Theoretical background of drug release

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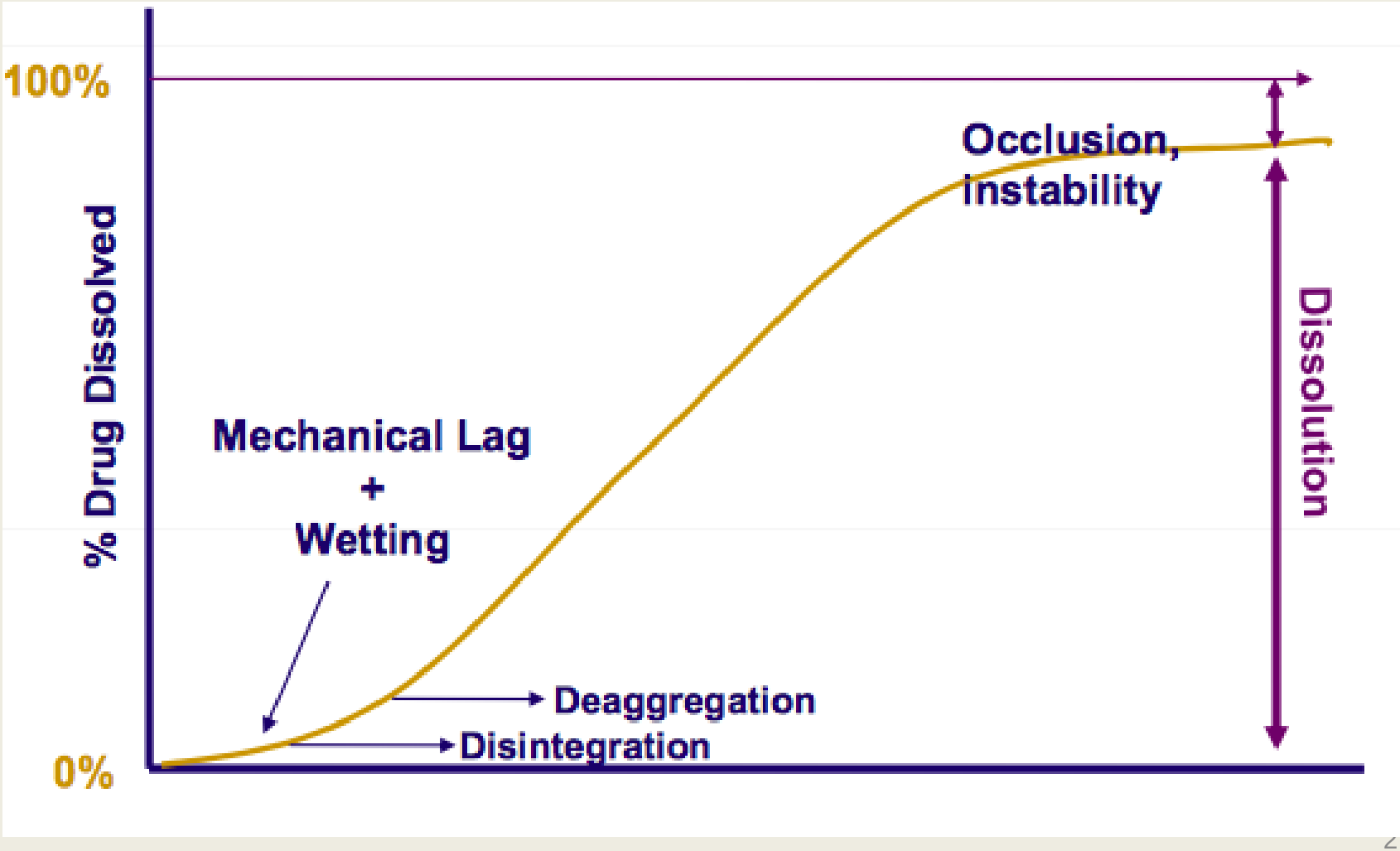
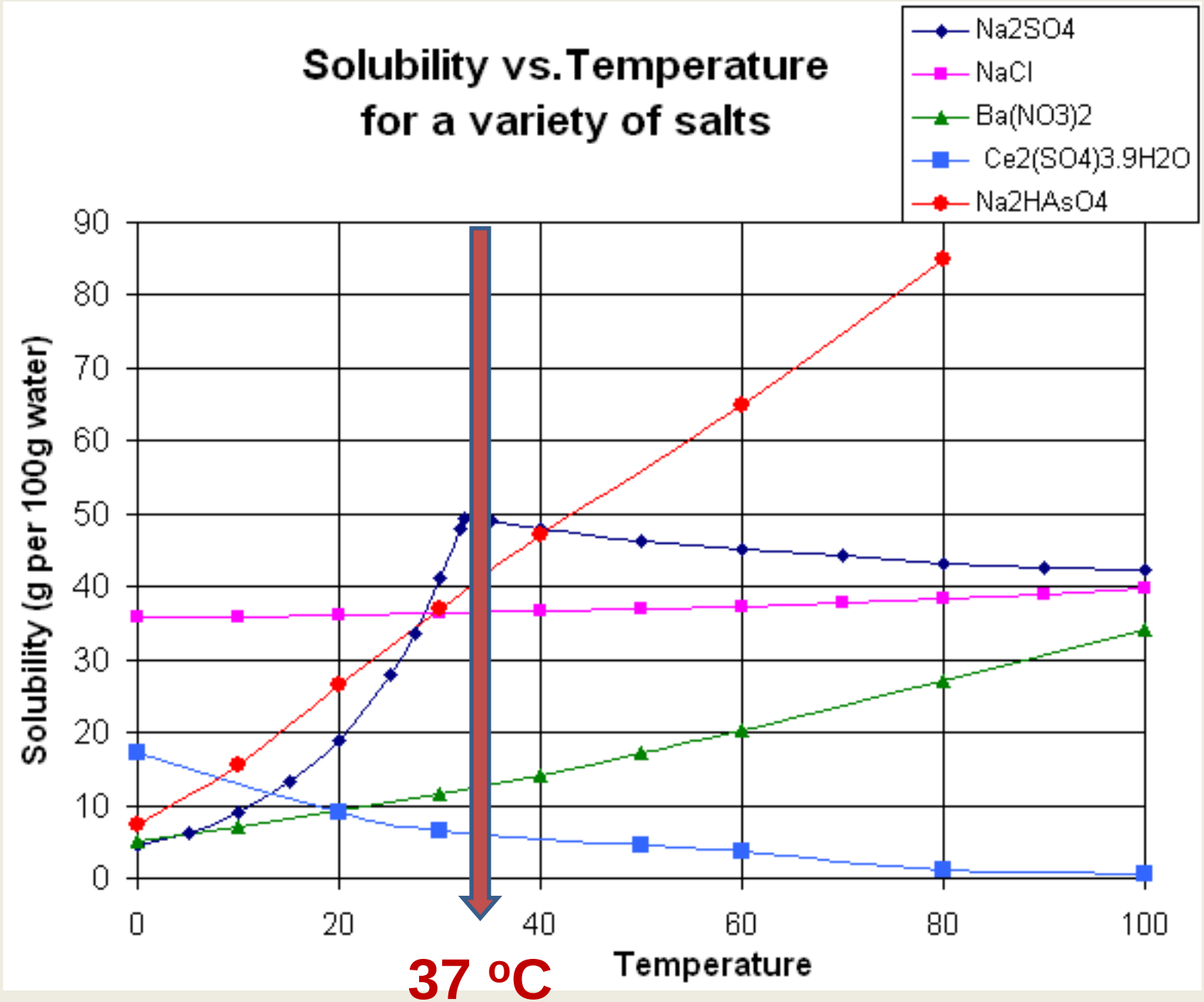
Liberation basics

