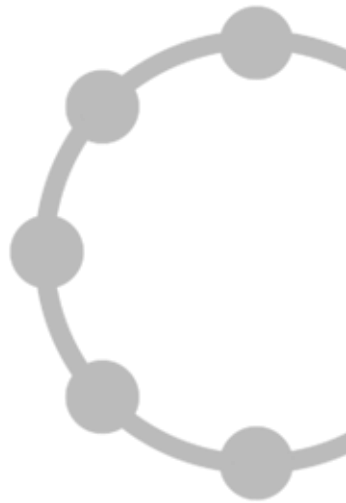




CARBOHYDE
REVOLUTION OF
CYCLODEXTRINS

Cyclodextrins

How do they work?



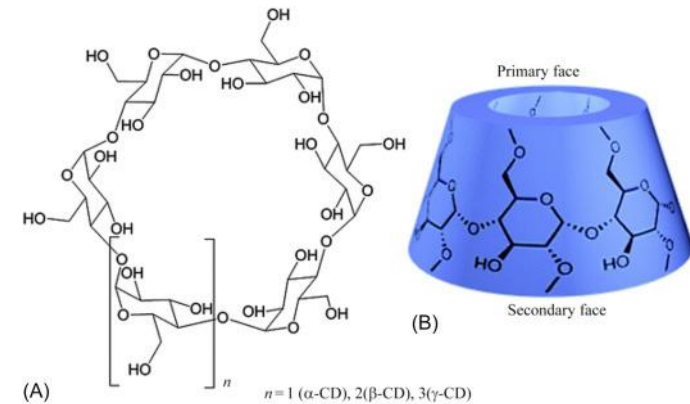


What are cyclodextrins?

Properties & applications

- Composed of sugars
- Cyclic molecules
- Naturally occurring
- 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

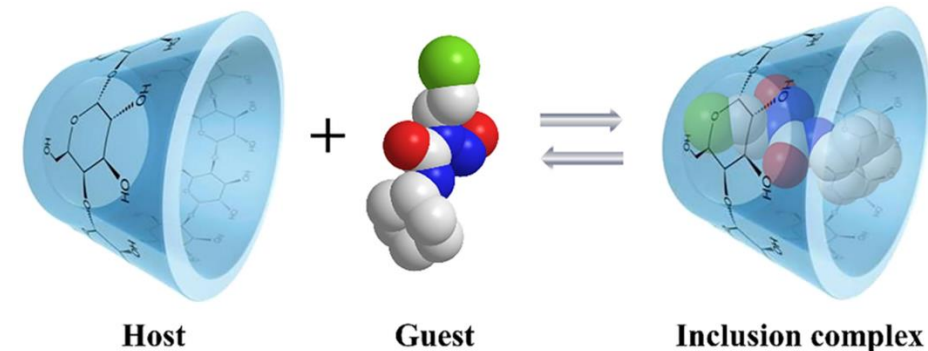
Structure & MoA





- NON-CONFIDENTIAL -

What are cyclodextrins?



Traditional pharma applications

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

Novel applications

- Active ingredients
- Monoclonal antibodies
- Gene therapy
- Targeted therapies
- Diagnostics & Theranostics
- Biotechnology

Common Advantages

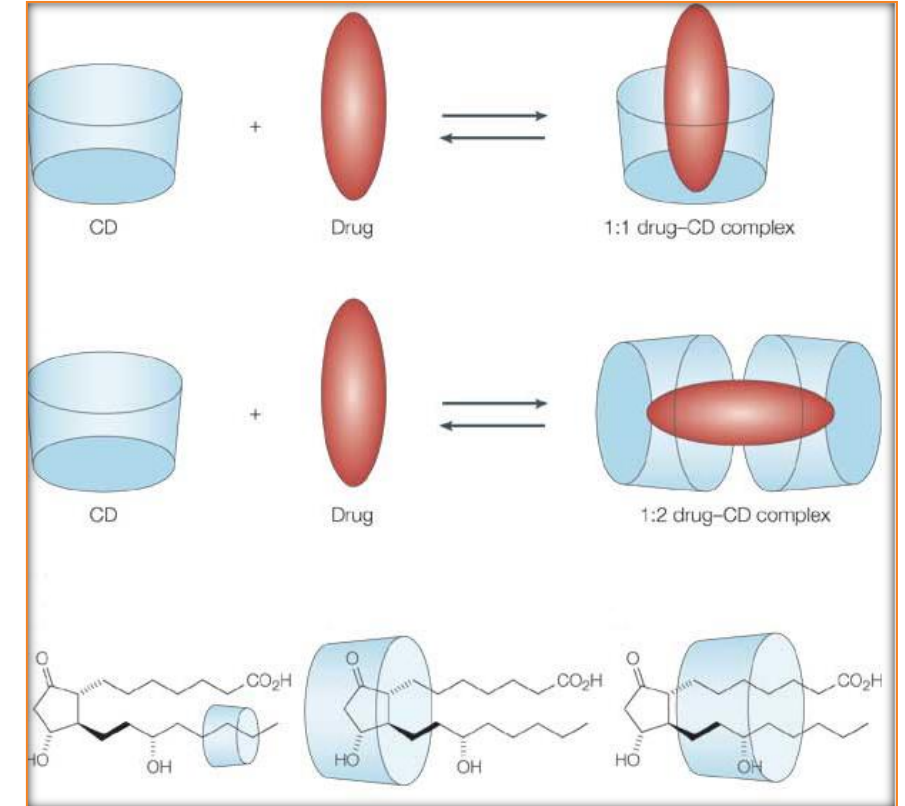
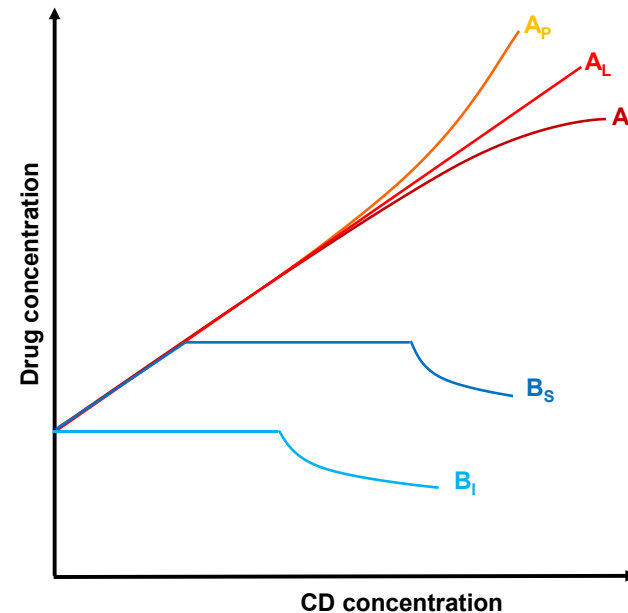
- Cyclodextrins may increase
 - Drug solubility
 - Wetting, dissolution rate
 - Drug stability
 - Absorbed quantity
- Cyclodextrins may decrease
 - API's dose for same efficacy
 - Taste
 - Side effects
 - Smell



