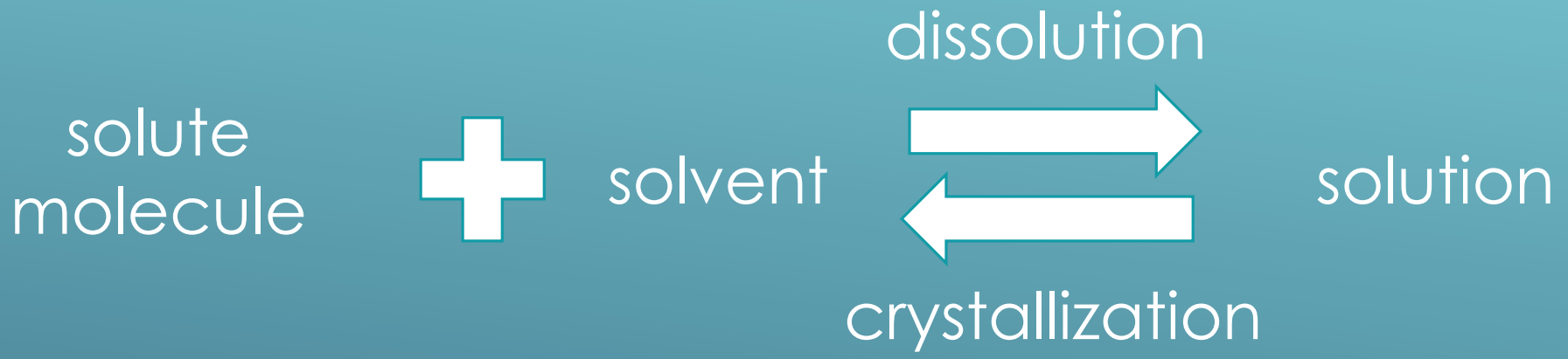
OPERATION OF DISSOLUTION

Institute of Pharmaceutical Technology and Biopharmacy

Vörös-Horváth Barbara

MECHANISM OF DISSOLUTION



Mechanism of dissolution

Thermodinamical solubility: equilibrial process, described with an endpoint.

Kinetic solubility: dissolution in time, described with the rate of dissolution

DEFINITION OF THE SOLUTION

Solute is dispersed in a solvent.

Particle size (d)	Type of Solution
< 1 nm	Real solution
1<d<1000 nm	Colloidal solution
>1000 nm	Disperse system (NOT SOLUTION, colloidal system)

OPERATION OF DISSOLUTION

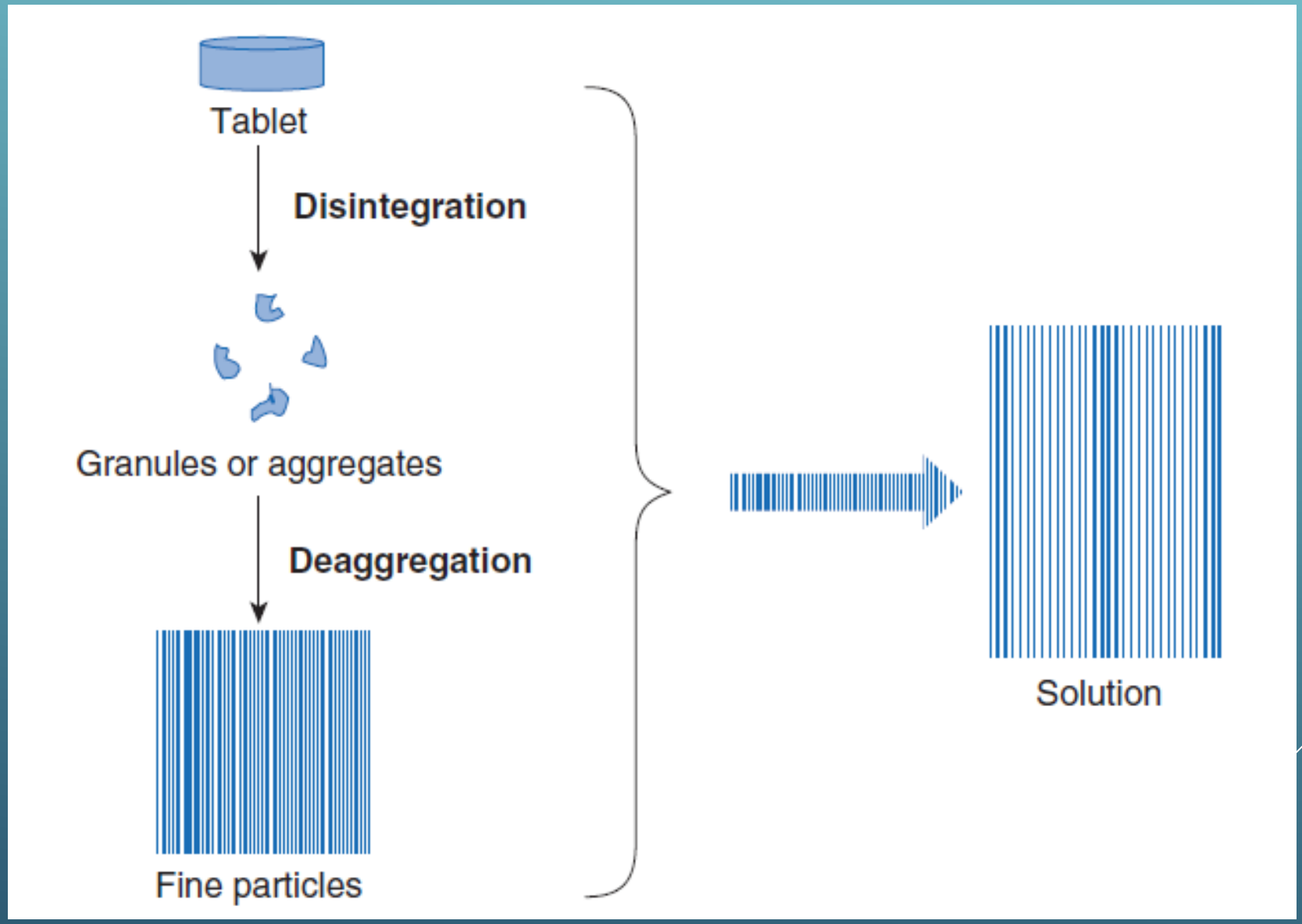
Operation of dissolution in phamaceutical technology

- Basic operation
- Forming operation (solution dosage form)

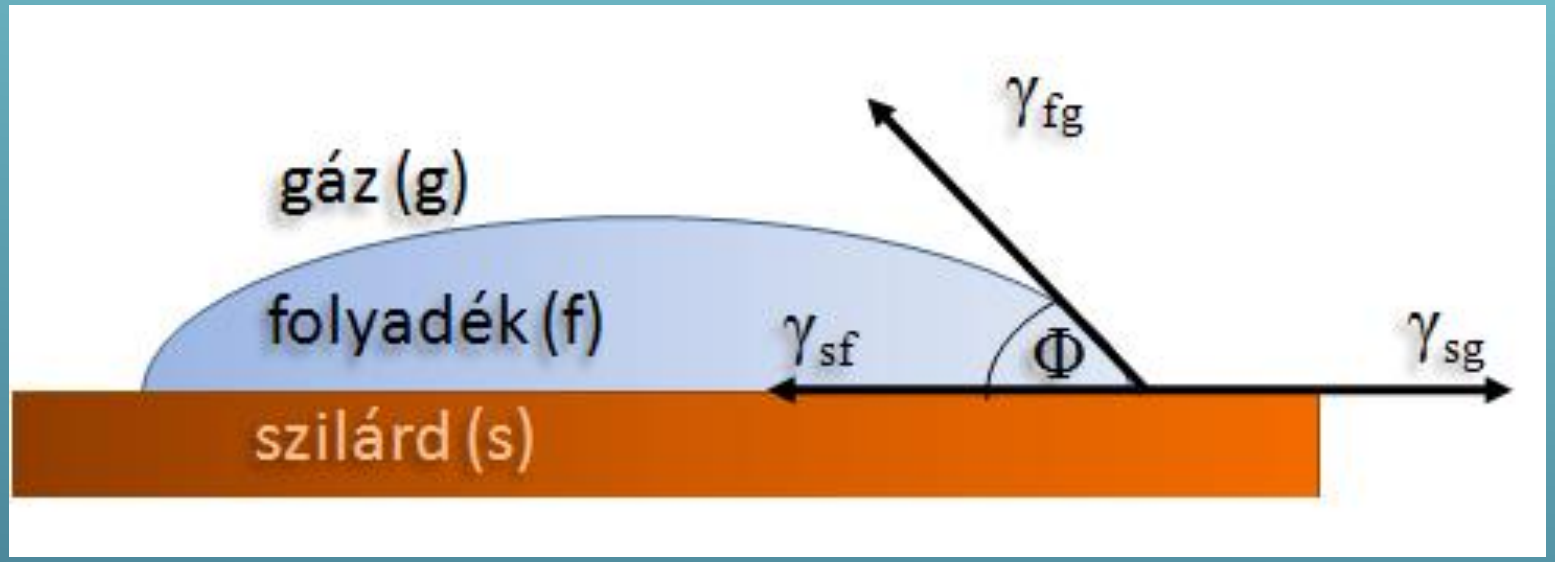
Operations are performed by procedure, for example mixing is performed by shaker, magnetic stirrer.

The properties of the solution/dissolution are important criteria of the absorption (biopharmacy).

