PRINCIPLES AND SYSTEMS OF DRUG DELIVERY · SEMINARS 9–10

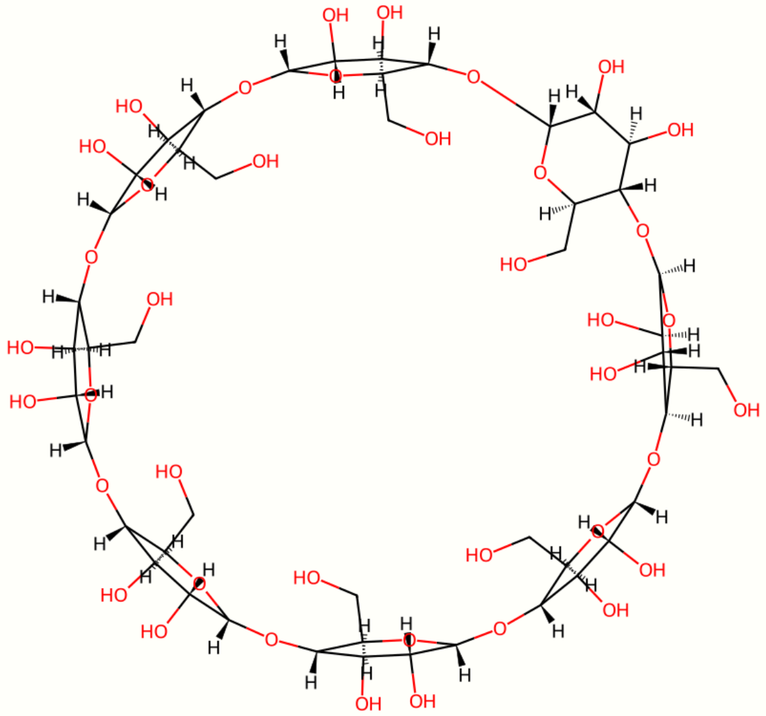
Cyclodextrins and the mathematics of drug release

Educational program “Pharmacy” · 4th year · Al-Farabi Kazakh National University

After these seminars you will be able to

1. Describe the structure of α-, β- and γ-cyclodextrins and how they form inclusion complexes
2. Read a phase-solubility diagram and calculate a 1:1 stability constant
3. Name marketed products that use modified cyclodextrins
4. Apply Fick’s first law and the Noyes–Whitney equation in simple calculations
5. Identify zero-order, first-order, Higuchi and Korsmeyer–Peppas release and use the Q10 method

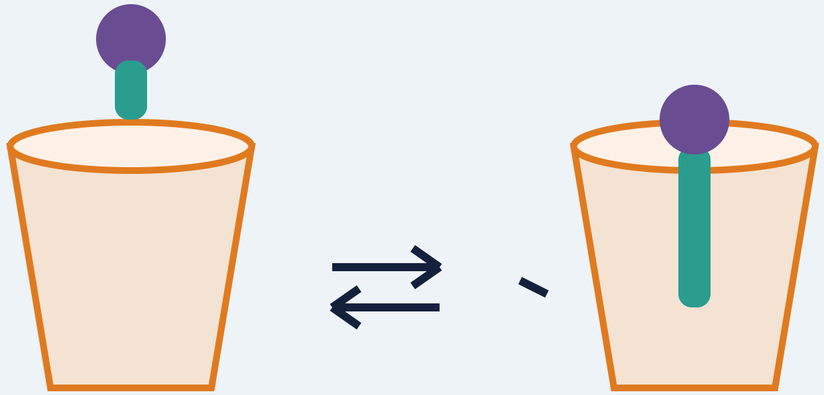
Cyclodextrins: rings of glucose



Property	α-CD	β-CD	γ-CD
Glucose units	6	7	8
Cavity, Å	4.7–5.3	6.0–6.5	7.5–8.3
Water solubility, mg/mL	145	18.5	232

Hydrophilic outside (–OH groups), **lipophilic cavity** inside: a molecular “cup” for the non-polar part of a drug.

Guest–host inclusion complexes



Non-covalent: hydrophobic and van der Waals forces; **reversible equilibrium**.

On dilution in body fluids the drug is released quickly.