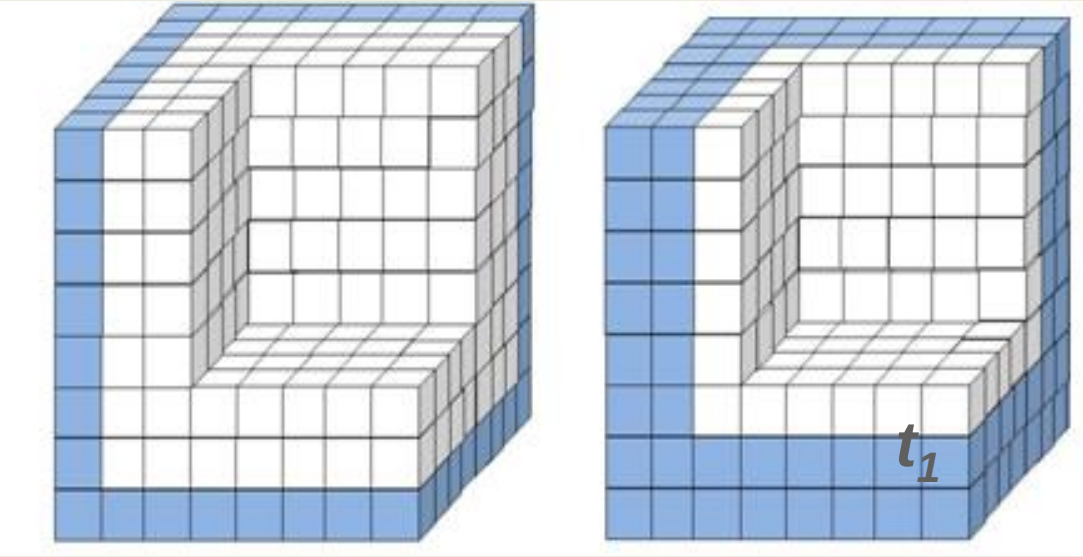


Temperature


Solubility vs.Temperature
for a variety of salts
Na2SO4
NaCl
Ba(NO3)2
Ce2(SO4)3.9H2O
Na2HAsO4
Solubility (g per 100g water)
0
10
20
30
40
50
60
70
80
90
0
20
40
60
80
100
Temperature
37 oC