ABSORPTION PRECEDING STEPS IN CASE OF TABLET DOSAGE FORM



MECHANISM OF DISSOLUTION – WETTING



Young equation

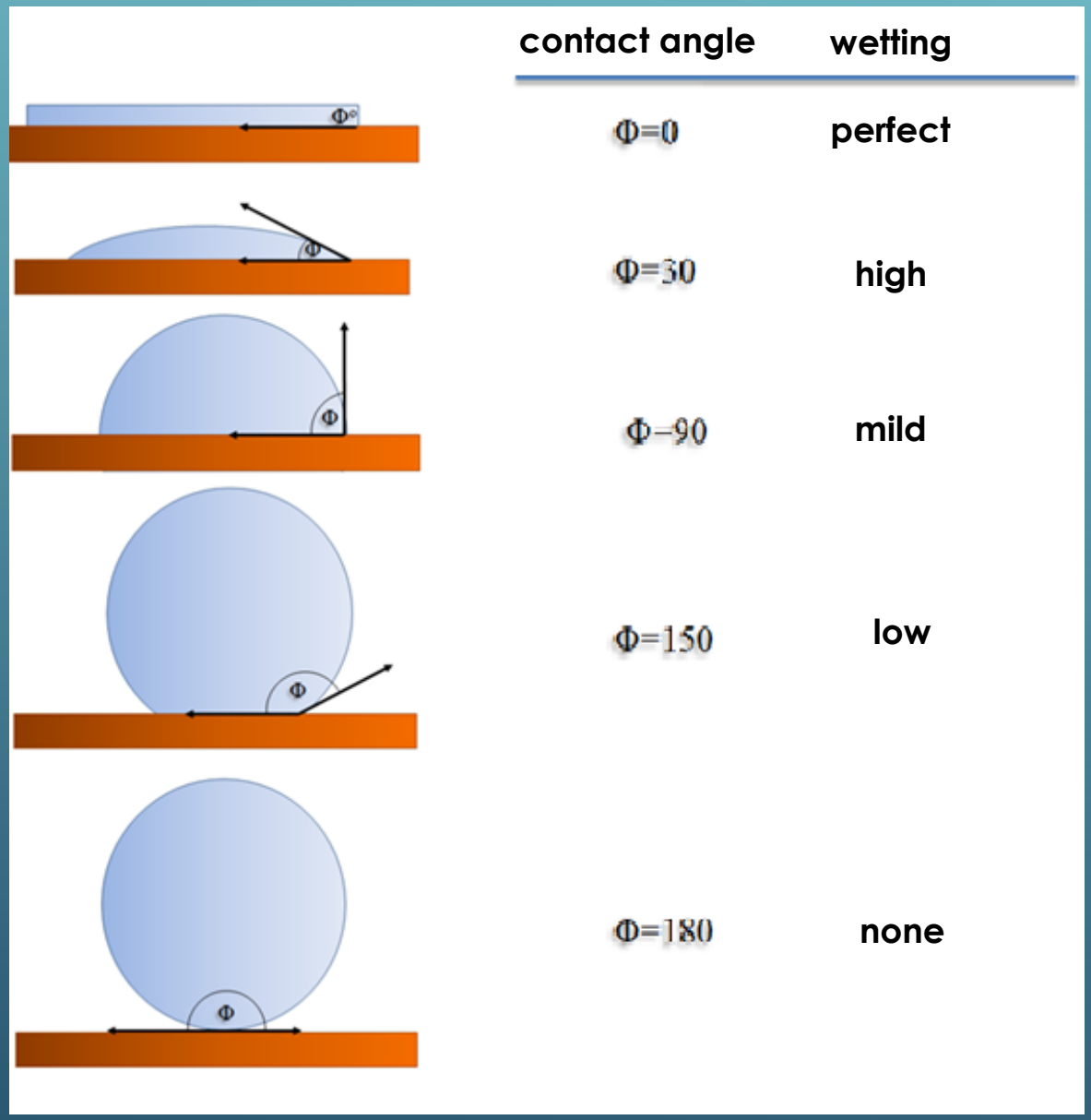
$$\gamma_{sg} = \gamma_{sf} + \gamma_{fg} \cos \theta$$

γ_{sg} = solid/gas surface tension

γ_{sf} = solid/liquid surface tension

γ_{fg} =liquid/gas surface tension.

