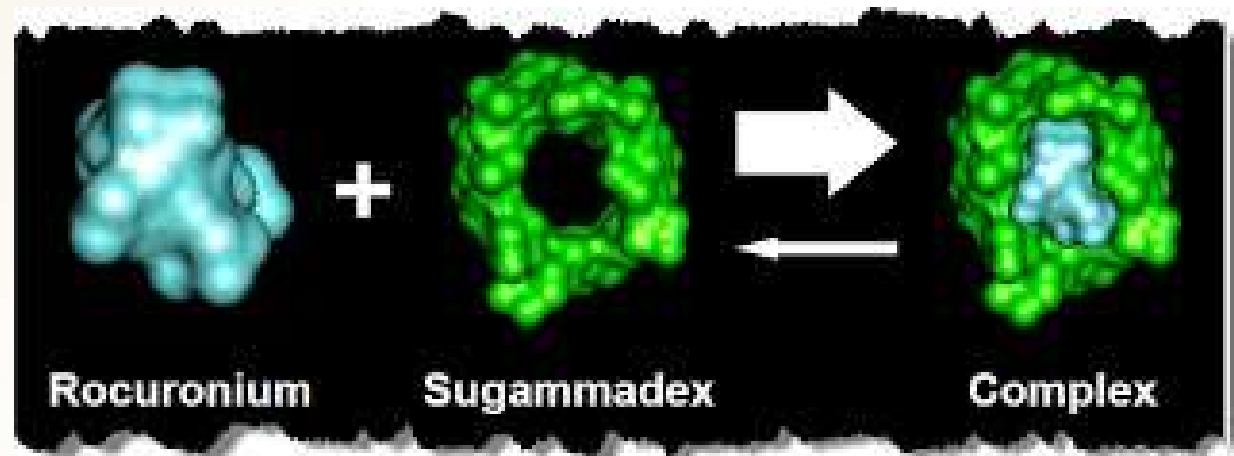
**Masking bitter  
taste**







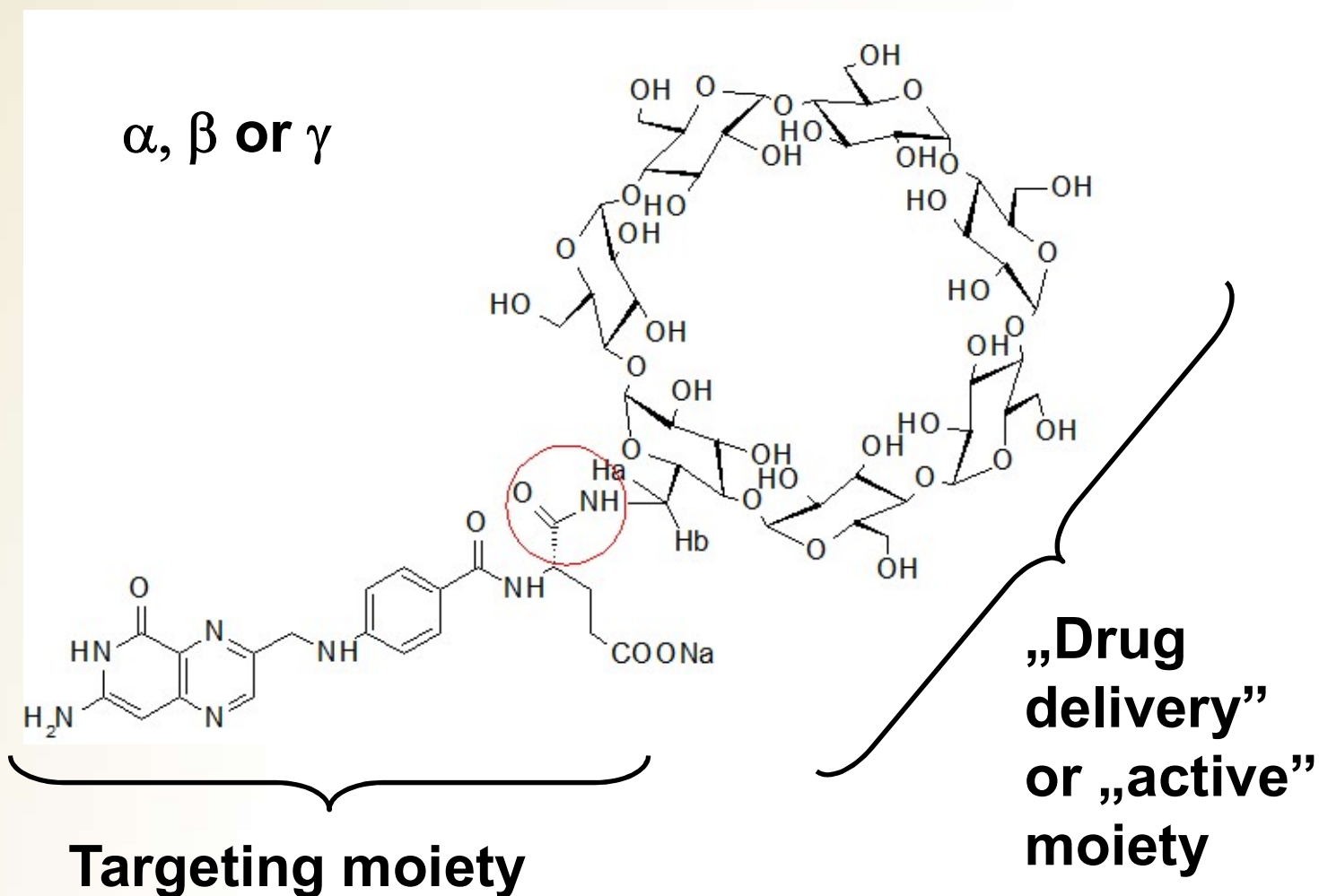
## Sugammadex: Revolution in anaesthesiology!



**The muscle relaxant is bound irreversibly**



## Folate