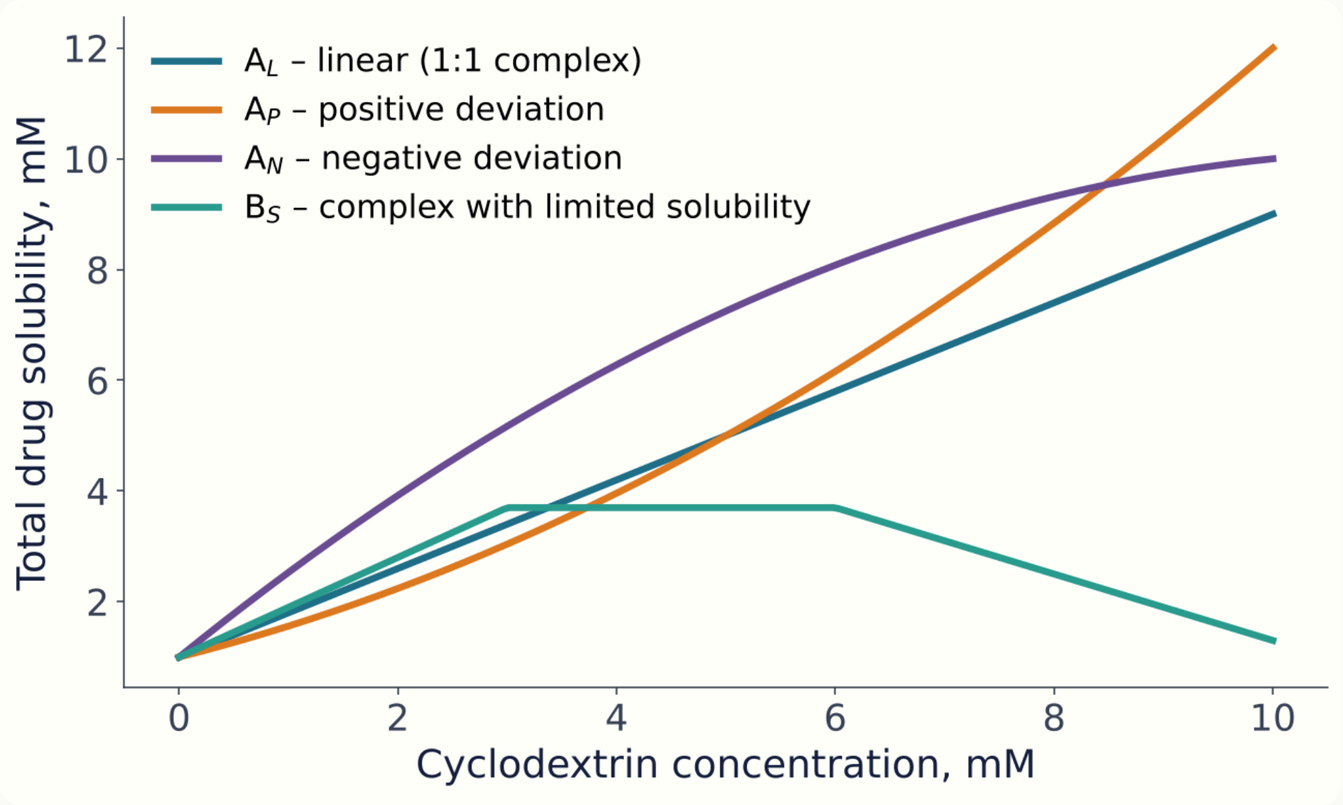
Uses: higher solubility and bioavailability, chemical stability, less irritation, taste masking, liquid → powder.

Modified cyclodextrins in marketed medicines

Cyclodextrin	Product (drug)	Purpose
HP-β-CD	Sporanox oral solution (itraconazole)	Solubilise a very insoluble antifungal
SBE-β-CD (Captisol)	Vfend IV (voriconazole)	Make an IV solution possible
SBE-β-CD	Veklury (remdesivir)	IV solubility
RM-β-CD	Nasal and ophthalmic products	Solubility and permeation
Modified γ-CD	Bridion (sugammadex)	The CD itself is the drug: traps rocuronium

Substitution breaks the hydrogen-bond belt → much higher solubility and lower kidney toxicity than parent β-CD.

Phase-solubility diagrams



Excess drug + increasing CD → measure dissolved drug.

For an A**L**-type line (1:1 complex):

$$\mathbf{K_{1:1} = slope\ /\ [S_0\ (1 - slope)]}$$

S_0 = intrinsic solubility (intercept). Typical K: 50–2000 M^{-1}.

