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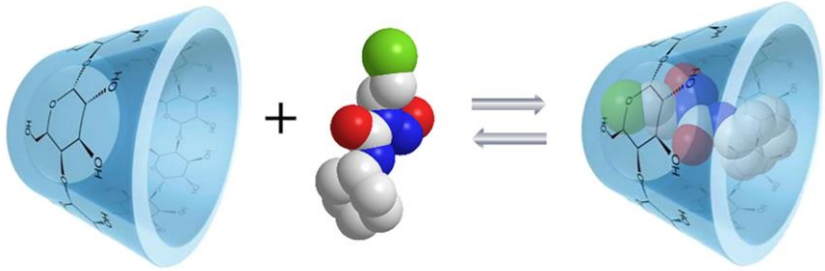
Cyclodextrins

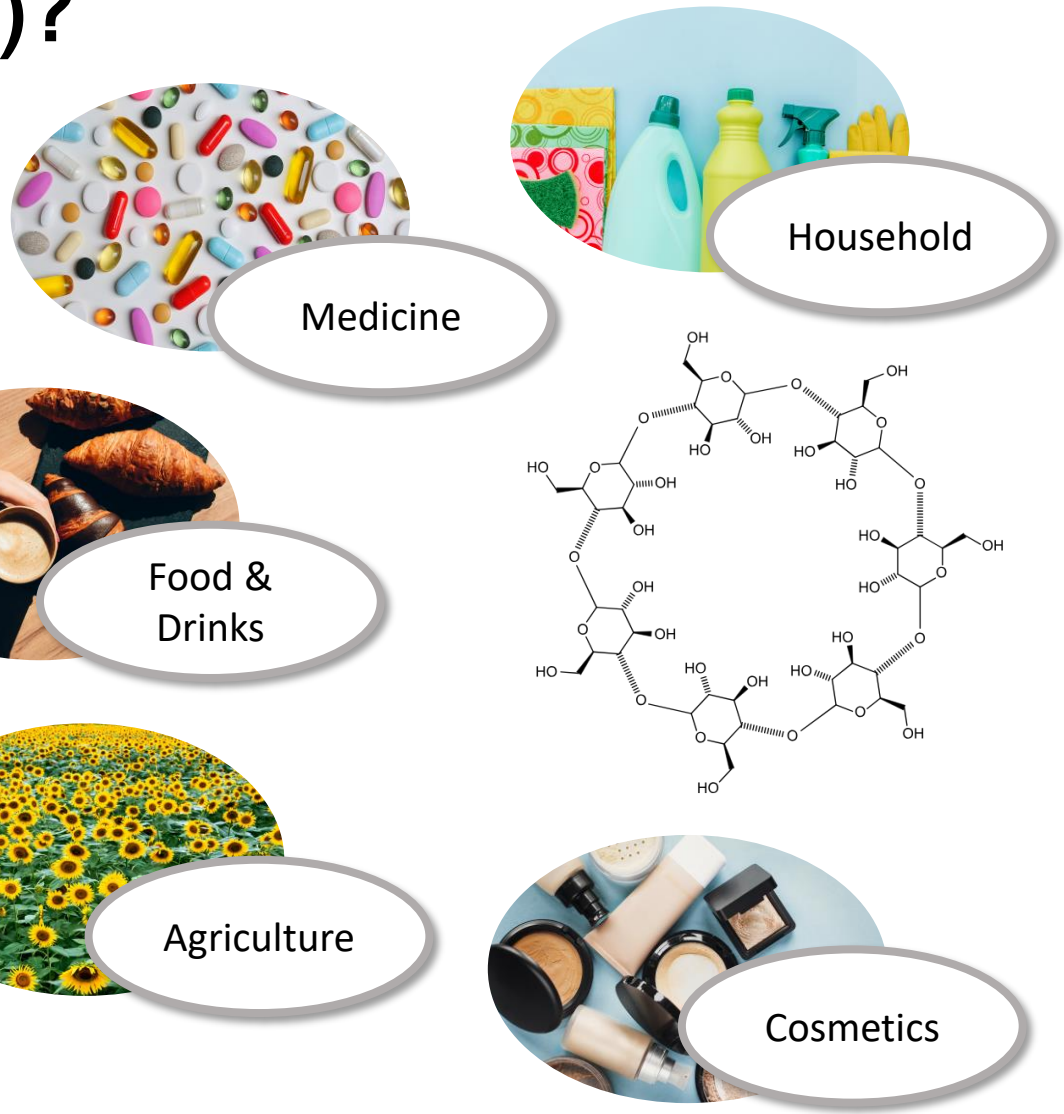
In Drug Delivery Systems
for Small Molecules

What are Cyclodextrins (CDs)?