MECHANISM OF DISSOLUTION– WETTING

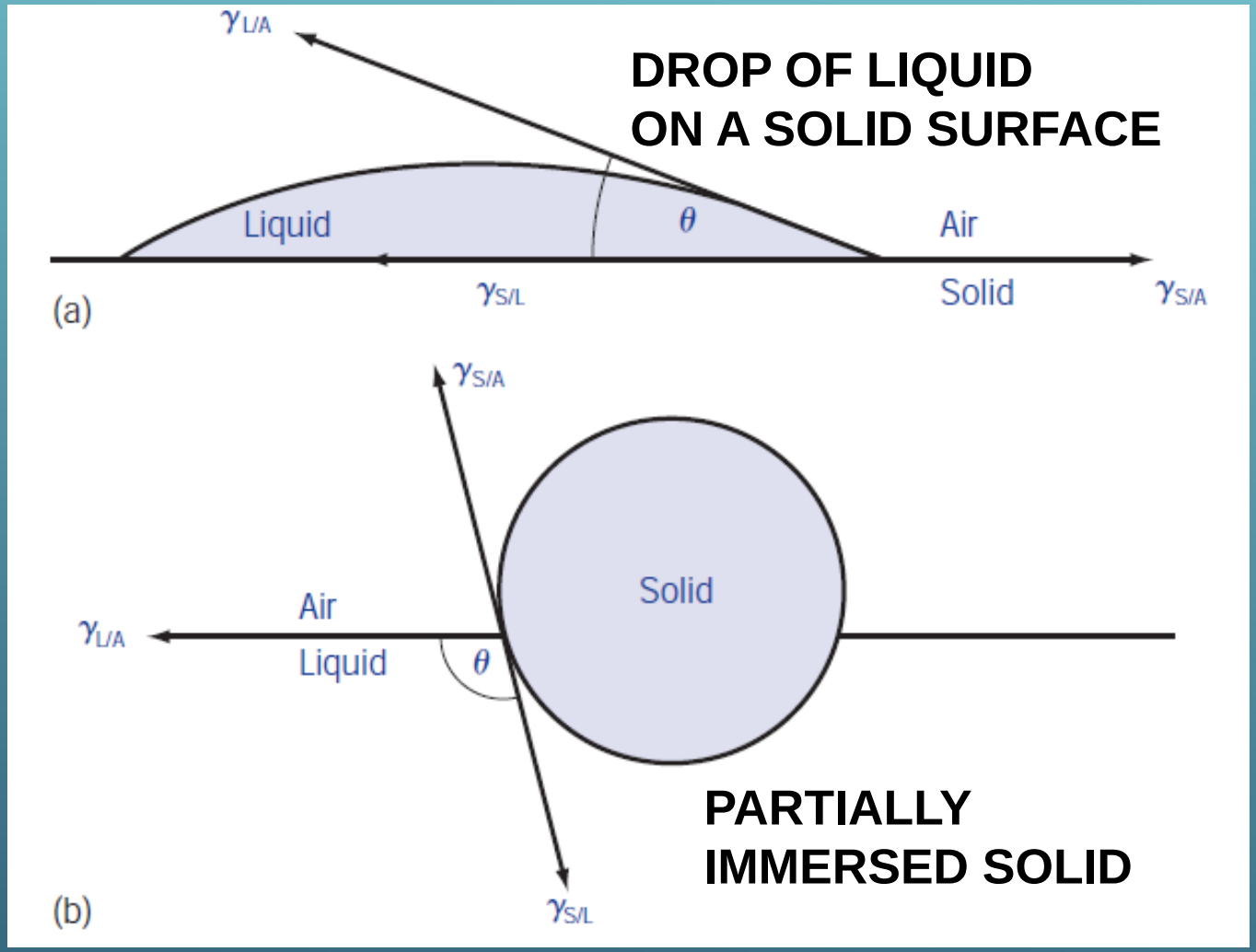


contact angle	wetting
Φ=0	perfect
Φ=30	high
Φ–90	mild
Φ=150	low
Φ=180	none

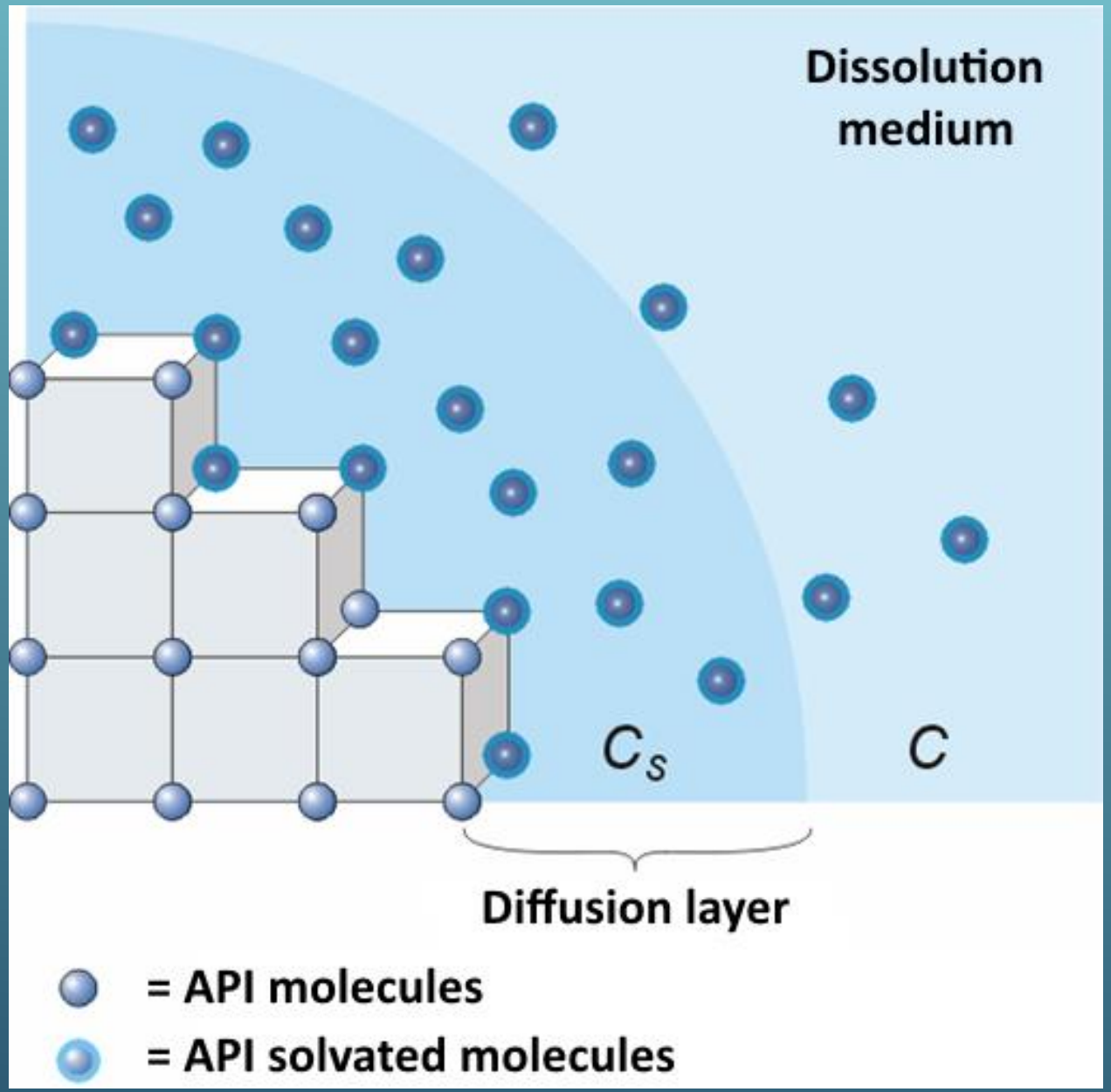
LIOPHILLIC

LIOPHOBIC

MECHANISM OF DISSOLUTION– WETTING

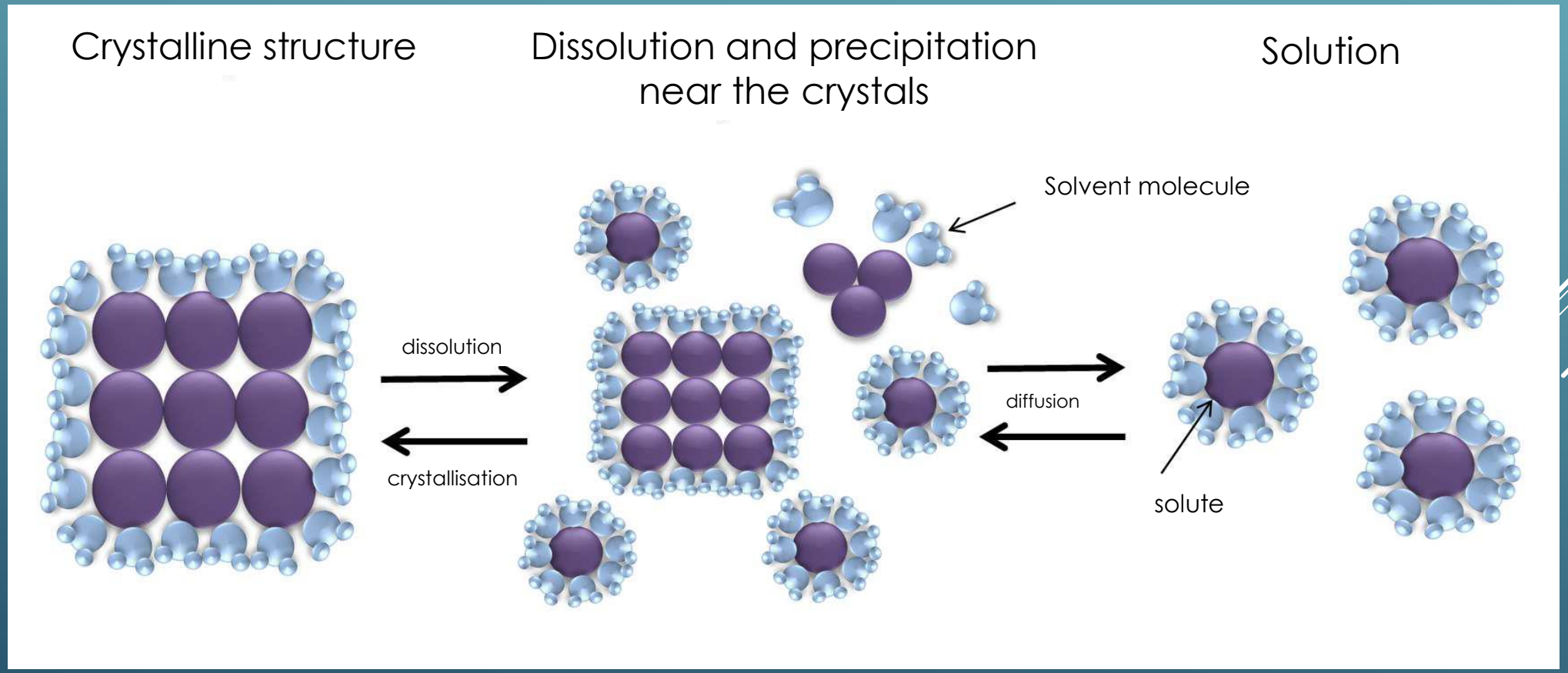


MECHANISM OF DISSOLUTION



DISSOLUTION OF CRYSTALLINE SUBSTANCES

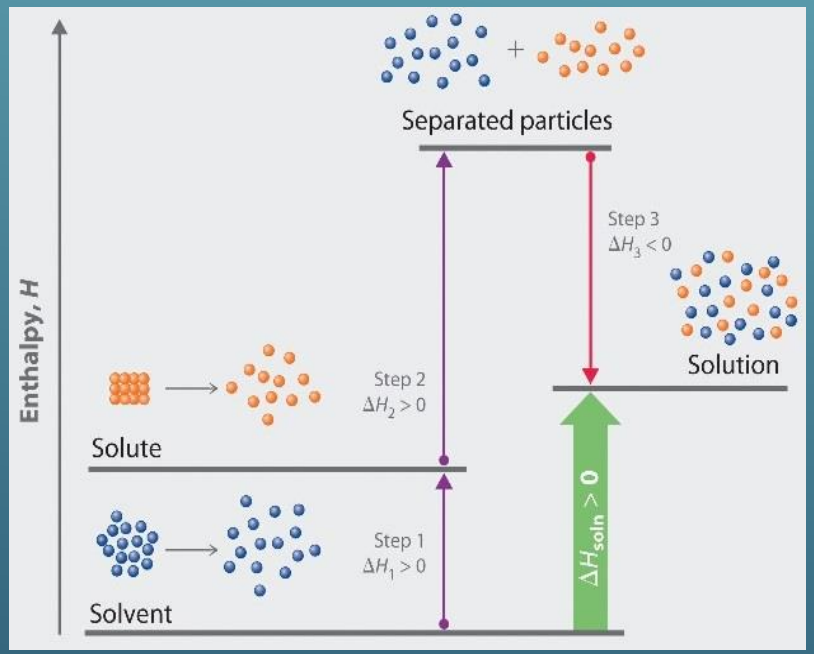
1. The disintegration of the solute crystalline structure. ($E_{lattice}$)
2. **Solvation:** Solute molecules are surrounded by the molecules of solvent. (E_{solv})
3. **Solvent diffusion**, concentration gradient equalisation.
4. Formation of **real solution.**



THERMODINAMICS OF DISSOLUTION

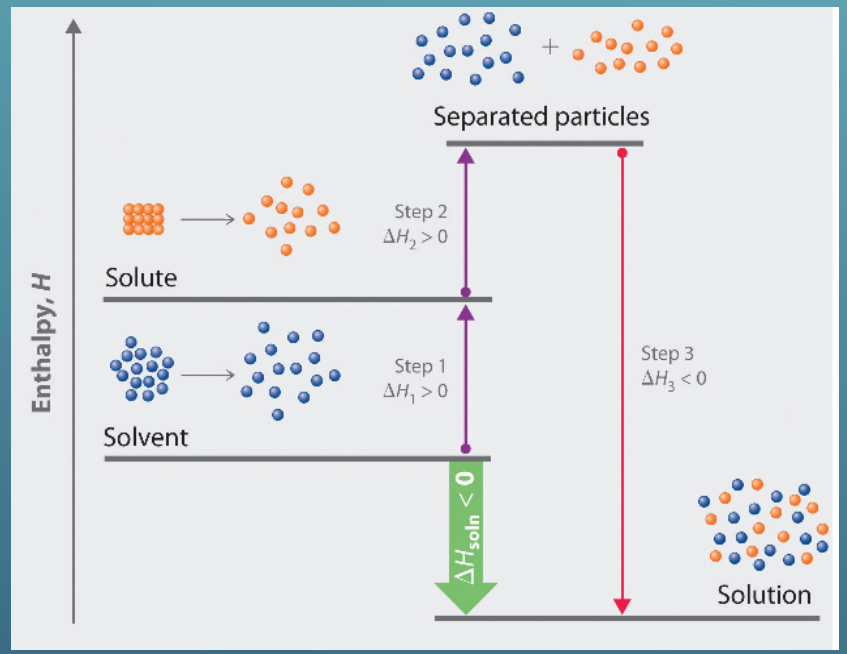
Dissolution can be an exotermic and an endothermic reaction.

- Heat of dissolution is dependent on the rate of the two procedure:
  - Dissocation of crystalline lattice is always endothermic reaction ($E_{lattice}$)
  - Solvatation always goes with energy release (E_{solv})



Endotermic dissolution

$E_{lattice} > E_{solv}$



Exotermic dissolution

$E_{lattice} < E_{solv}$

Enthalpy of dissolution

$\Delta H = E_{lattice} + E_{solv}$

$$\ln \frac{S_{T1}}{S_{T2}} = \frac{\Delta H}{R} \frac{(T_2 - T_1)}{T_1 T_2}$$

S_t a total solubility
ΔH enthalpy difference during solubilization (**heat of solution**)

SOLVENT-SOLUTE INTERACTIONS DURING SOLVATION

- In case of polar hydrophillic solvents

  Hydrogen bond, ion-dipole interaction, dipole-dipole interactions

- Ionic solvents

  Ionic interactions

- Apolar solvents

  van der Waals interactions

DEFINITIONS REGARDING DISSOLUTION

- **THERMODINAMIC SOLUBILITY**

Concentration of solute in saturated solution . (T=const.)

- **KINETIC SOLUBILITY**

Measured be reducing the solubility of the solute in a given system. (T=const.)

- **INTRINSIC SOLUBILITY**

Thermodinamic solubility measured at a pH value where the API is fully ionised.

- **APPARENT SOLUBILITY**

Thermodinamical solubility measured at different pH values or in different buffer solutions.

RATIO OF IONIC/ NON-IONIC FORM

API ionic (dissociated) and non ionic (non dissociated) form carries great importance in biopharmacy→ **absorption occurs only in non-ionic form.**

Ratio of IONIC/NONIONIC form depends on:

- pH in GI tract
- pK value of the API (Henderson-Hasselbach equation)

The equilibrium between ionic and non-ionic form is determined by the solubility (S_0) of the API and the dissociation coefficient (K_d) (on a given pH):

$$[HA]_{solid} \overleftrightarrow{S_0} [HA]_{solution} \overleftrightarrow{K_d} [H^+] + [A^-]$$

$$S_t = [HA] + [A^-]$$

HA: non ionic form

A^-: ionic form

RATIO OF IONIC/ NON-IONIC FORM

Henderson-Hasselbach equation

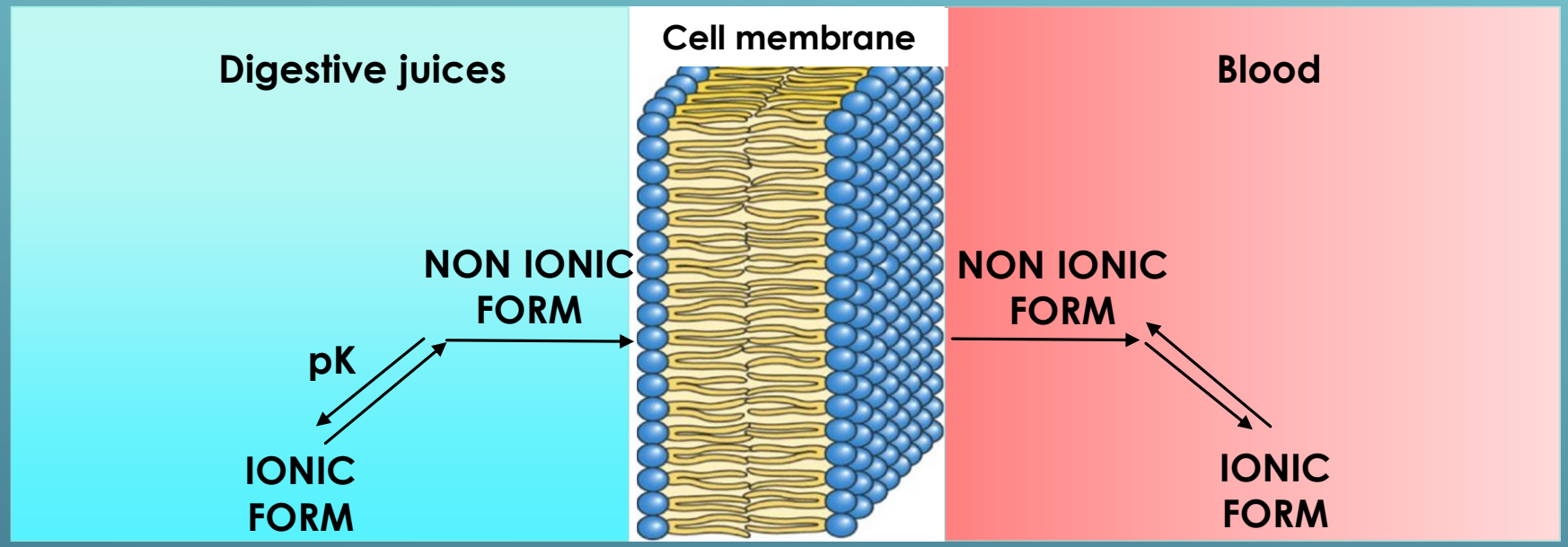
Weak acid:

$$pK_a = pH - \log \frac{[A^-]}{[HA]}$$

Weak base:

$$pK_a = pH - \log \frac{[B]}{[BH^+]}$$

ABSORPTION IN THE GI TRACT



Brodie partition theory: membranes are permeable only for the non-ionic form

Factors determining the distribution of the API in GI tract:

- Solubility
- Rate of dissolution
- Diffusion
- pH /pK_a values

Membrane diffusion determining factors:

- Partition coefficient (logP)
- Lipinski's rule of five

P – PARTITION COEFFICIENT

Partition between two inmiscible liquids

The lipophilicity of the API is described with the partition coefficients:

$$P = \frac{c_o}{c_w}$$

- c_o: API concentration in octanol phase
- c_w: concentration of API in water phase

If P>>1, the API is lipophillic.