Porosity

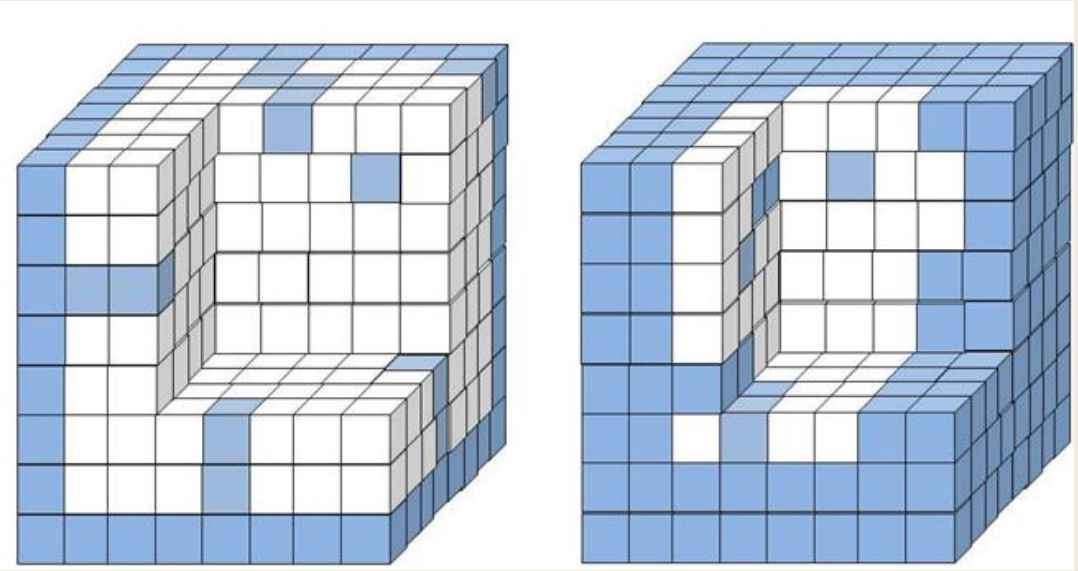
Homogeneous systems

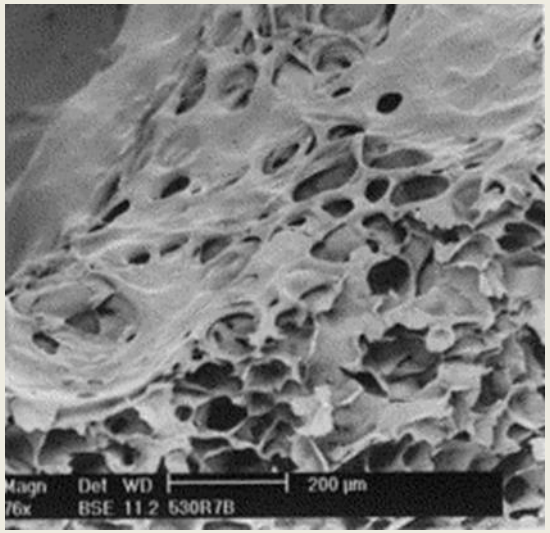


The system's matrix has regular structure.

Penetration of the medium occurs evenly through the layers.

Heterogeneous systems



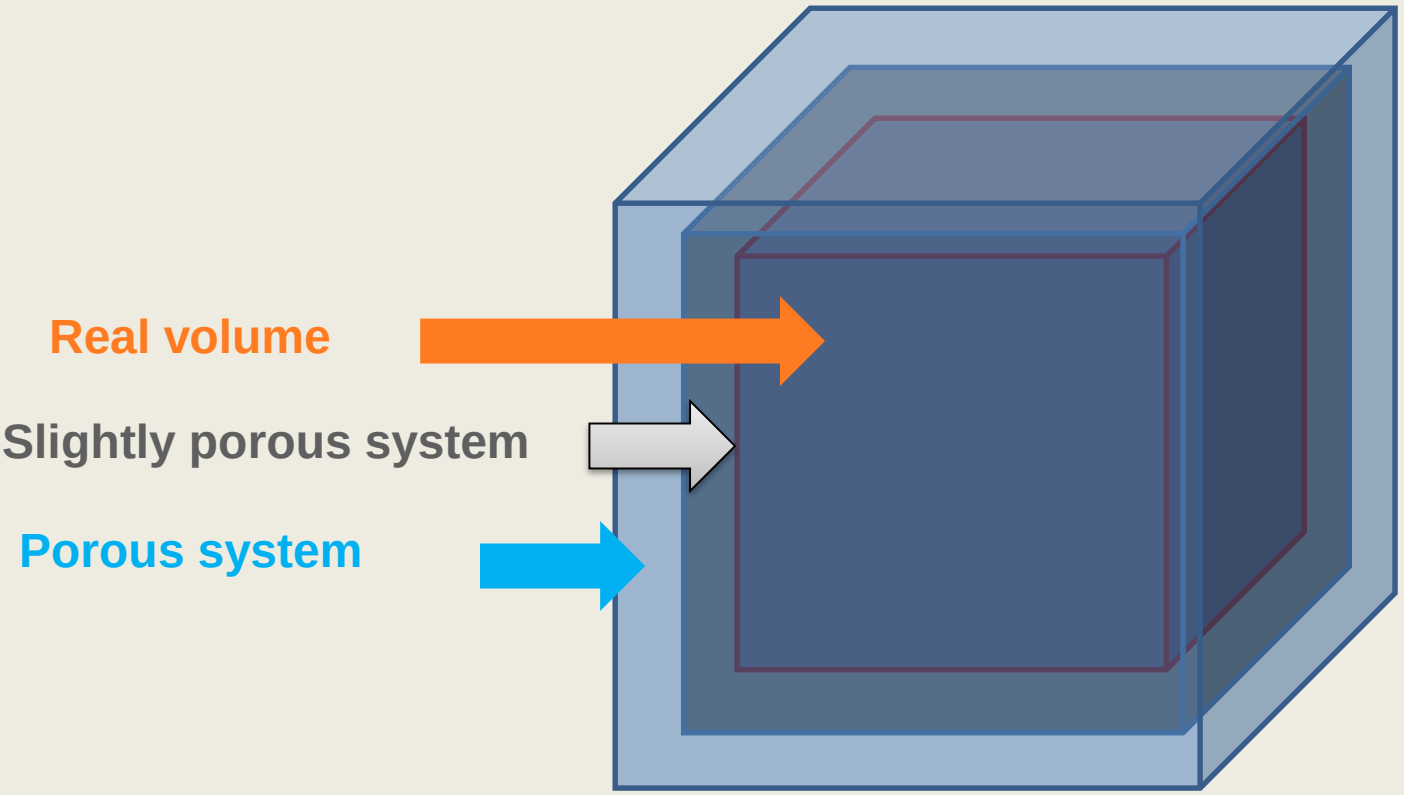


Heterogenity in the homogen matrix causes different dissolution profile compared to the homogeneous system.

The penetration through the deeper layers slows down.