appended cyclodextrins



*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*



## Cyclodextrins in colloidal drug delivery:

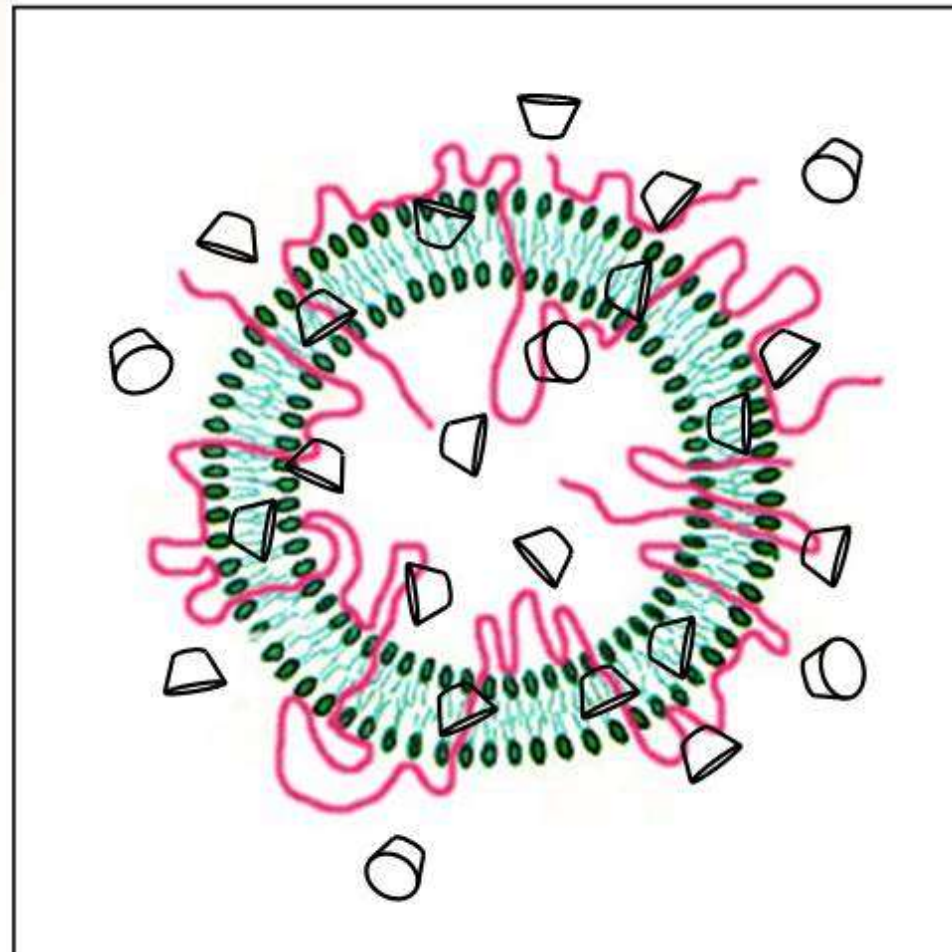
### *Liposomes in combination with host-guest chemistry*