It gives information possibility of absorption.

GENERAL SOLUBILITY EQUATION

General Solubility Equation (GSE)

$$\log S_0 = 0{,}5 - 0{,}01 \cdot (T_{op} - 25) - \log P$$

- S_0 – intrinsic equilibrium solubility
- T_{op} – melting point
- P – octanol-water partition coefficient

DIFFUSION – EINSTEIN-STOKES RELATION

$$D = \frac{kT}{6\pi\eta r}$$

- k – Boltzmann constant
- T = absolute temperature
- η – viscosity
- r – radius of molecule
- D – diffusion coefficient

Assumes a spherical molecule.

Not valid for a long chain polimers.

DISSOLUTION RATE

Noyes-Whitney equation:

$$\frac{dc}{dt} = k \cdot (c_s - c)$$

- k – dissolution rate coefficient

Modified Noyes-Whitney equation (Nernst-Brunner)

$$\frac{dc}{dt} = \frac{AD}{Vh} \cdot (c_s - c)$$

- D – diffusion coefficient
- h – diffusion layer thickness
- A – surface area of undissolved solid
- c_s – concentration of solution at a given time
- c- concentration

If $c_s >> c$ SINK CONDITIONS/CRITERIA are fulfilled.

EUROPEAN PHARMACOPOEIA TERMS FOR DESCRIBING SOLUBILITY

Descriptive term	Approximate volume of solvent (mL) necessary to dissolve 1 g of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparsingly soluble	30-100
Slightly soluble	100-1.000
Very slightly soluble	1.000-10.000
Practically insoluble	>10.000

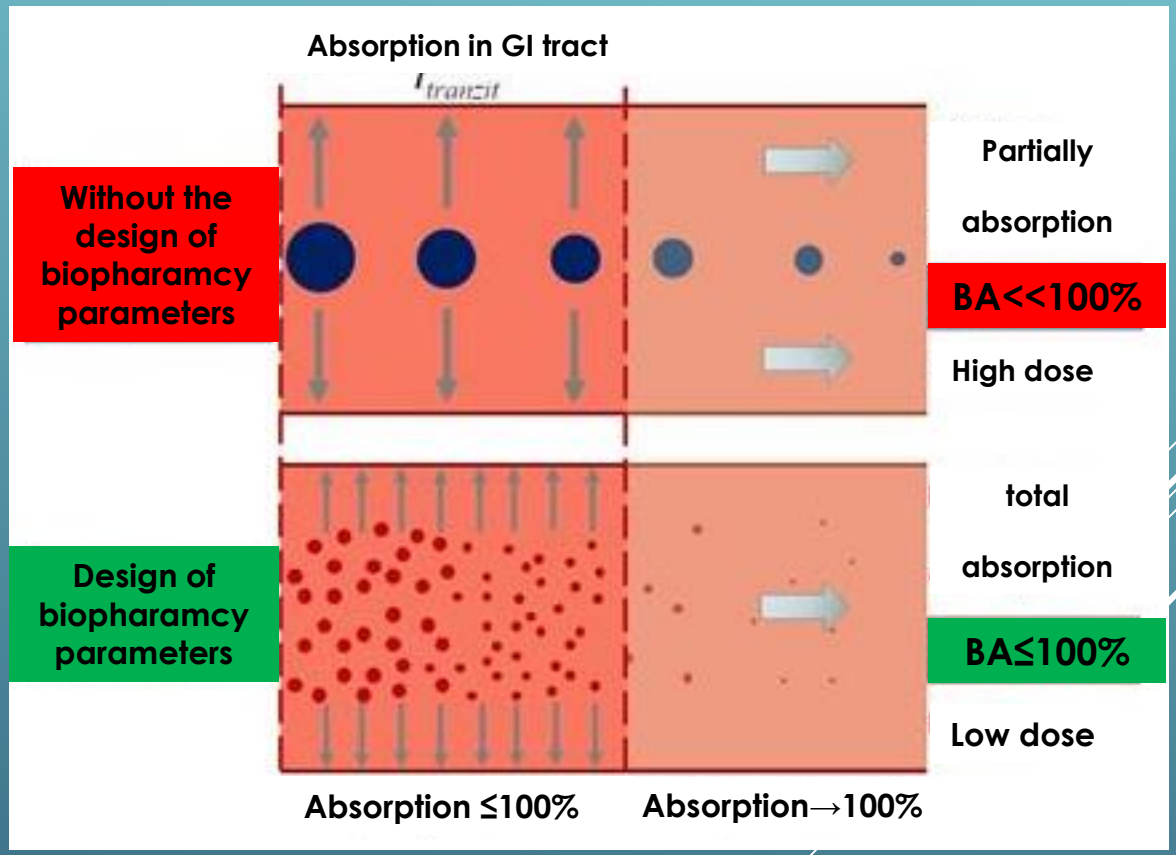
SOLUBILITY, DISSOLUTION RATE, TRANSIT TIME

The absorption is faster in case of solution dosage form because the API molecules are „ready to be absorbed".

$T_{tranzit}$ – time until the total absorption

In case of partial dissolution:

- low bioavailabilty
- high dose



SOLUTIONS CAN BE ADMINISTERED IN THE FOLLOWING WAYS

- Oral (buccal)
- Peroral
- Dermal and transdermal
- Ocular
- Auricularia (used for the treatment of the earcavity)
- Nasalia
- Rectal
- Vaginal

SOLUBILITY AND PERMEABILITY OF API

Biofarmaceutical Classification System - BCS

classification	Solubility	Permeability
I.	GOOD	GOOD
II.	POOR	GOOD
III.	GOOD	POOR
IV.	POOR	POOR

ENHANCEMENT OF API SOLUBILITY

Enhancement solubility

- Different API derivatives
- Salt formation
- Crystal structure (polimorphy, amorphous form)

Enhancement of dissolution rate

- Solid dispersion
- Nanonisation
- Solvent mixing
- Surfactants
- Compleces

ENHANCEMENT OF DISSOLUTION RATE – SALT FORMATION

The selection of salt form depends on:

- Solubility
- Hygroscopy
- Stability
- Toxicological properties

$$\Delta G_{solvent} = \Delta G_{cation} + \Delta G_{anion} - \Delta G_{lattice}$$

The selection of the appropriate salt form is based on experiments, the solubility cannot be properly calculated or predicted beforehand.

- Na, K, Ca, hydrochlorid, methan-sulfonate(mesylate)
- E.g.: ephedrine → ephedrine hydrochloride , phenobarbital → phenobarbital -sodium

ENHANCEMENT OF DISSOLUTION RATE – SALT FORMATION

Different salt formation approaches

Basic (API)

- hydrochloride
- mesylate
- acetate, fumarate, succinate, tartrate
- sulphate, phosphate, nitrate, carbonate

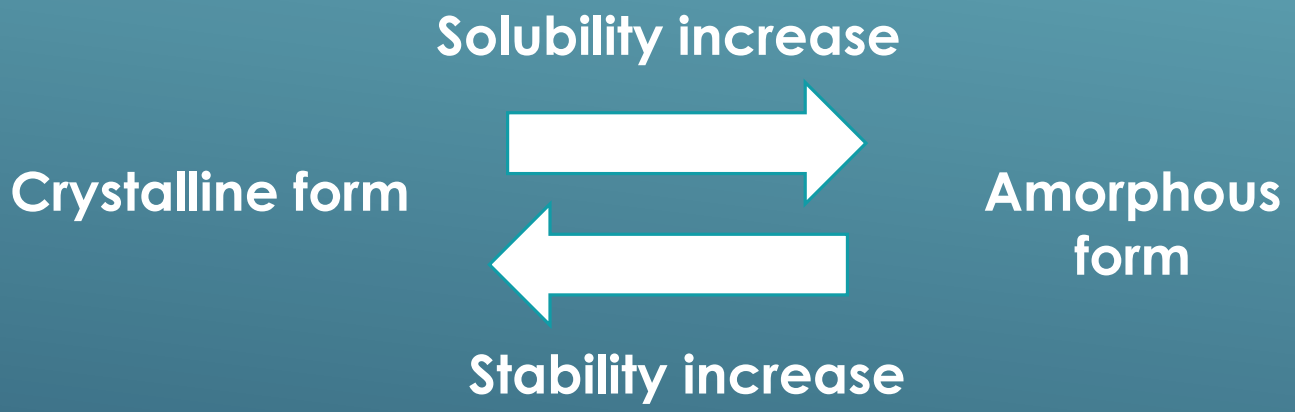
Acidic (API)

- Na^+, K^+, Ca^+
- tromethamine

ENHANCEMENT OF DISSOLUTION RATE – STRUCTURE

- Polymorphy
- Amorphous or crystalline structure

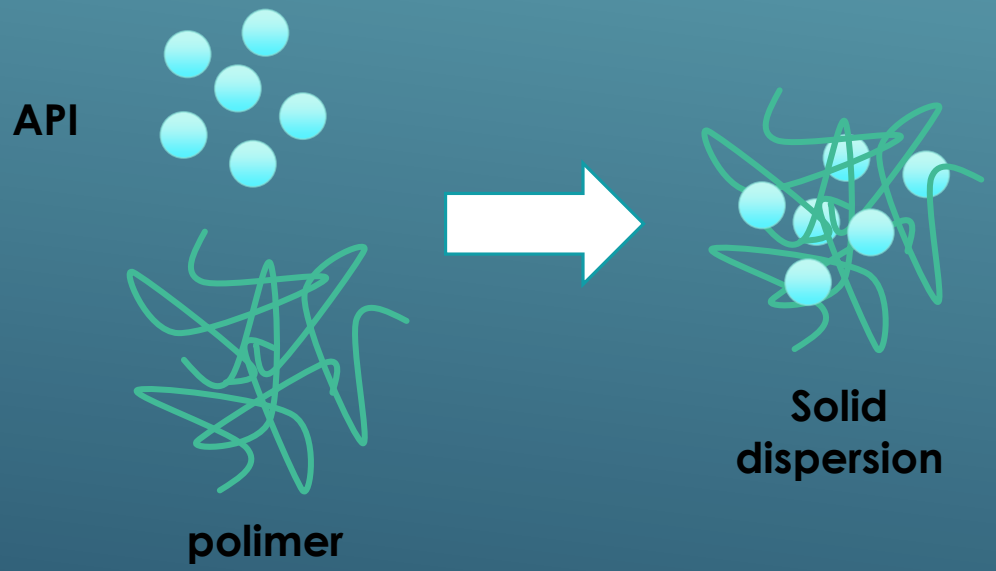
The crystalline structure determines the process of solvation.