Properties

- Naturally occurring cyclic molecules, composed of sugars
- Toroid structure with **interior hydrophobic cavities** of 0.5 to 1.0 nm in diameter and **exterior hydrophilic rims**
- Diverse range of **applications**: food, pharmaceuticals, drug delivery, chemical industries, agriculture, etc.
- Often, the **aim** is to increase the solubility, dissolution rate, and stability of poorly soluble APIs.





The structure and application areas of CDs

Complex Preparation Process

Define

- the **objective of the project**
- **limitation** based on the future application
- targeted solubility, stability, etc.

Select

- applied **technologies** for complexation
- solvents to use
- **CD type** (based on phase solubility studies and other methods)

Modify

complexation efficiency by the effect of:

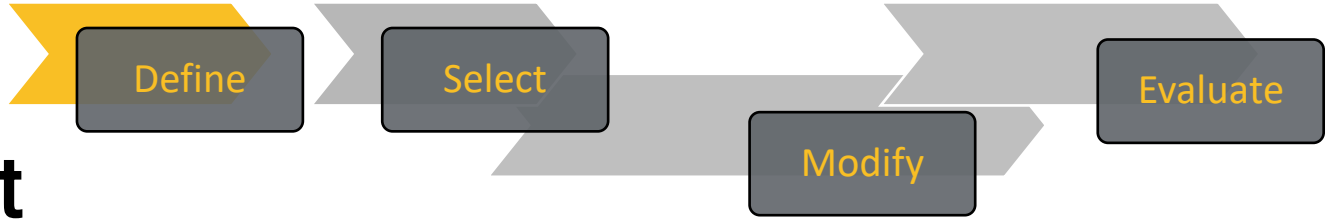
- pH adjustment
- **additional excipients**

Evaluate

Physicochemical properties to better understand:

- optimal components and ratio of components
- best methods for production
- stability of complexes

Define
Objective of the Project



Traditional pharma applications

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

Common Advantages

Cyclodextrins may **increase**

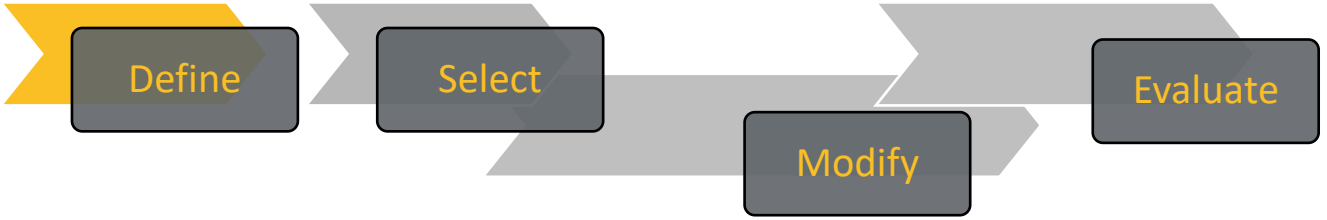
- Drug solubility, dissolution rate
- Wetting
- Drug stability
- Absorbed quantity

Cyclodextrins may **decrease**

- API's dose for same efficacy
- Taste
- Side effects
- Smell

Loftsson J. Incl. Phenom. Macrocycl. Chem. 2014, 80,1-7
Challa et al. AAPS PharmSciTech 2005, 6(2), E329-E357

Define Limitations of CDs



Generic development

- Supergeneric approach
  - Innovation in the delivery route (chewing gum/tablet, ODT, sachet)
  - The orally applied CD complex is rarely bioequivalent
  - Instead of supergeneric approach:
    - Preclinical (toxicology) studies
    - Dose finding studies
  - with the cyclodextrin complexes of drug candidates