Porosity

Real volume, porosity



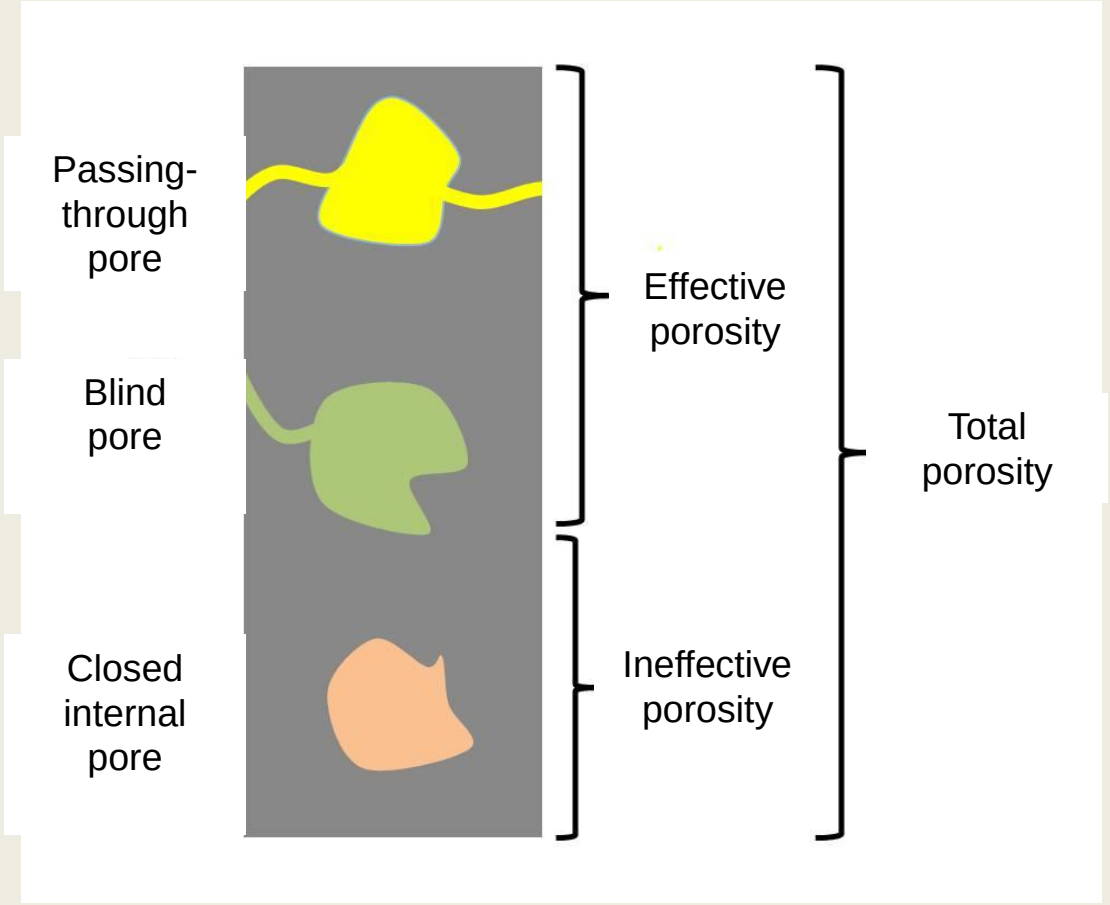
V_1

V_2

V_3

Porosity

Real volume, porosity



Porosity

Real volume, porosity

$$\Phi = \frac{V}{V_t}$$

V total volume of gaps and holes,
V_t total volume of the preparation

Porosity

Real volume, porosity

Total porosity ($\Phi_p{}^t$) contains the effective ($\Phi_p{}^e$) and the ineffective ($\Phi_p{}^{ie}$) porosity.