ENHANCEMENT OF DISSOLUTION RATE– SOLID DISPERSIONS

Solid dispersion: API is dispersed in solid hydrophillic solvents.

- Solvent: different polimers, mixtures of polimers
- Excipients: plasticizer
- Manufacturing: melting method, solvent evaporation method , spray drying



Characteristics:

- Amorphous API
- Hidrophillic basis → increase of water solubility

↓

Increased absorption

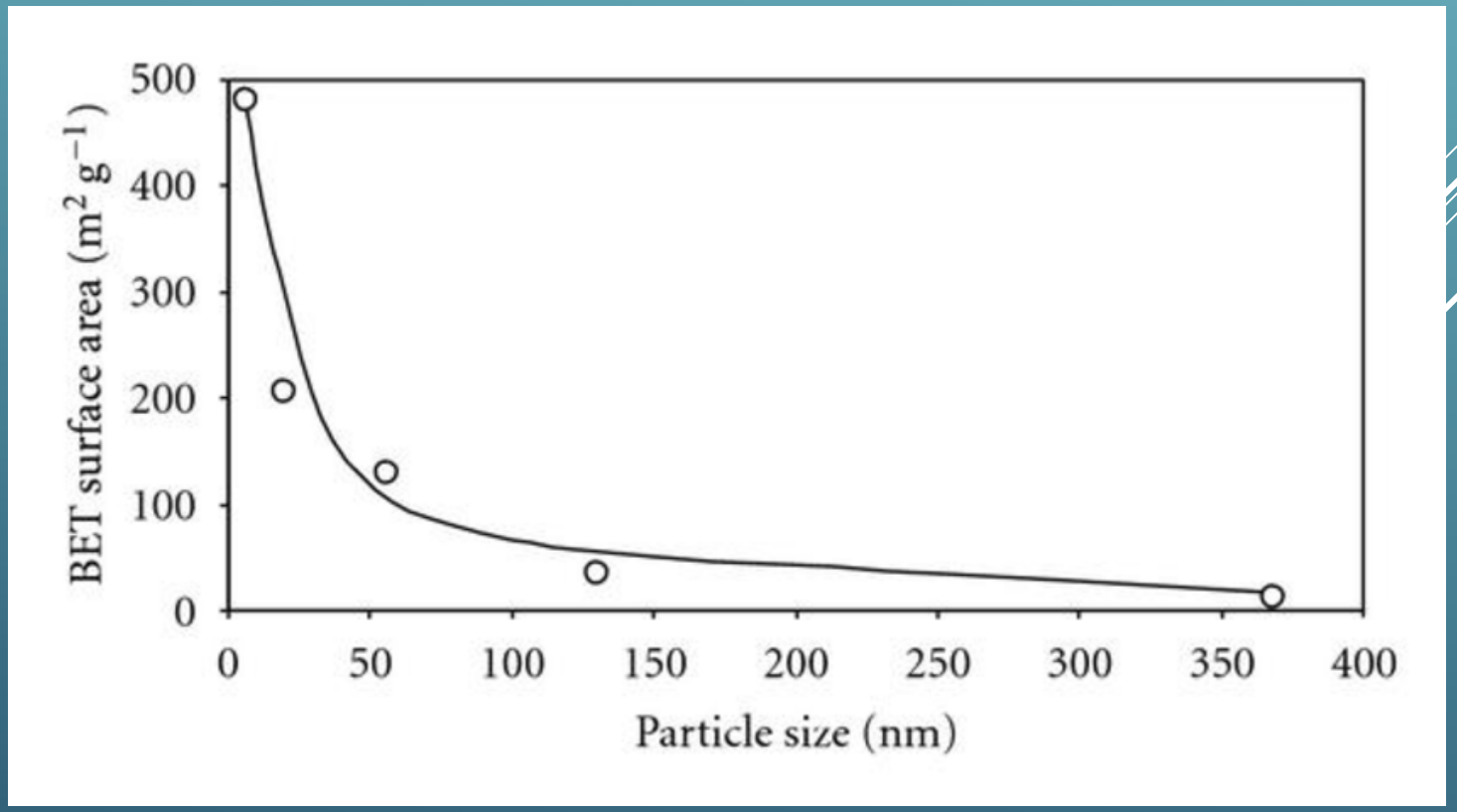
ENHANCEMENT OF DISSOLUTION RATE – API NANOCRYSTALS

For the formulation of APIs with low solubility/bioavalability:

preparation of nanocrystals→increased specific surface area→increased solubility rate

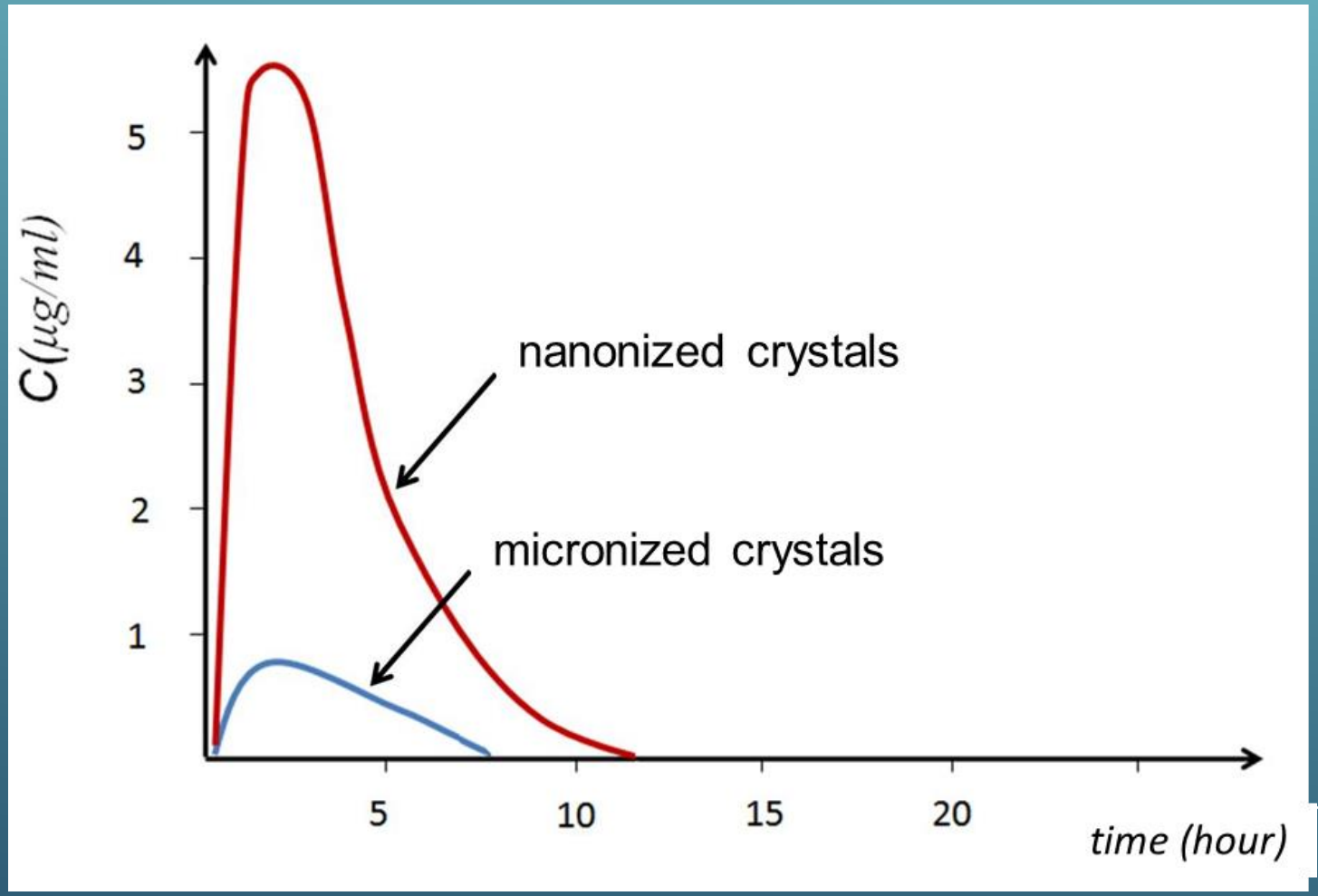
Modifed Noyes-Whitney equation (Nernst-Brunner)

$$\frac{dc}{dt} = \frac{AD}{Vh} \cdot (c_s - c)$$



ENHANCEMENT OF DISSOLUTION RATE – SOLVENT NANOCRYSTALS

Blood level curve in the case of micronized (2000nm) and nanonized (120nm) API



ENHANCEMENT OF DISSOLUTION RATE– SOLVENT MIXTURES

Most frequently used solvents

- Demineralised water, ethanol, isopropyl-alcohol, glycerine, propylene-glycol, PEG, oils

Cosolvenses

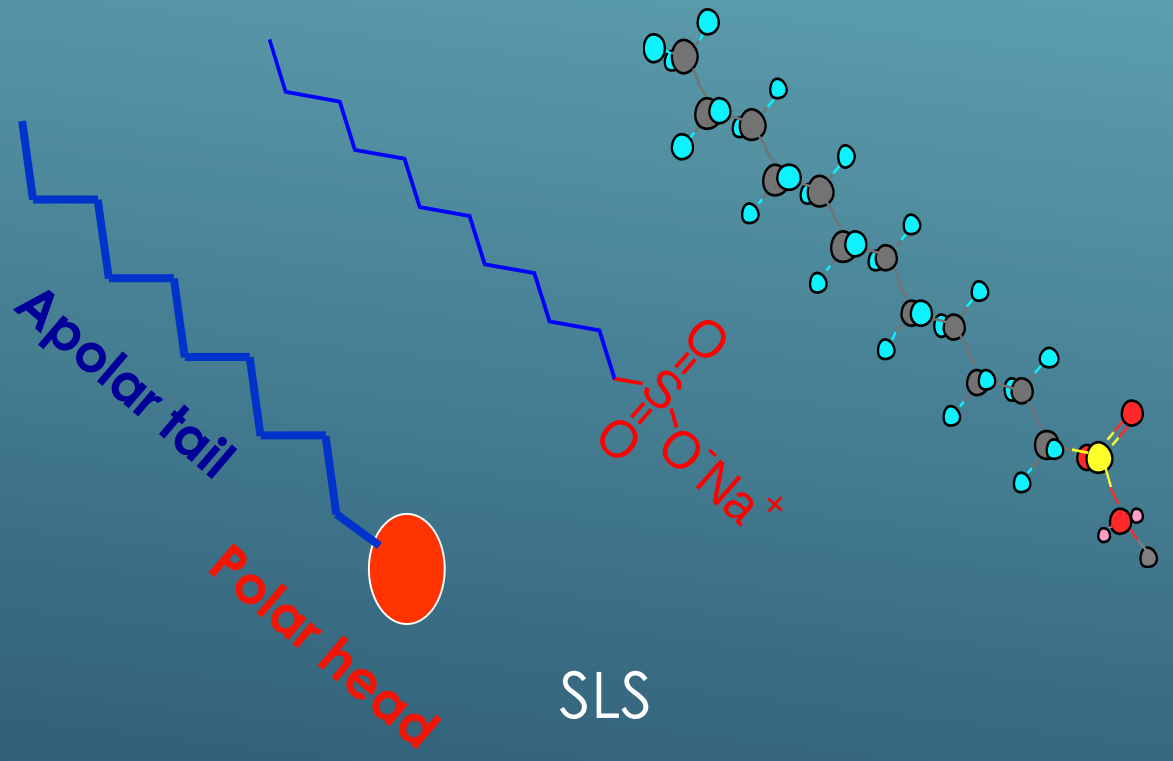
- The aim is the increase of solubility
- Alcohols, syrups
- Solvent permittivity can be altered
  - Permittivity increased → the solubility of polar substances increases
  - Permittivity decreased → the solubility of apolar substances increases
  - The relation between the relative permittivity of the solvent and solubility can be described with an exponential relation.