Other complex-forming carriers

Ion-exchange resins

Drug bound to a sulfonate or carboxylate polymer; released by Na^+, K^+, H^+ in GI fluids (dextromethorphan polistirex)

Dendrimers

Branched PAMAM or polylysine molecules; drugs inside cavities or on the surface

Polymer–drug conjugates

Covalent link to HPMA or PEG polymer, cleaved at the target

Albumin binding

Paclitaxel bound to albumin (Abraxane); fatty-acid drugs bind albumin in blood

Fick’s laws of diffusion

First law (steady state)

$$J = -D \cdot dC/dx$$

Through a membrane of thickness h:

$$J = D \cdot K \cdot \Delta C / h$$

J – flux; D – diffusion coefficient; K – partition coefficient

Second law (changing)

$$\partial C/\partial t = D \cdot \partial^2 C/\partial x^2$$

Describes how the concentration profile changes over time, e.g. in a matrix that is being emptied.

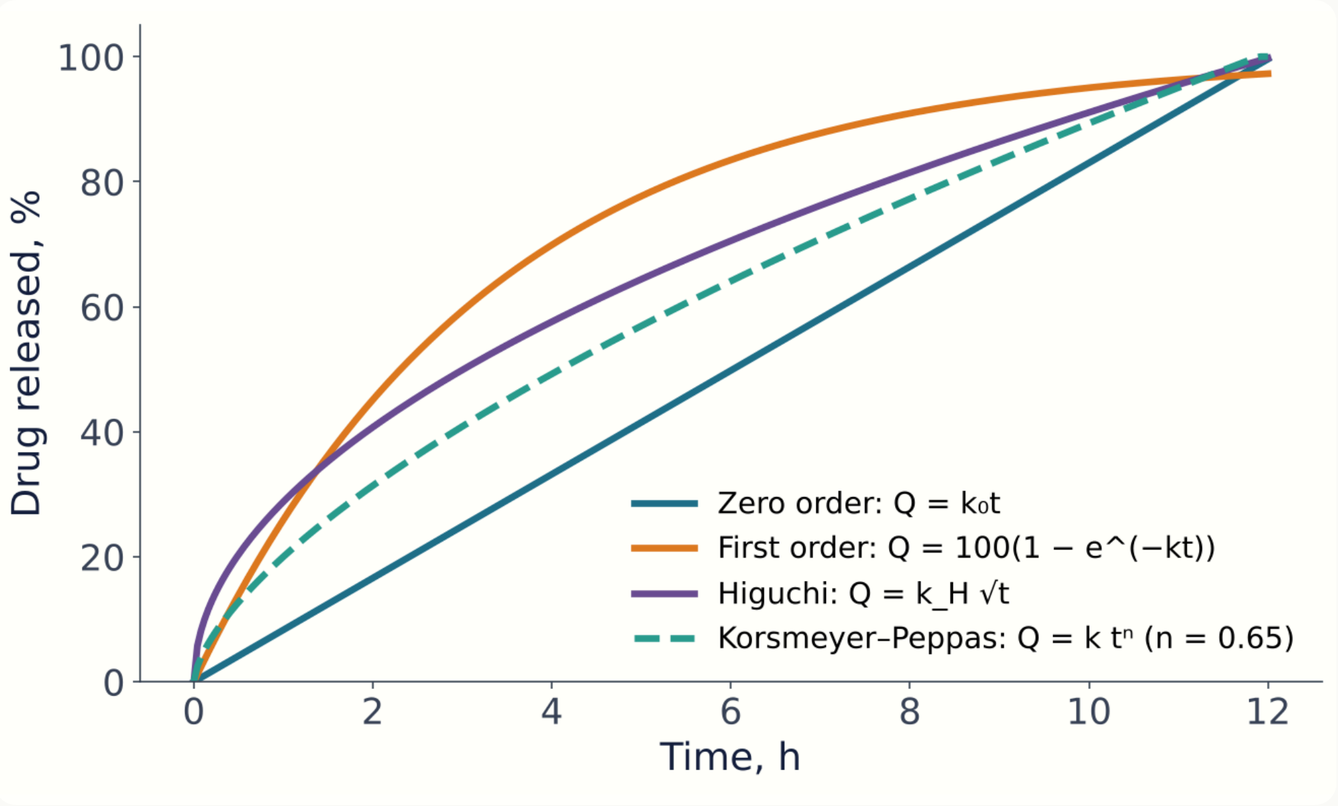
Solutions give the √t (Higuchi) law.

NOYES–WHITNEY EQUATION (1897), NERNST–BRUNNER FORM

$$\frac{dm}{dt} = D \cdot S \cdot (C_s - C) / h$$

Faster dissolution: smaller particles (↑S), higher solubility (↑Cs, salts, cyclodextrins), stirring (↓h), sink conditions (C ≈ 0).