$$\Phi_p{}^t = \Phi_p{}^e + \Phi_p{}^{ie}$$

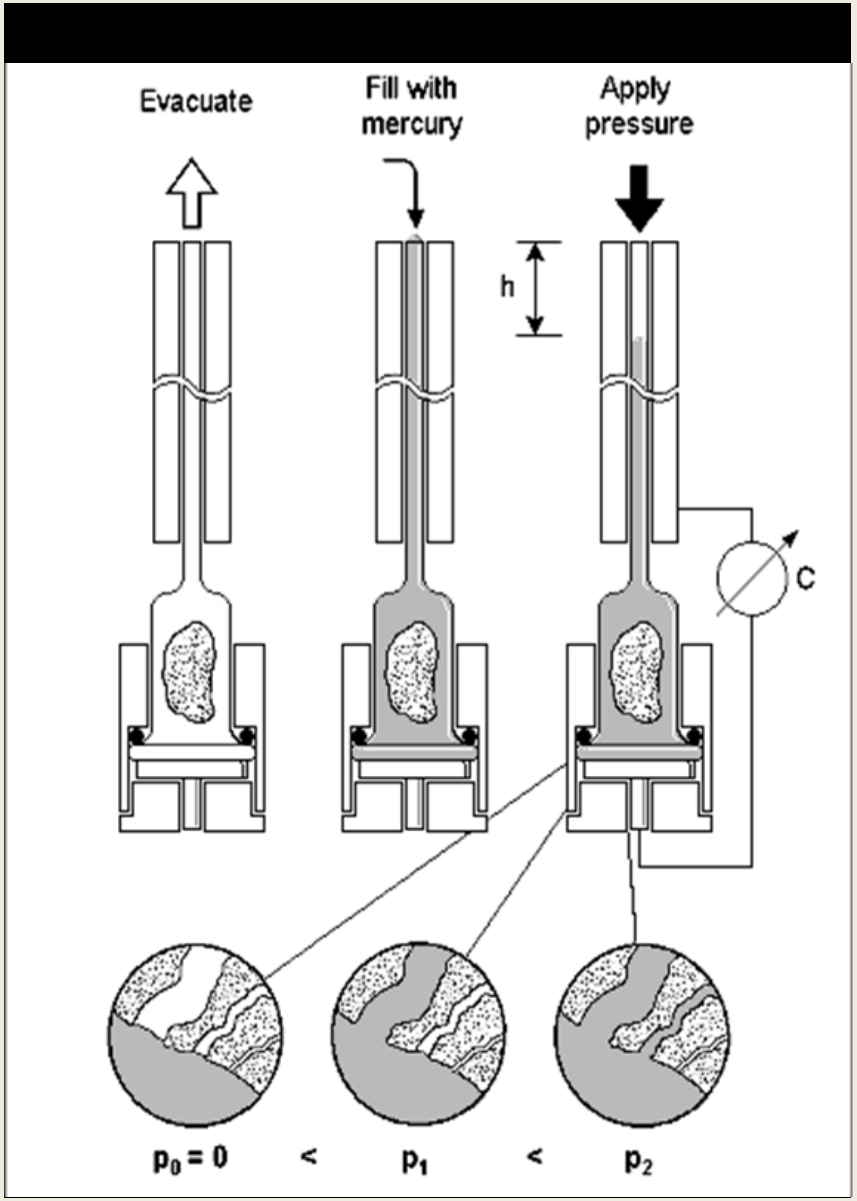
Porosity

Mercury intrusion porosimetry

Washburn – equation

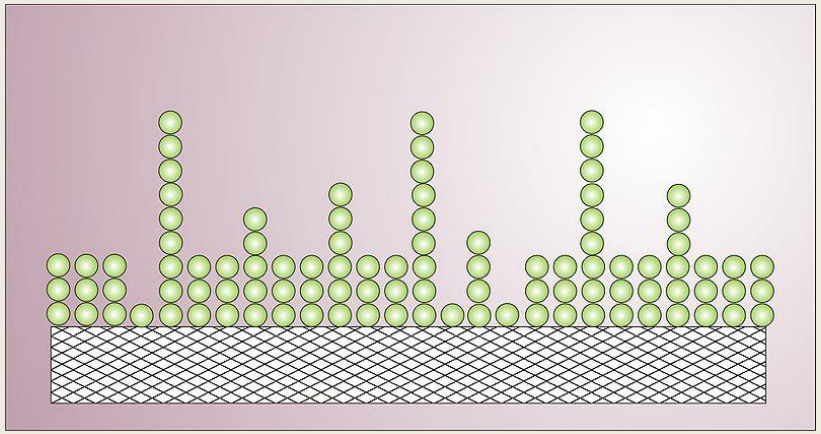
$$L_p^2 = \frac{\gamma \cos \Theta r t}{2\eta}$$

Lp	penetration of the liquid
γ	surface tension
θ	contact angle
r	pore radius
η	viscosity
t	time