The effect of solvent relative permittivity on the attraction between ion can be described with relative permittivity and dielectric constant (ε).

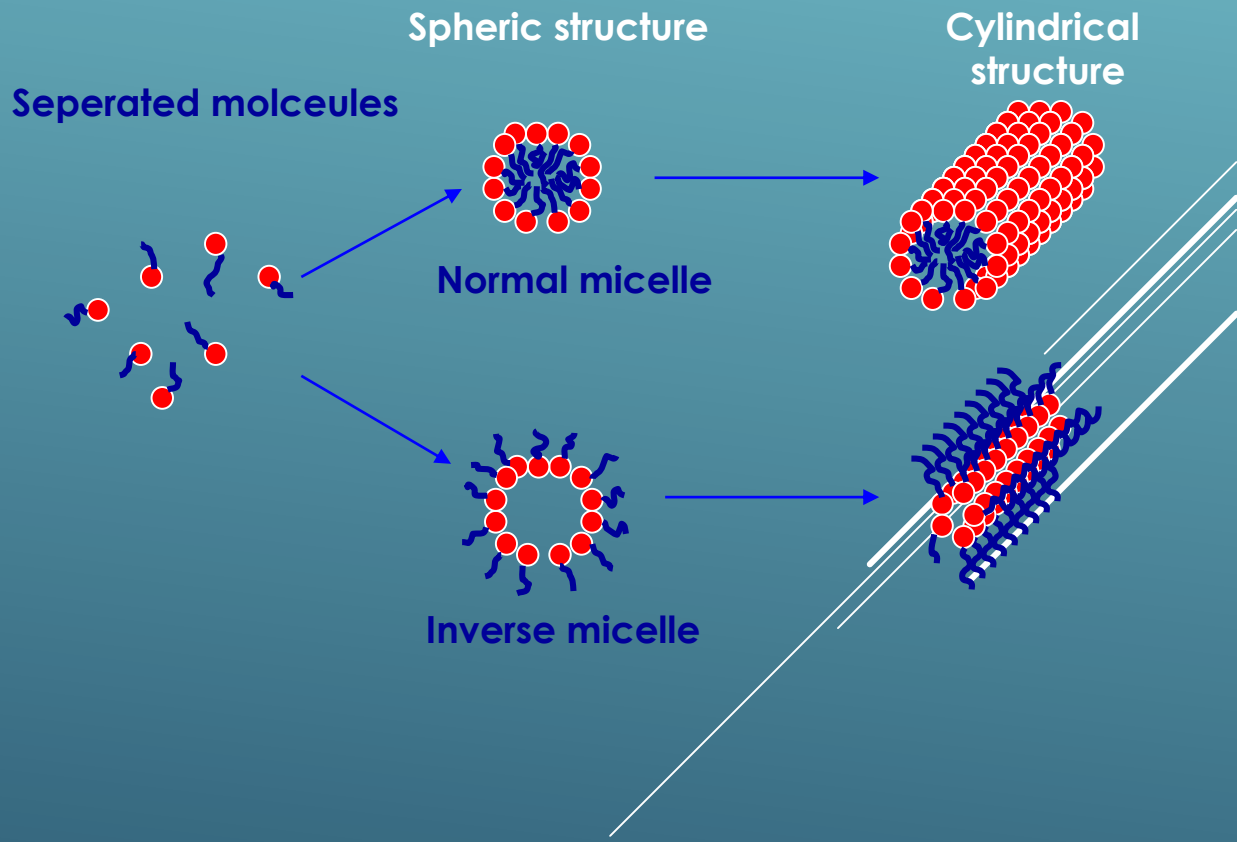
Polar liquids: ε>15 (pl.: water, ethanl, DMSO), Apolar liquid: ε<15

ENHANCEMENT OF DISSOLUTION RATE – SURFACTANTS

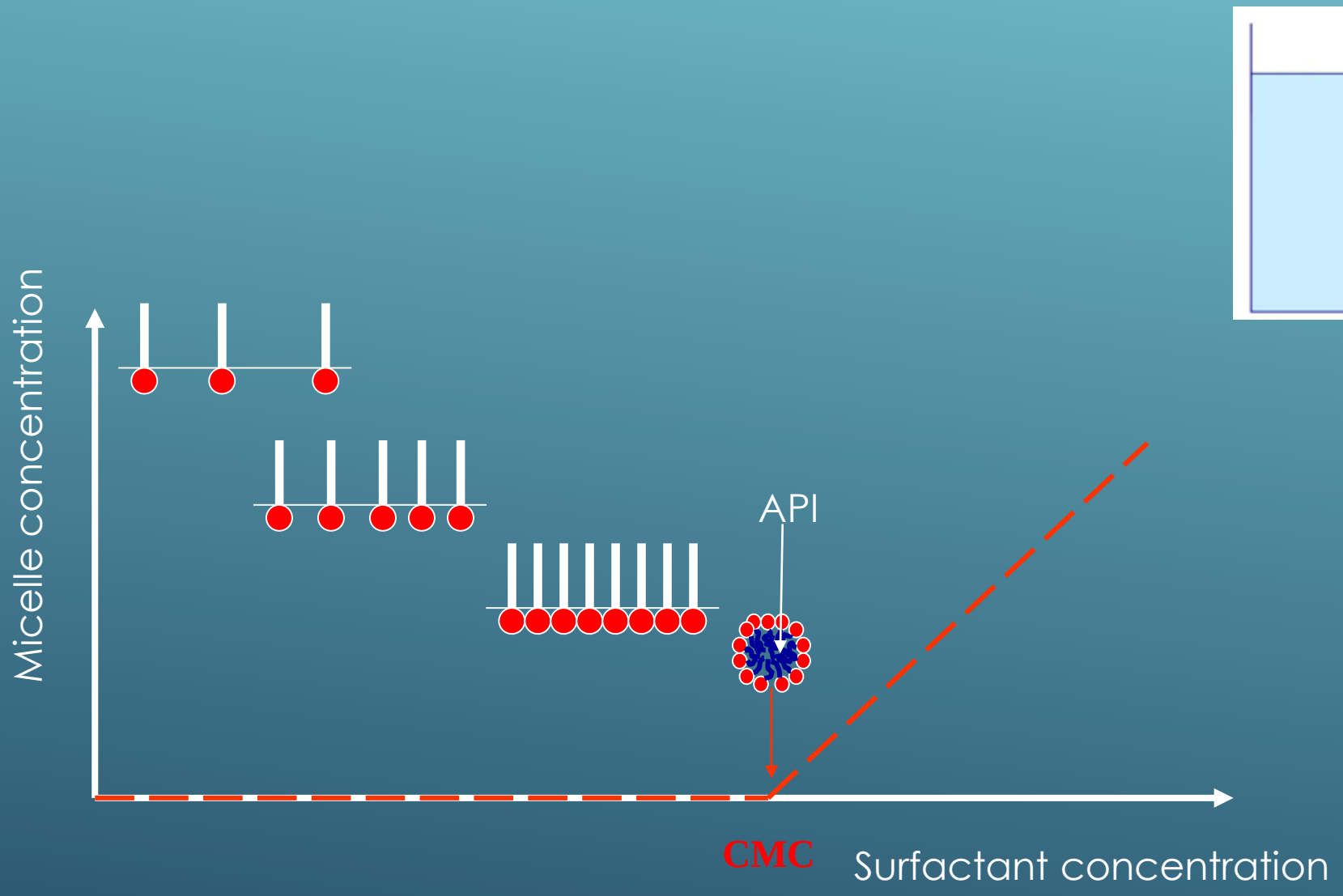
Most frequently used solubilizing agents are the surfactants.

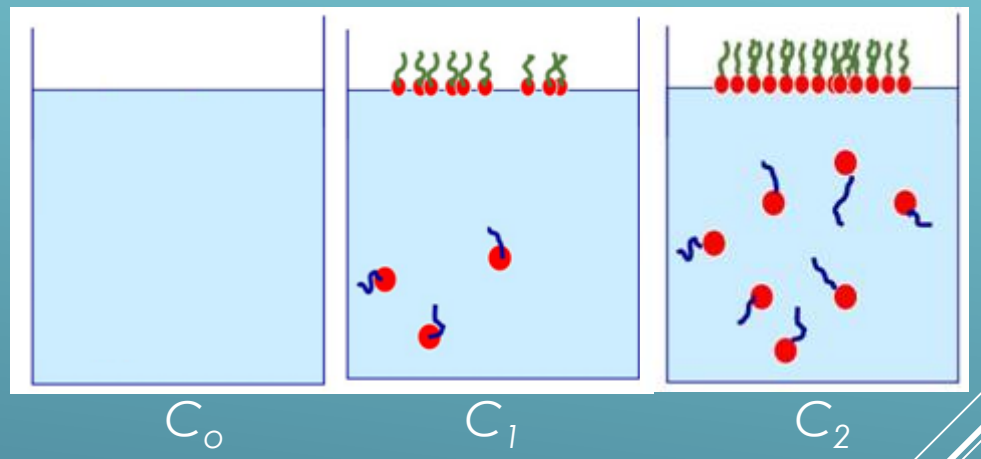


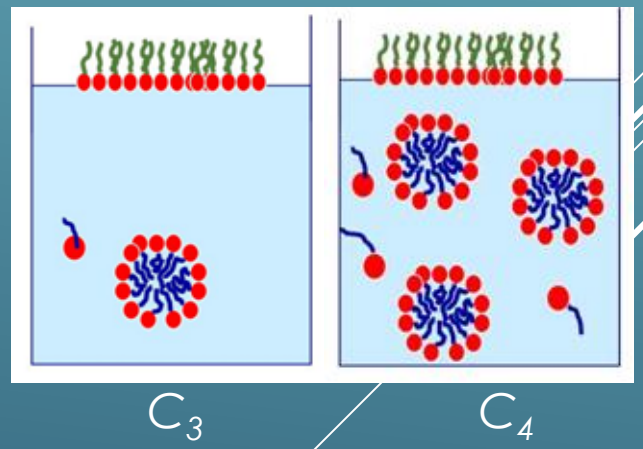
SLS



ENHANCEMENT OF DISSOLUTION RATE – SURFACTANTS







ENHANCEMENT OF DISSOLUTION RATE – SOLUBILIZING AGENTS

Solubility in the presence of surfactant:

$$S = pS_w + K_{ms} \cdot (c_s - CMC)$$

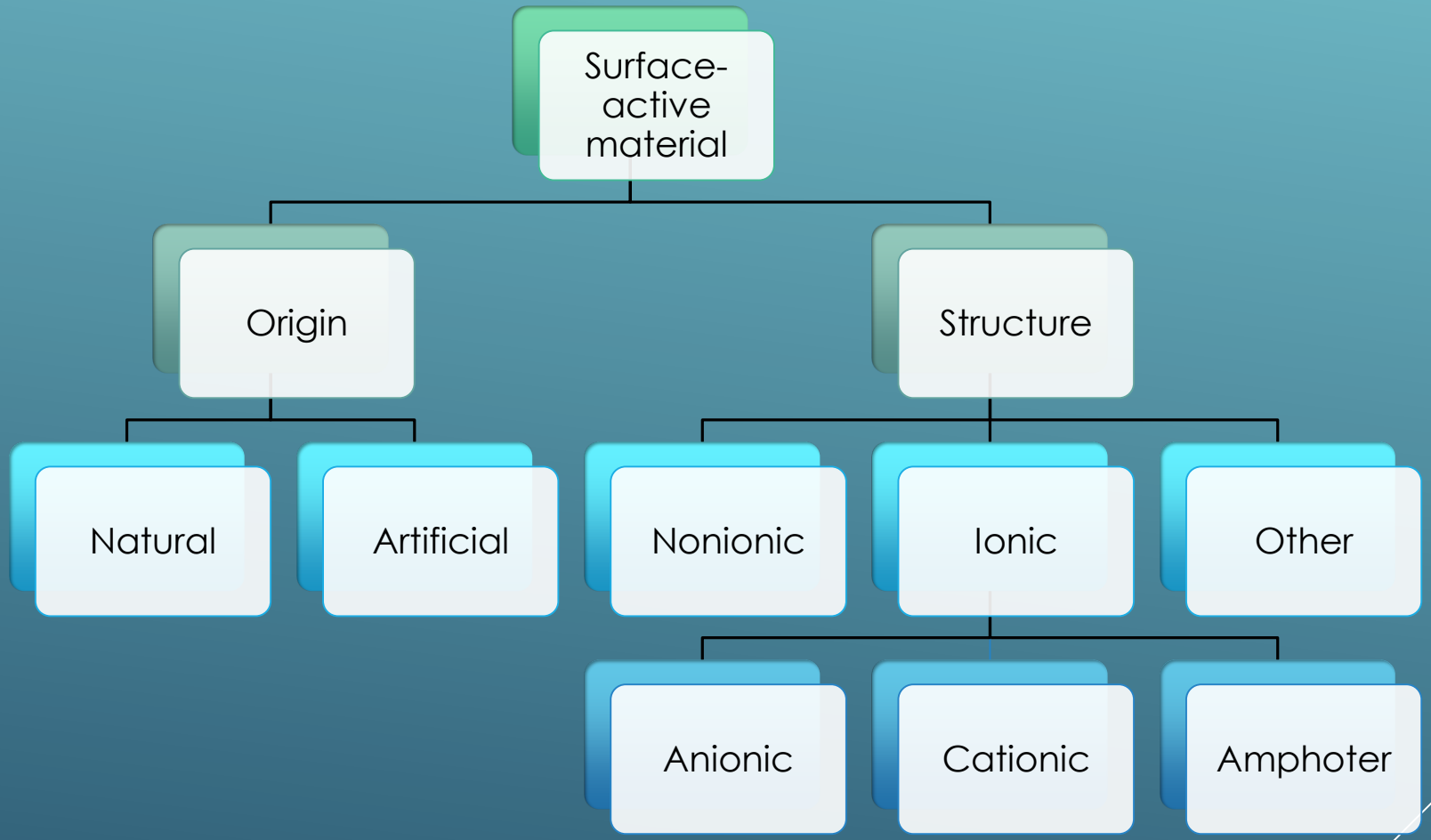
K_{ms} – solubilization affinity of certain micelle

c_s – concentration of surfactant

p – other effect of surfactant on solubility

S_w- solubility in water

ENHANCEMENT OF DISSOLUTION RATE – SURFACTANTS



ENHANCEMENT OF DISSOLUTION RATE – SOLUBILIZING AGENTS

RELATION OF HLB VALUE AND SOLUBILITY

Surface active substances	HLB value
Non dispersible	1-4
Slightly dispersible	3-6
Dispersion (milk-like)	6-10
Colloid solution (opalescence)	10-13
Colloid solution (clear)	**> 13**

ENHANCEMENT OF DISSOLUTION RATE – SURFACE ACTIVE SUBSTANCES

HLB VALUE AND USAGE IN PAHARMACEUTICS

Usage	HLB value
Defoamers	1-3,5
W/O emulsifying agents	3,5-8
Moistening agents	7-9
O/W emulsifying agents	8-16
Detergens	13-16
Solubilizing agents	**16-40**

ENHANCEMENT OF DISSOLUTION RATE – COMPLEX FORMATION

Types of compleces:

- Inorganic complex
  - chelate compleces (Pb, Hg, As intoxication)
  - Water soluble
- „loose compleces"
  - Compleces with hydrotropic agents
  - H- bridge compleces (OH, NH_2 groups)
- „molecular compleces"
  - polimers
- Inclusion – association compleces
  - ciclodextrins

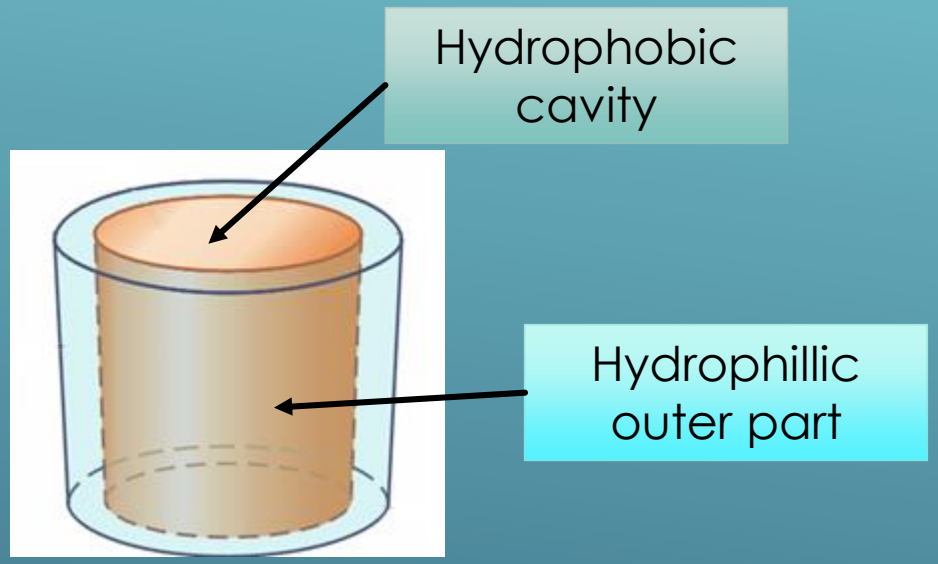
ENHANCEMENT OF DISSOLUTION RATE – HYDROTROPIC MATERIALS

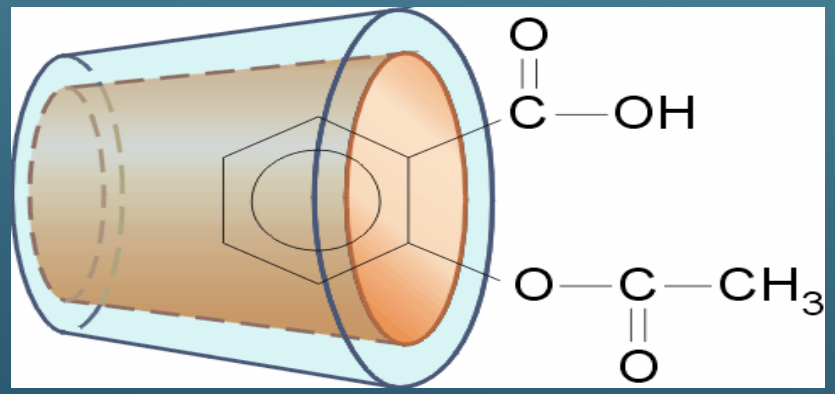
Hydrotropic materials are substances with one or two –OH groups ,or alcohol derivatives

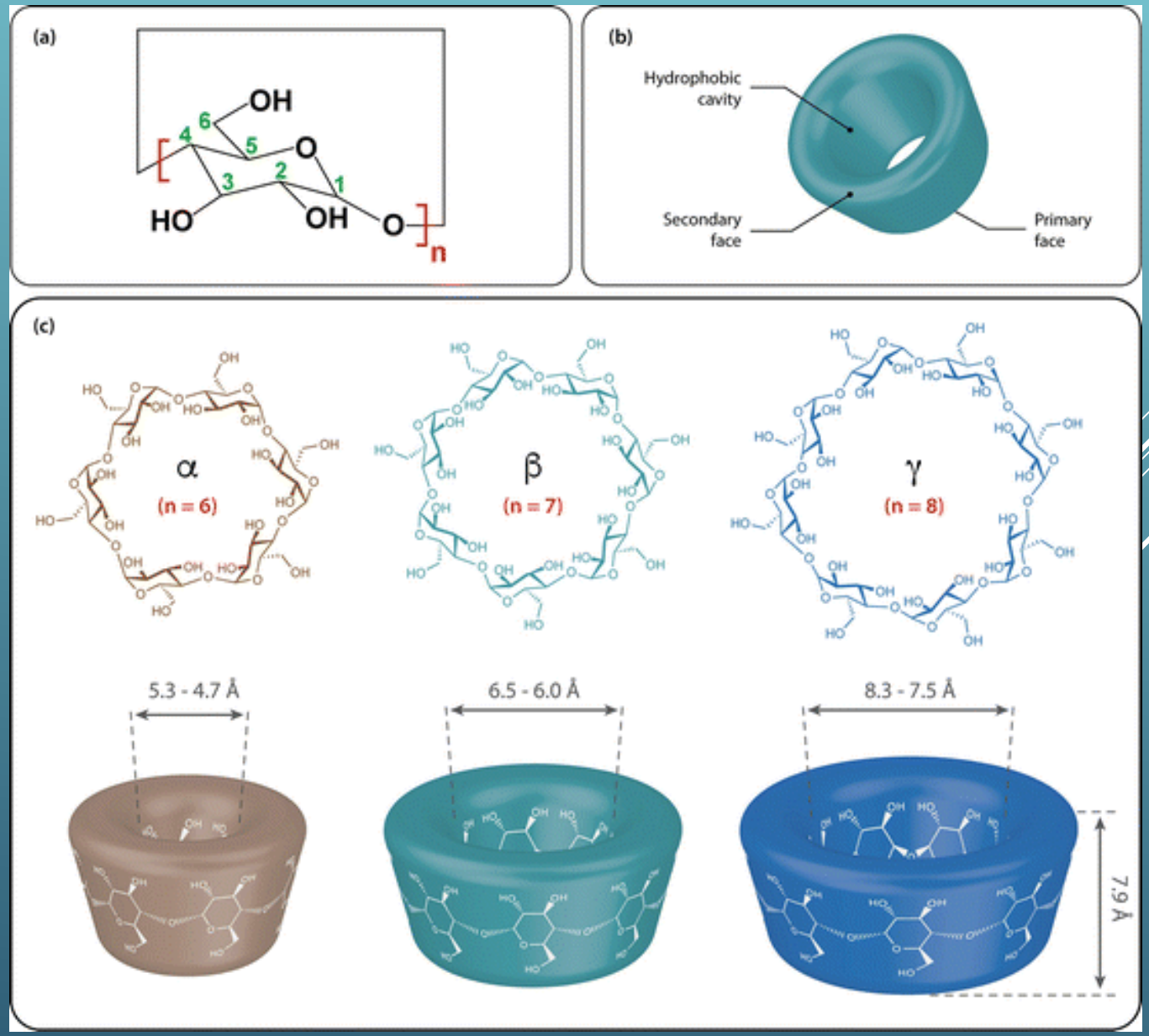
- Formation of loose complexes, H-bridges
- Decrease of surface tension
- Change of permittivity