Influencing release

- Ideal for immediate release and fast onset
- On its own, not suitable for extended release
- On its own, not suitable for controlled release
- On its own, not suitable for targeted delivery

In vivo stabilization

- Physical/chemical stabilization usually occurs in the VIAL, not in the BODY

Select The Type of CD

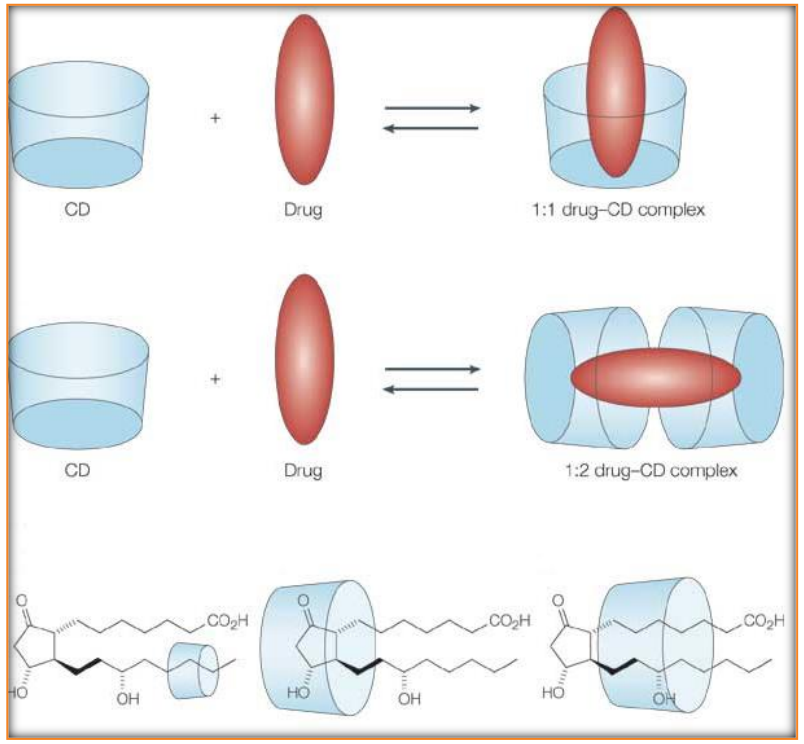
100+ products on the market

- Tool: CDs as drug complexing agents in drug delivery
- Goal: solubilizing, stabilizing, etc.
- Numbers: 130 approved pharmaceutical products in 2023

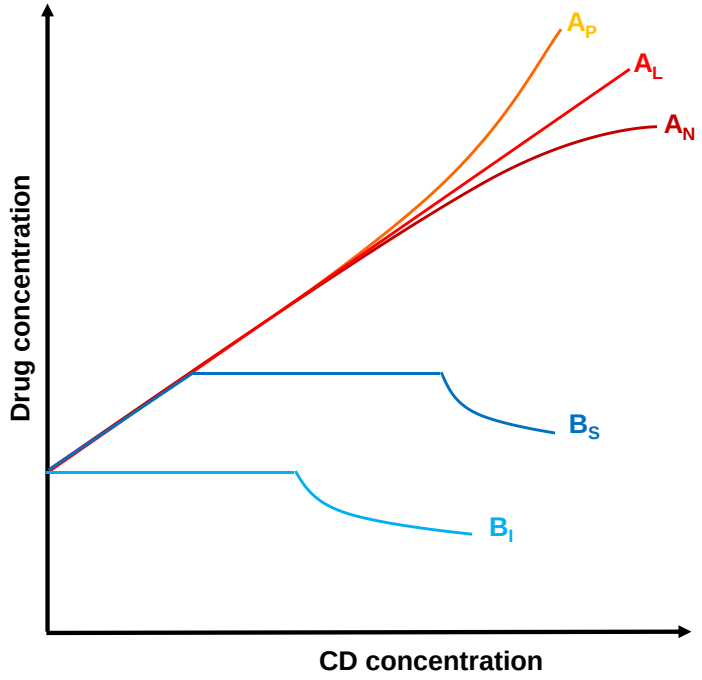
	α-CD	β-CD	γ-CD	HP-β-CD	SBE-β-CD	RM-β-CD	HP-γ-CD
Oral		X	X	X	X		
Nasal						X	
Rectal		X		X			
Dermal		X	X	X			
Ocular		X		X	X	X	X
Parenteral	X			X	X		X