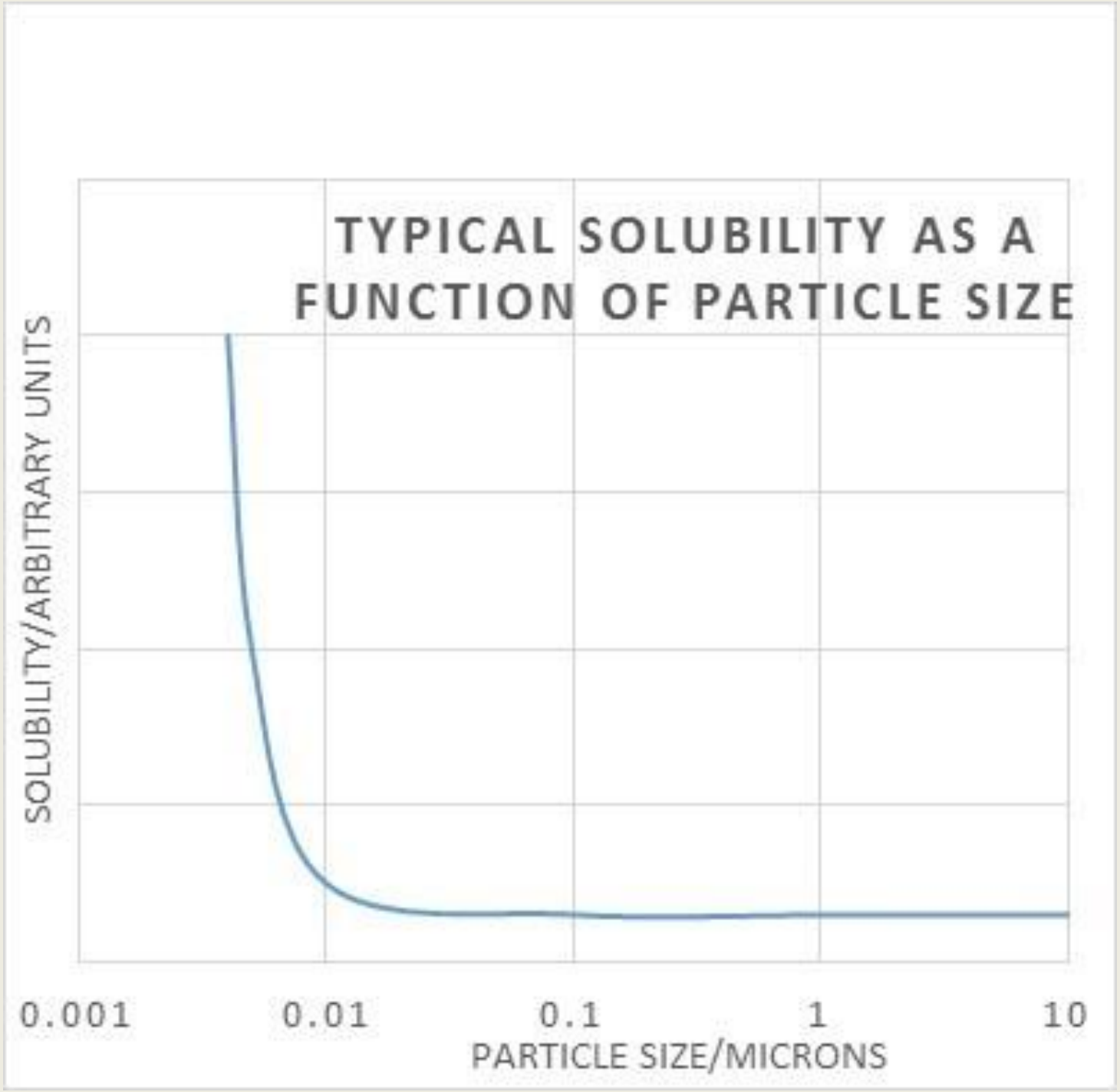
Porosity

BET gas adsorption

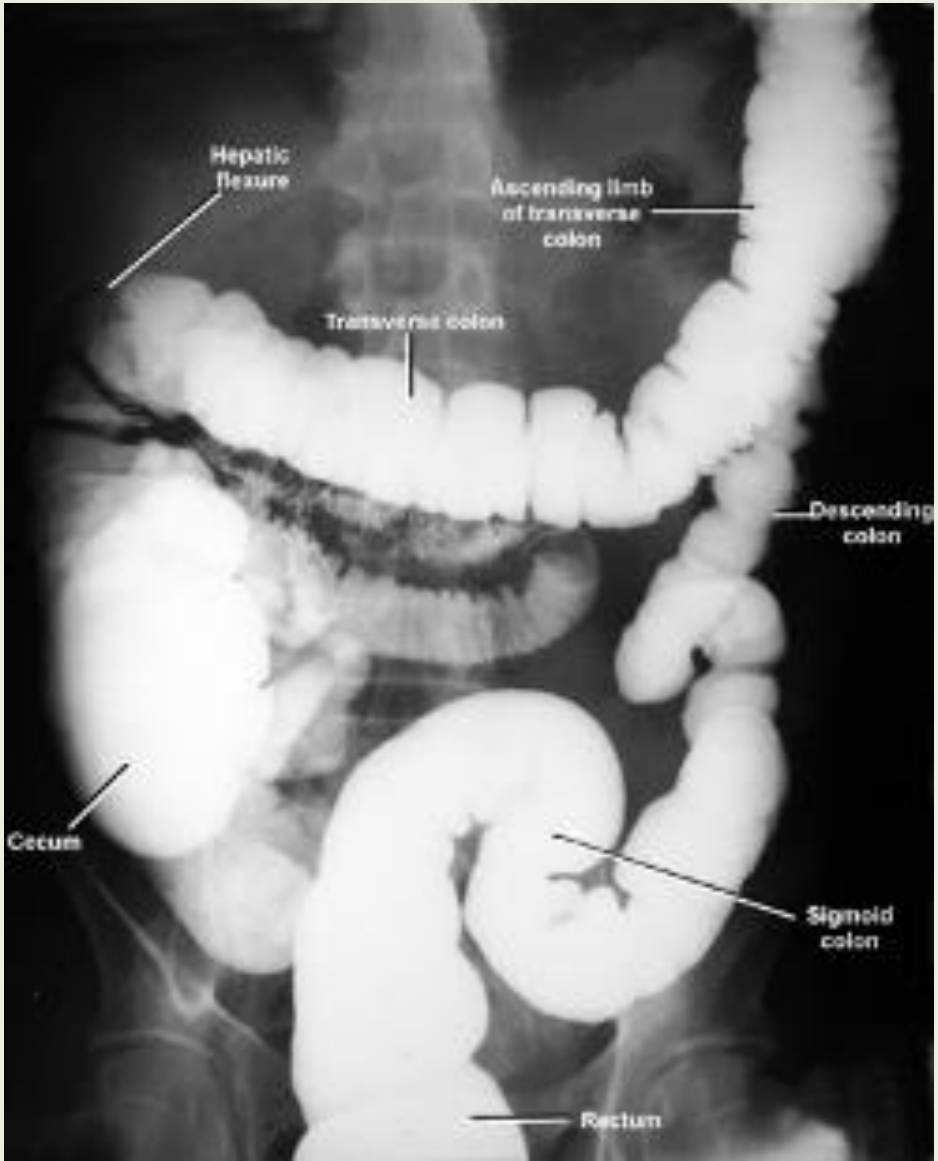


Multi-layer adsorption

Particle size


TYPICAL SOLUBILITY AS A FUNCTION OF PARTICLE SIZE
SOLUBILITY/ARBITRARY UNITS
0.001
0.01
0.1
1
10
PARTICLE SIZE/MICRONS

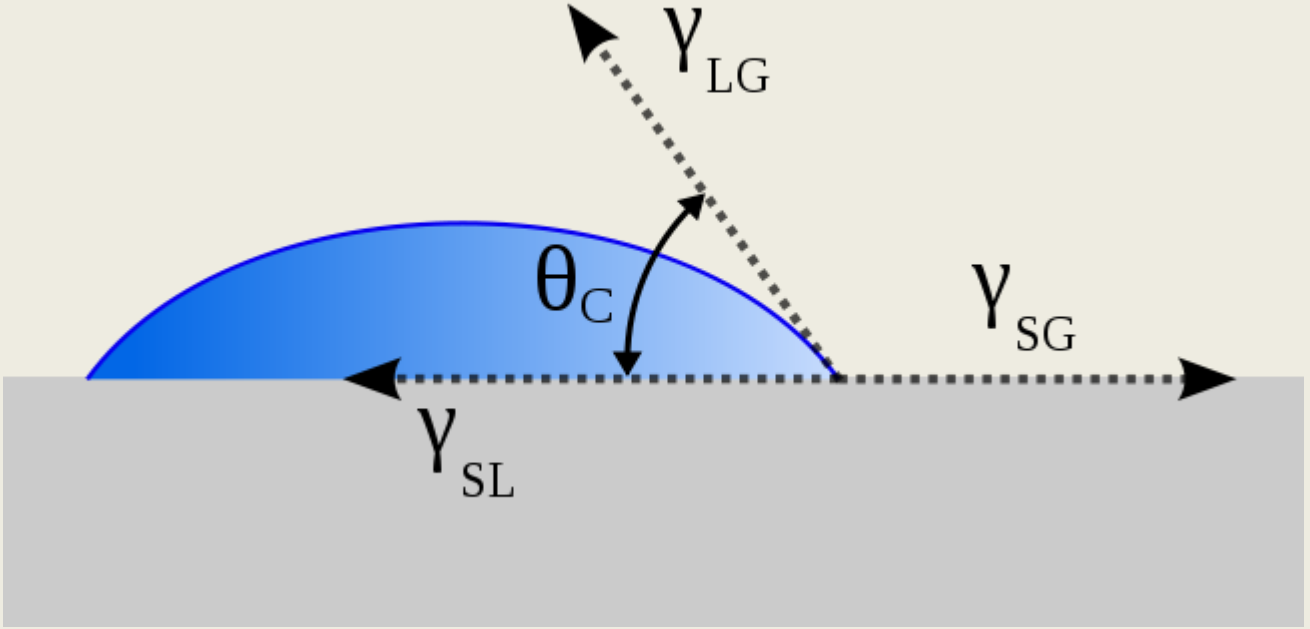
Barii sulphas



Glibenclamid

Wettability

Wettability



θ	contact angle on the solid surface
γ_{sg}	solid/gas surface tension
γ_{sl}	solid/liquid surface tension
γ_{lg}	liquid/gas surface tension