**Cyclodextrin**



**Polymer**



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

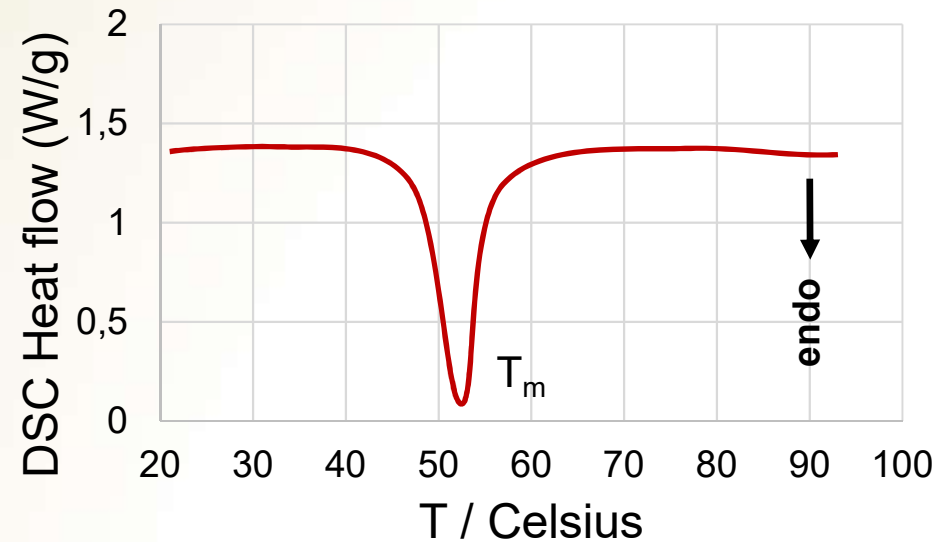


# Thermosensitive liquid crystalline drug/cyclodextrin assemblies:

## *Amiodarone / gamma-CD construct*

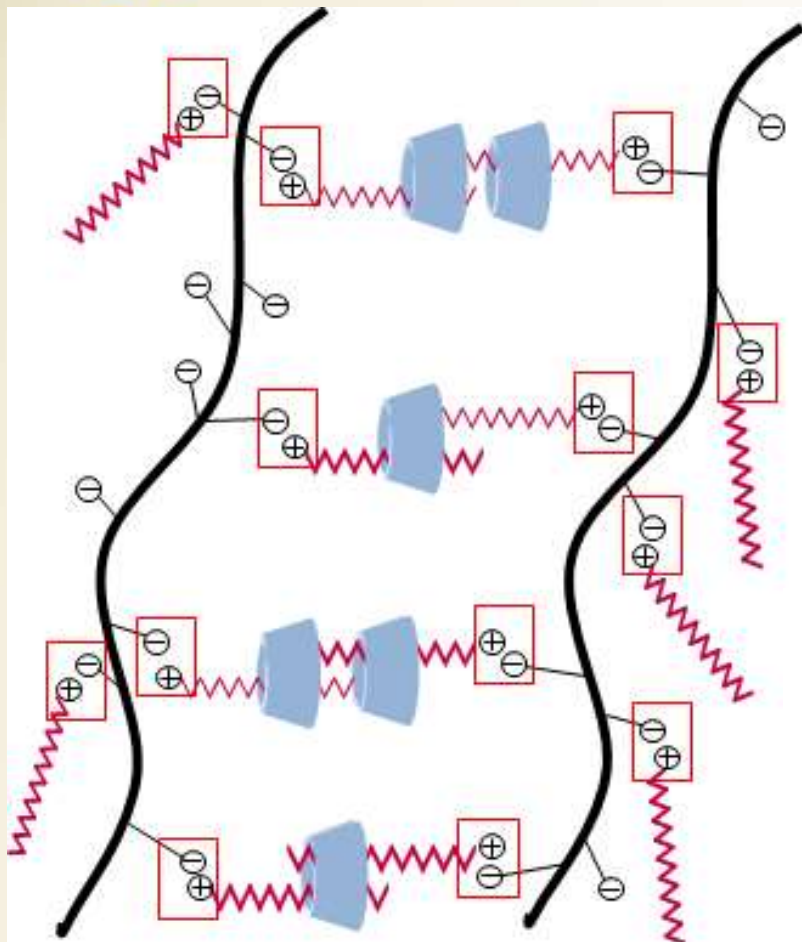


**Room temperature:  
Liquid crystal**



**Elevated temperature:  
Sol**

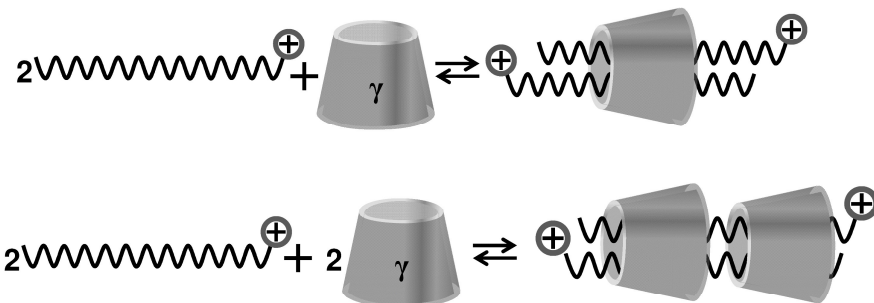
# $\gamma$ -CD / surfactant / hyaluronic acid supra-colloidal construct



gamma-CD

**surfactant (HHDDP)**  
(Hexadecyl(2-hydroxyethyl)  
dimethylammonium dihydrogen phosphate)

hyaluronic acid

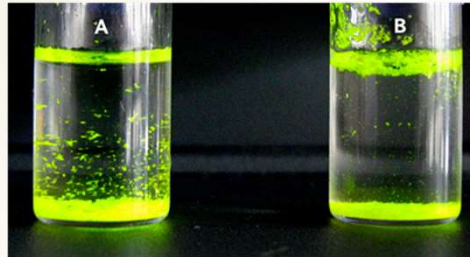






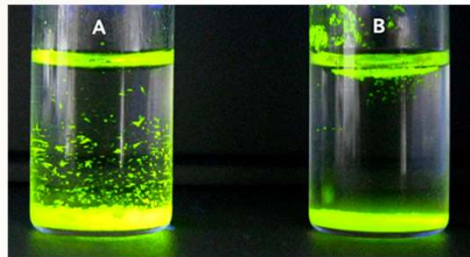
## In vitro disassembly of non-covalent polymer matrix containing fluorescent bovine serum albumin