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

Select
The Type of CD



CDs can form complexes with different CD:API ratios



Phase-solubility profiles and classification of drug/CD complexes according to Higuchi and Connors

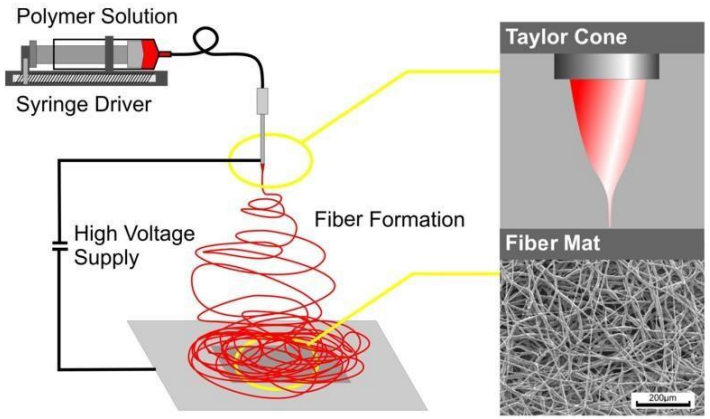
Phase solubility studies are used to study the interaction between the CD and the API.

Based on the shape of the isotherm curves the ratio of **API:CD**

- A_L type: first-order with respect to the CD (e.g., 1:1 and 2:1)
- A_P type: first-order with respect to the drug (e.g., 1:2)
- A_N type: other components interfering
- B types: complex with limited solubility

Higuchi, T., Connors, K.A., Phase-solubility techniques, Adv. Anal. Inst.,4, 117-212 (1965)

Select
Preparation method



Preparation methods:

Techniques for liquid formulations

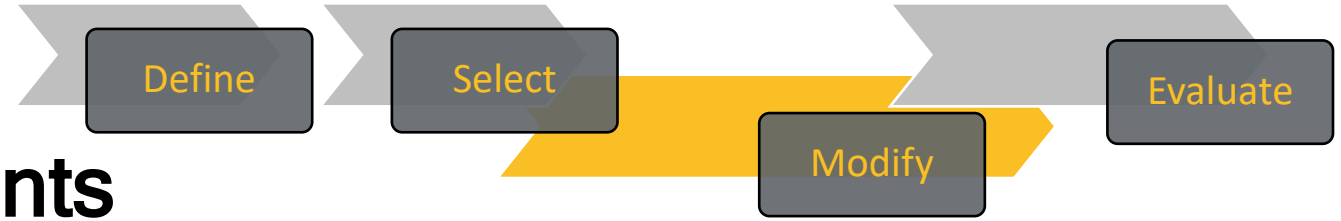
- Aqueous solutions
- Suspensions

Techniques for solid complexes

- Grinding and kneading methods
- Suspension method
- Co-evaporation
- Co-precipitation
- Electrospinning

Solid complexes are made from solutions, suspensions or slurry

Modify
With additional excipients



Modification of complexation efficiancy

- Binary cyclodextrin compositions:
  - the apparent binding constant mainly dependent of pH and temperature is often a limiting factor of attainable drug concentration.
- Ternary cyclodextrin compositions:
  - Besides pH and temperature
  - Choosing the right type and amount of component can increase the complexation efficiency

As a result of these effects, less CD is needed for solubilizing the same amount of API.