Wettability

Young – equation

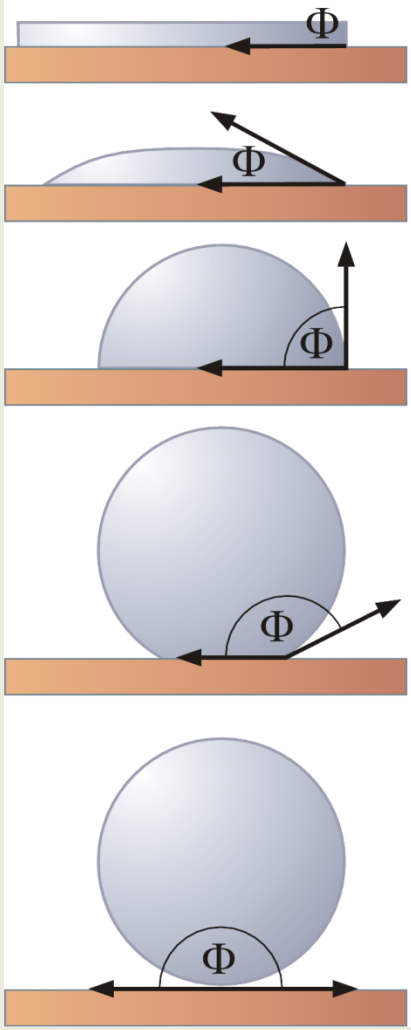
$$\gamma_{sg} = \gamma_{sl} + \gamma_{lg} \cos\Theta$$

III. *An Essay on the Cohesion of Fluids.* *By* Thomas Young, *M. D. For. Sec. R.S.*

Read December 20, 1804.

θ	contact angle on the solid surface
γ_{sg}	solid/gas surface tension
γ_{sl}	solid/liquid surface tension
γ_{lg}	liquid/gas surface tension

Wettability



contact angle	wettability
Φ = 0	perfect
Φ = 30	good
Φ = 90	medium
Φ = 150	poor
Φ = 180	no wetting

hydrophil

hydrophobe

Wettability

Darcy – equation

Porous systems

$$v = k_p \frac{\Delta p}{\eta}$$

v	permeation speed
k_p	permeability of the porous system
Δp	difference in pressure
η	liquid viscosity