**purified  
water  
time 0**

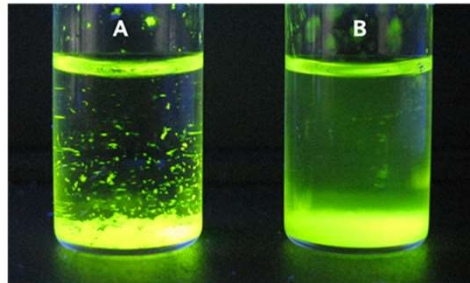


**in isotonic 0.9 % NaCl**

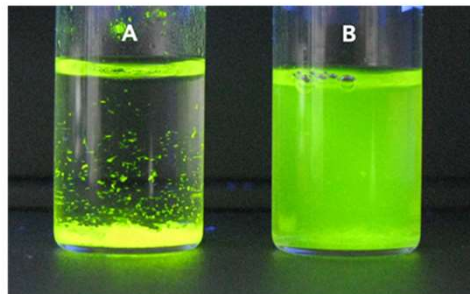
**24 hours**



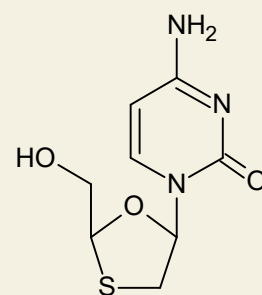
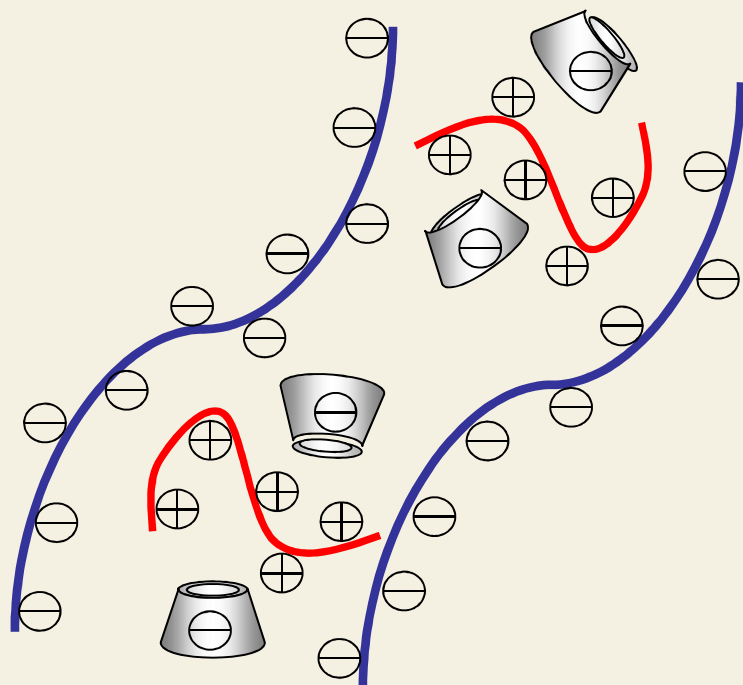
**36 hours**



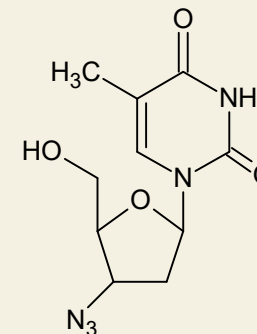
**48 hours**



# Supra-colloidal assembly for sustained release of antiretroviral drugs



**lamivudine**



**zidovudine**



Polylysine



Hyaluronic acid



SBE- $\beta$ -CD





# Conclusions

- **Major benefits of using CDs in drug formulations:**
  - Enhancing bioavailability
  - Successful injectable formulations of poorly soluble drugs
  - Stabilization (physical / chemical)
- **Limitations:**
  - Administration routes of some CDs are limited
  - Supergeneric strategy was not a success
- **Opportunities:**
  - CD complexes of special tunable colloidal forms
  - Designed (smart) CD-derivatives for drug delivery



# Acknowledgements

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