Non-binary formulations		
Third „booster" component	Examples	Mechanism
hydroxy acids	citric, tartaric acid, etc.	hydrogen bond modulators, chaotropic agents, (not simply a pH effect)
amino acids	arginine, lysine, etc.	
water soluble polymers	PVP, PEG, HPMC, etc.	co-solvents
metals	Mg2+, Cu2+, etc.	chelat formation, coordinating hydroxy groups

Evaluate
Physico-chemical properties

Characterization of electrospun and lyophilized formulations

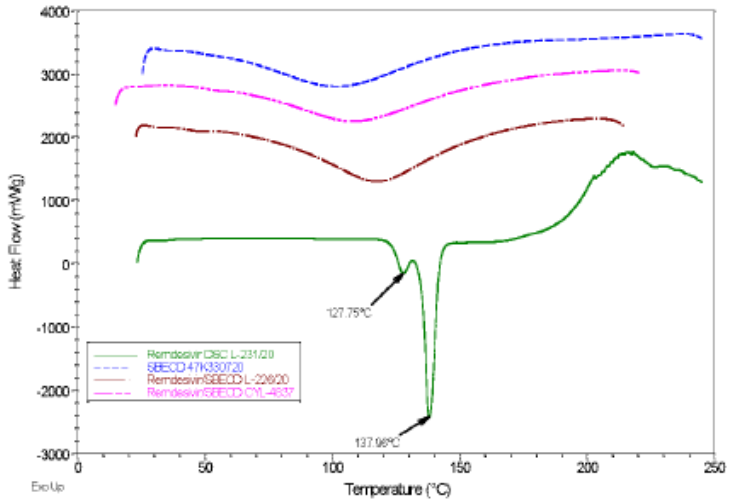


Figure 3 Overlaid DSC thermograms of REM (green), Dexolve SBECD (blue), REM/SBECD freeze-dried form (purple) and REM/SBECD electrospun nanofiber (brown)

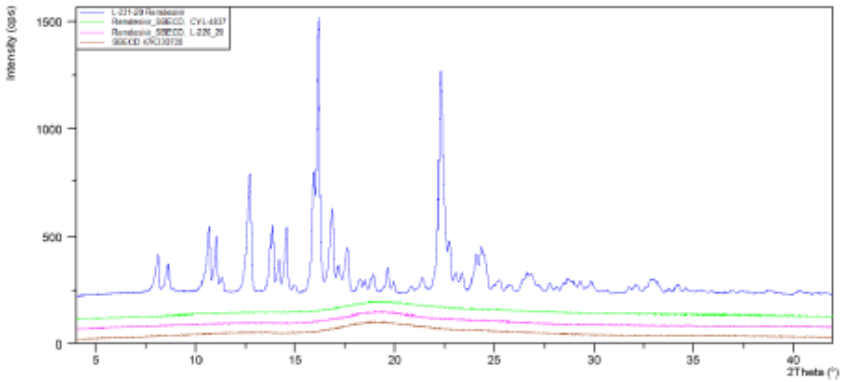


Figure 2 Overlaid X-ray powder diagrams of REM (blue), Dexolve SBECD (brown), REM/SBECD freeze-dried form (purple) and REM/SBECD electrospun nanofiber (green)

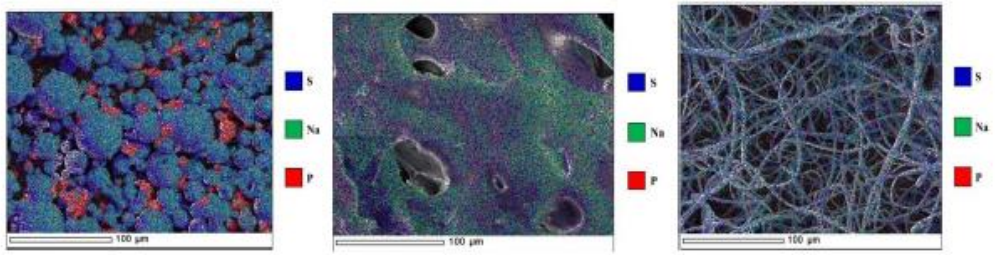


Figure 5 SEM-EDS micrographs of physical mixture (left) the liophylized (middle) and electrospun nanofiber form (right) of REM-SBECD formulations

Sohajda et al. Cyclodextrin-enabled remdesivir to fight SARS-CoV-2 characterization of electrospun and lyophilized formulations

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