Four models of drug release



Zero order: osmotic pumps, reservoir patches

First order: porous matrices, IR forms

Higuchi: insoluble matrix tablets

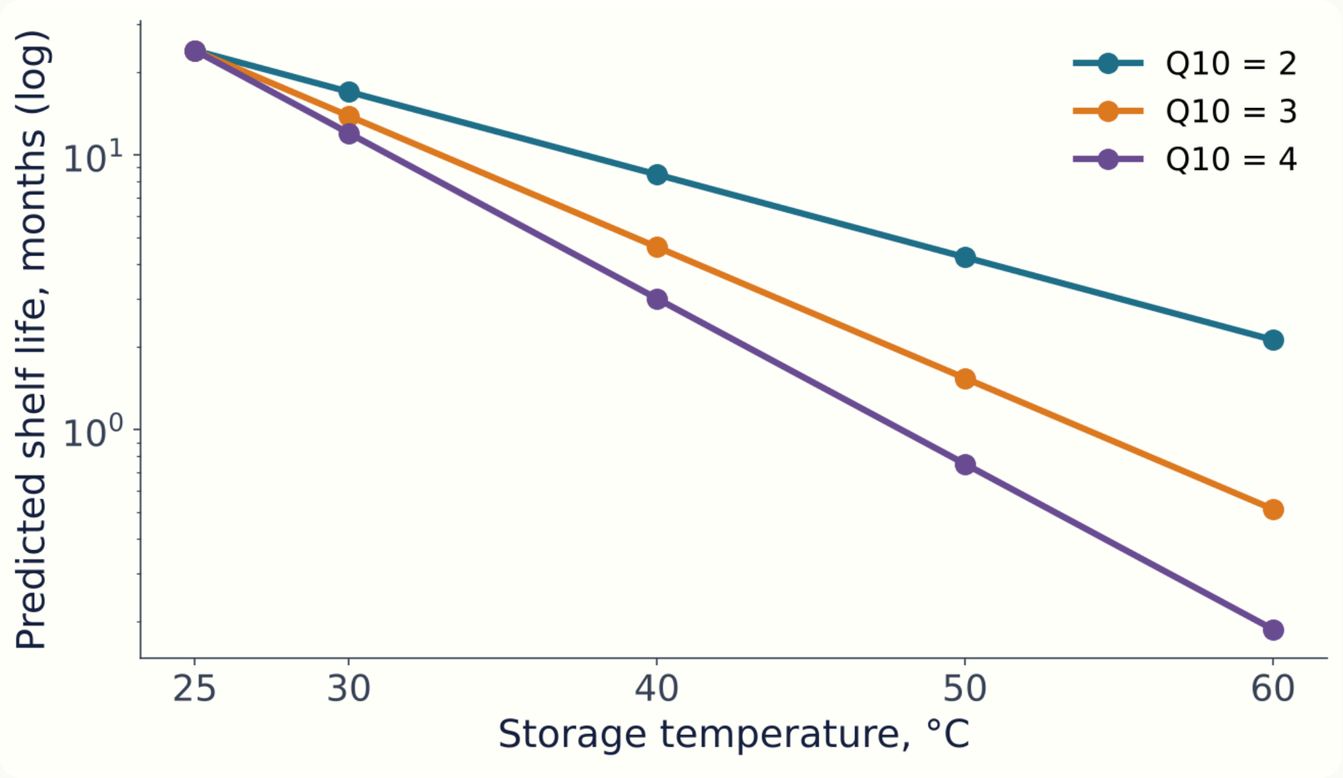
Korsmeyer–Peppas: swelling polymers; n tells the mechanism

Reading the exponent n: $M_t/M_\infty = k \cdot t^n$

n (thin film)	n (sphere)	Mechanism
0.5	0.43	Fickian diffusion
0.5 – 1.0	0.43 – 0.85	Anomalous: diffusion + polymer relaxation
1.0	0.85	Case II transport: swelling-controlled, zero order
> 1.0	> 0.85	Super case II

Use only the first 60% of release for the fit.

The Q10 method for shelf-life estimation



Q10 = how many times the reaction rate rises per 10 °C

$$t_{90}(T_2) = t_{90}(T_1) / Q10^{(\Delta T/10)}$$

Q10 of 2, 3, 4 ≈ activation energy of about 50, 85, 110 kJ/mol near room temperature.

Questions and quick calculations

1. Why is HP-β-CD used for injections instead of parent β-CD?
2. S_0 = 0.2 mM, slope 0.5. Calculate $K_{1:1}$.
3. Which three terms of Noyes–Whitney does micronisation change?
4. Release data give the best line for Q versus √t. Which mechanism?
5. Korsmeyer–Peppas n = 0.89 for a film. What does it mean?
6. Shelf life is 36 months at 25 °C, Q10 = 2. Predict it at 45 °C.

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