- theobromine + Na-acetate
- oxytetracycline + salicilate, oxytetracycline + benzoate
- theophyllin + Na-salicilate
- coffein + Na-benzoate

ENHANCE OF DISSOLUTION RATE – CYCLODEXTRINS

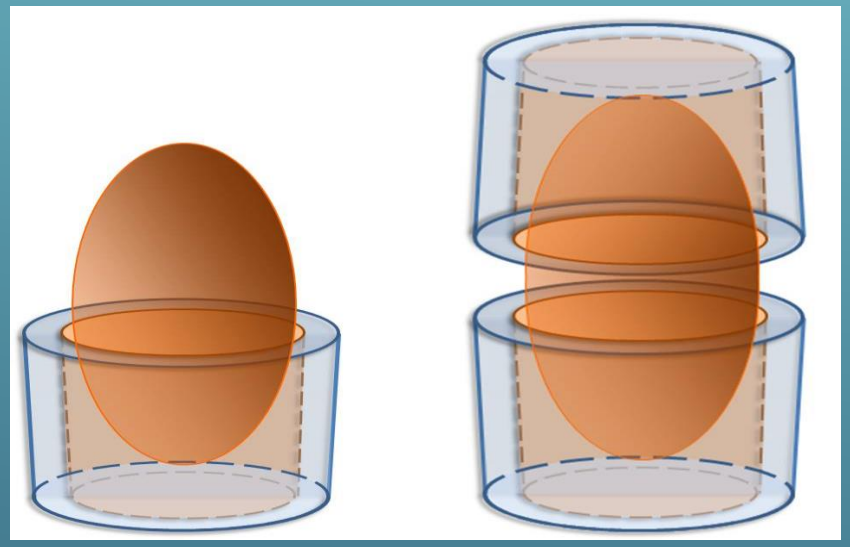






ENHANCEMENT OF DISSOLUTION RATE – CYCLODEXTRINS

API : ciclodextrin



1:1 **1:2**

$$K_{1:1} = \frac{[API_{in\ complex}]}{[API_{free}] \cdot [CD_{free}]}$$

$[API_{n\ complex}]$ – concentration of API in complex

$[API_{free}]$ – free API concentration

$[CD_{free}]$ – free cyclodextrin concentration

$K_{1:1}$ – complex stability constant

ENHANCEMENT OF DISSOLUTION RATE – CYCLODEXTRINS

Increased solubility of the API in case of 1:1 ratio complex :

$$S_t = S_0 + \frac{K_{1:1} \cdot S_0}{1 + K_{1:1} \cdot S_0} \cdot [CD_{total}]$$

S_t – solubility in presence of cyclodextrin

S_0 - solubility without cyclodextrin

$[CD_{total}]$ – total concentration of cyclodextrin in solution

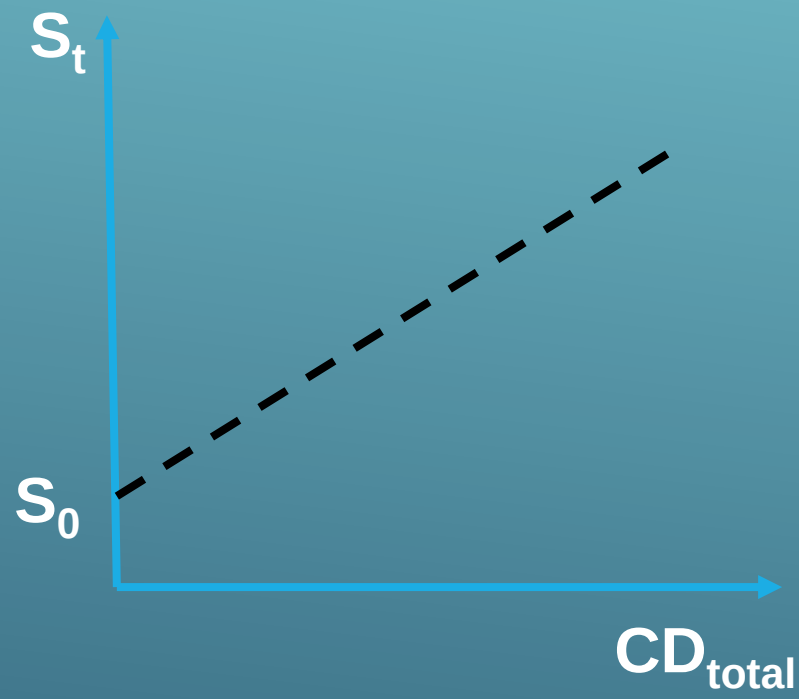
ENHANCEMENT OF DISSOLUTION RATE – CYCLODEXTRINS

Determination of stability constant, K1:1 by Higuchi-Connors

$$S_t = S_0 + \frac{K_{1:1} S_0}{1 + K_{1:1} S_0} \cdot [CD_{total}]$$

$$S_t = S_0 + R[CD_{total}]$$

$$\boldsymbol{K_{1:1} = \frac{R}{S_0(1 - R)}}$$



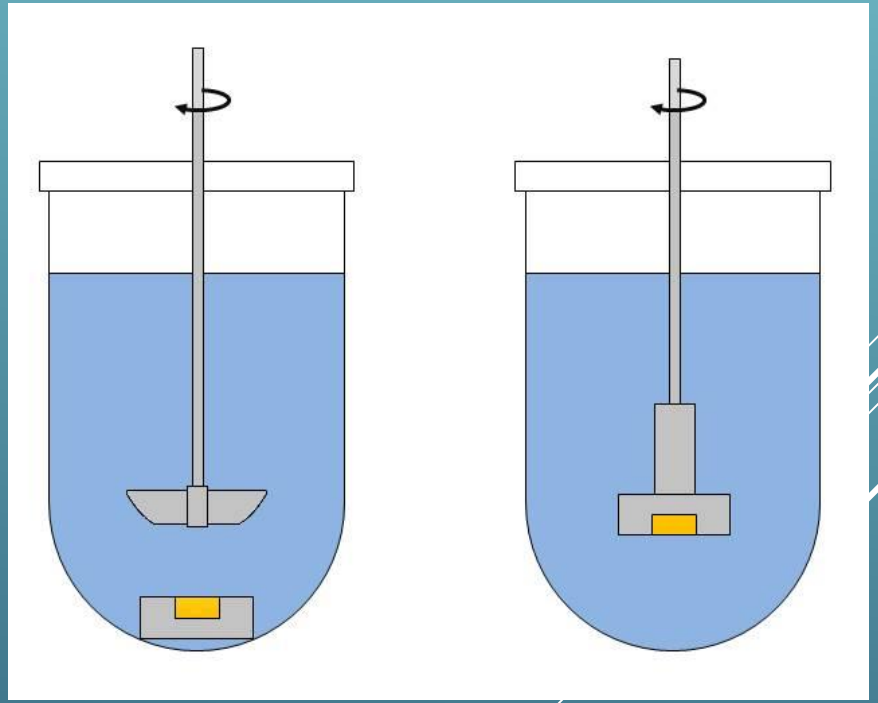
$K_{1:1}$ – complex stability constans
R – slope
S_0 – intersection on solubility graph

DISSOLUTION RATE

The operation of dissolution is applied at drug delivery examination.

Standard circumstances:

- in prescribed flask (size, geometric properties),
- with appropriate, suitable stirrer (plate, rotating basket dissolution apparatus),
- with controlled speed,
- in a medium on appropriate temperature, in certain volume, with an desired pH.



DISSOLUTION RATE

Hixson-Crowell equation:

$$m_t^{\frac{1}{3}} - m_0^{\frac{1}{3}} = k \cdot t$$

m_0 –mass of active ingredient in dosage form at t=0

m_t – mass of active ingredient undissolved at t time point

k – rate coefficient

Higuchi-Hiestand correlation:

$$r^2 = r_0^2 - \frac{2Dc_s}{\rho} \cdot t$$

r_0 – radius of diffusion layer

D - diffusion coefficient

c_s –concentration in the diffusion layer surrounding the particles

ρ - density

REAL SOLUTIONS VS. COLLOID SOLUTIONS

Colloid solutions are a transition between real solutions and coarse dispersed systems.

Colloidal dispersed systems grouped by the dispersed particle type:

- **Sols:** paticles with well defined surface dispersed in continuous phase (1<d<500nm)
- **Solutions of association colloid:** amphipatic molecules grouped to micelles
- **Macromolecular colloids**: the diameter of the particles dispersed in liquid d<100 nm. Pl.: proteins, polimer solutions.

Manufacturing:

- Milling of coarse disperse system
- Precipitation of real solution

In pharmaceutical practice colloidal solution prepared first swelling of the substance, then slow mixing and heating.

OPERATION OF DISSOLUTION

Manufacturing intermediate products:

- Stock solutions
- Solutions for preparation of ointments
- Solutions for preparation of granulating fluid
- Syrups
- Mucilage for stabilization of suspensions
- **Dissolution in practice:**
- In Pharmacy:
  - Beaker, stirring rod, magnetic stirrer and magnetic rod
  - Patendula: small amounts
- In Industry :
  - in glass or steel jars with motor-operated mixers

OPERATION OF DISSOLUTION

- per oral solutions,
- dermal solutions,
- painting solutions,
- injection solutions,
- infusion solutions,
- hemodialysis solutions,
- peritoneal solutions,
- dialysis solutions,
- solutions used for organ transplantation,
- perfusion solutions,
- enemas,
- eye wash solutions,
- decoctions,
- infusions,
- per oral drops,
- nose drops,
- ear drops,
- eye drops,
- inhalants,
- oral aerosols,
- nasal sprays,
- throat sprays,
- aerosols applied on intact skin and mucosa

SUMMARY

Major determining factors of the APIs biopharmaceutical classification:

- Solubility
- Rate of dissolution– Noyes-Whitney equation!
- Ionic-non ionic form: diffusion, membrane permeability

Methods for improving the APIs solubility/dissolution rate

THANK YOU FOR YOU ATTENTION