Complex association and dissociation mechanism

Influenced by:

- Concentration ratios
- Isotherm type
- Binding affinity (CD type)
- Dilution
- Temperature
- Competition





What can a cyclodextrin do? (and what they can't do?)

- in drug delivery -

Traditional uses

- 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

- 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



Cyclodextrins in drug products - **limitations**

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



Formulation technologies

Table 1

Advantages and some drawbacks of the methods to prepare inclusion complexes (for more information, please see the associated reference).

Methods	Advantages	Drawbacks	Reported or affirmed by
Co-precipitation	• One of the most common methods.		(Jiang et al., 2019)
Kneading	• Simplicity and efficiency • Moderately simple method • High efficiency • Scalable		(da Silva Júnior et al., 2017)
Super critical carbon dioxide	• Scalable for commercial use • Perfect separation between the processed products and the supercritical solvent		(Wadhwa et al., 2017) (Banchero, 2021)
Grinding	• Simple, fast and highly effective technique to produce inclusion complexes in the solid state • Avoid solubility problems • Economic technology and environmentally desirable • Simple and common technique in the pharmaceutical industry • Not require solvents • Clean and environmentally friendly		(Jug & Mura, 2018) (Borba et al., 2015)
Microwave irradiation	• Lack of residues originated from the spend of organic solvents • Higher yields • Shorter reaction times • Cost-effective and time-saving		(Hernández-Sánchez et al., 2017) (Das & Subuddhi, 2015; Kaur et al., 2019)
Spray drying	• One of the common and oldest methods • Easy to apply on an industrial level • High yield • Fast drying • Appropriate for mass production within the food industry	• Restricted to water dispersible or water soluble carrier matrix material • Complex equipment	(Watson et al., 2017) (Liu et al., 2020b)



Formulation technologies



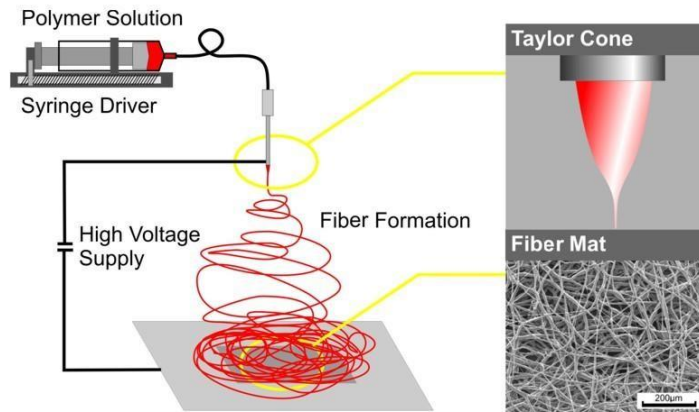
Techniques for liquid formulations

Aqueous solutions
Suspensions

Techniques for solid complexes

Kneading method → Grinding
Suspension method
Co-evaporation
Co-precipitation
Electrospinning

Solid complexes are made from solutions, suspensions or slurry





Cyclodextrins in drug products

100+ products on the market

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



	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



Cyclodextrins in drug products

Appearance in pharmacopeia



	A-CD	B-CD	G-CD	HP-B-CD	SBE-B-CD	RM-B-CD	HP-G-CD	SULFOLIPO CD
PH. EUR	X	X	X	X	X			
USP-NF	X	X	X	X	X			
JPC	X	X	X					



Useful references to learn more

<https://doi.org/10.3311/PPch.21222> | 1
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Periodica Polytechnica Chemical Engineering

Recent List of Cyclodextrin-Containing Drug Products

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Abstract

The number of the cyclodextrin-containing drug formulations on the market has been continuously growing since the first drug (prostaglandin E1 formulated with α -cyclodextrin) was launched in Japan in 1976. We have collected a list of drugs from various sources available on the internet to find 130 approved pharmaceutical ingredients formulated with either parent cyclodextrins or their hydroxypropyl, sulfobutyl, random methylated or sulfolipo derivatives. We have sorted the drug products according to the cavity size of the cyclodextrins, the administration route and dosage forms.

Keywords

approved pharmaceutical products, cyclodextrins, hydroxypropyl cyclodextrin, sulfobutyl cyclodextrin, random methylated cyclodextrin



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2017
EMA/CHMP/495747/2013
Committee for Human Medicinal Products (CHMP)

Questions and answers on cyclodextrins used as
excipients in medicinal products for human use



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