Wettability

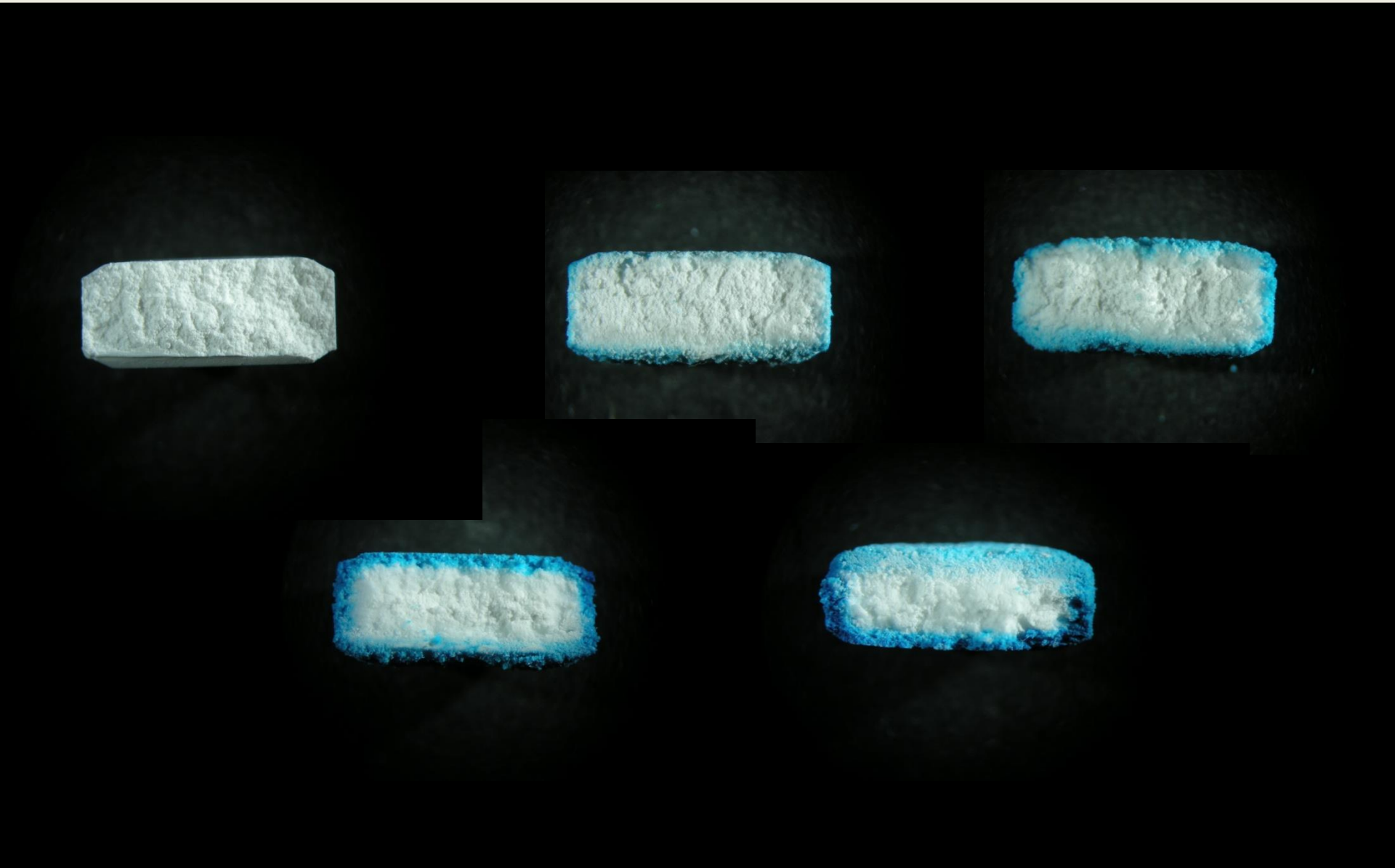
Kozeny – equation

Porous systems

$$k_p = \frac{\kappa \varepsilon^2}{\psi A^2}$$

k_p	permeability of the porous system
κ	shape parameter
ε	porosity
ψ	tortuosity (labirinth factor, convolution factor)
A	specific surface of the pores and canals

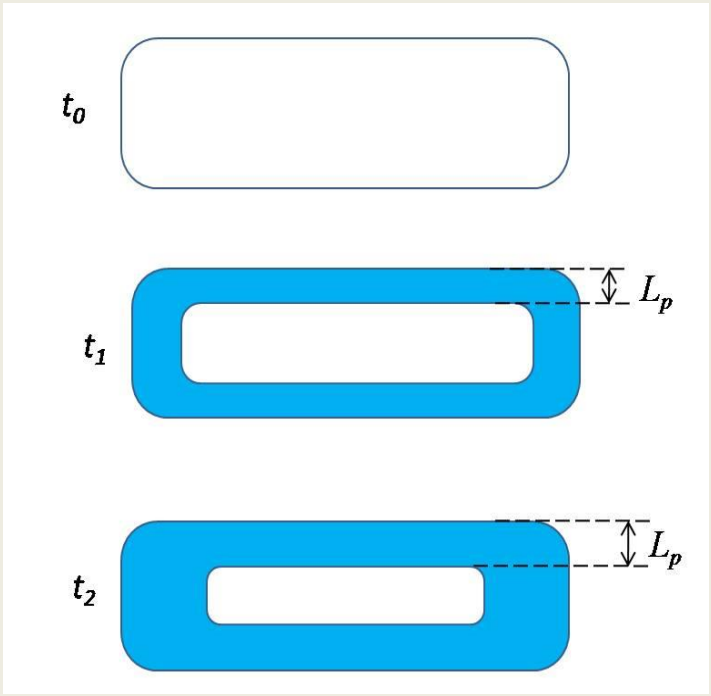
Wettability

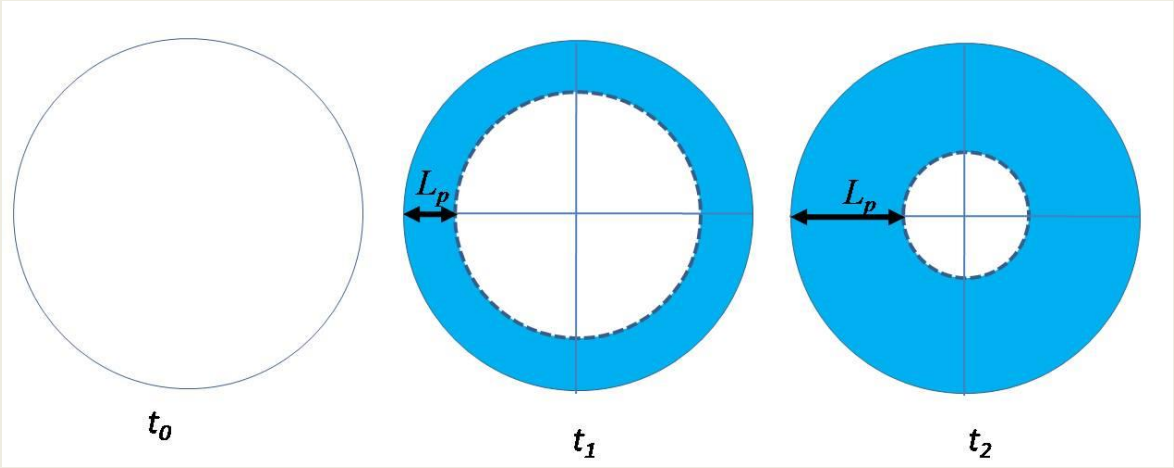


Wettability

$$\frac{dL_p}{dt} = kt$$

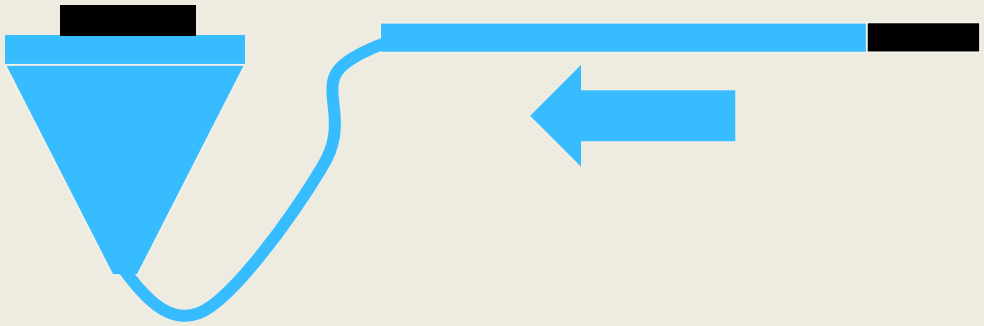
Lp wetting distance



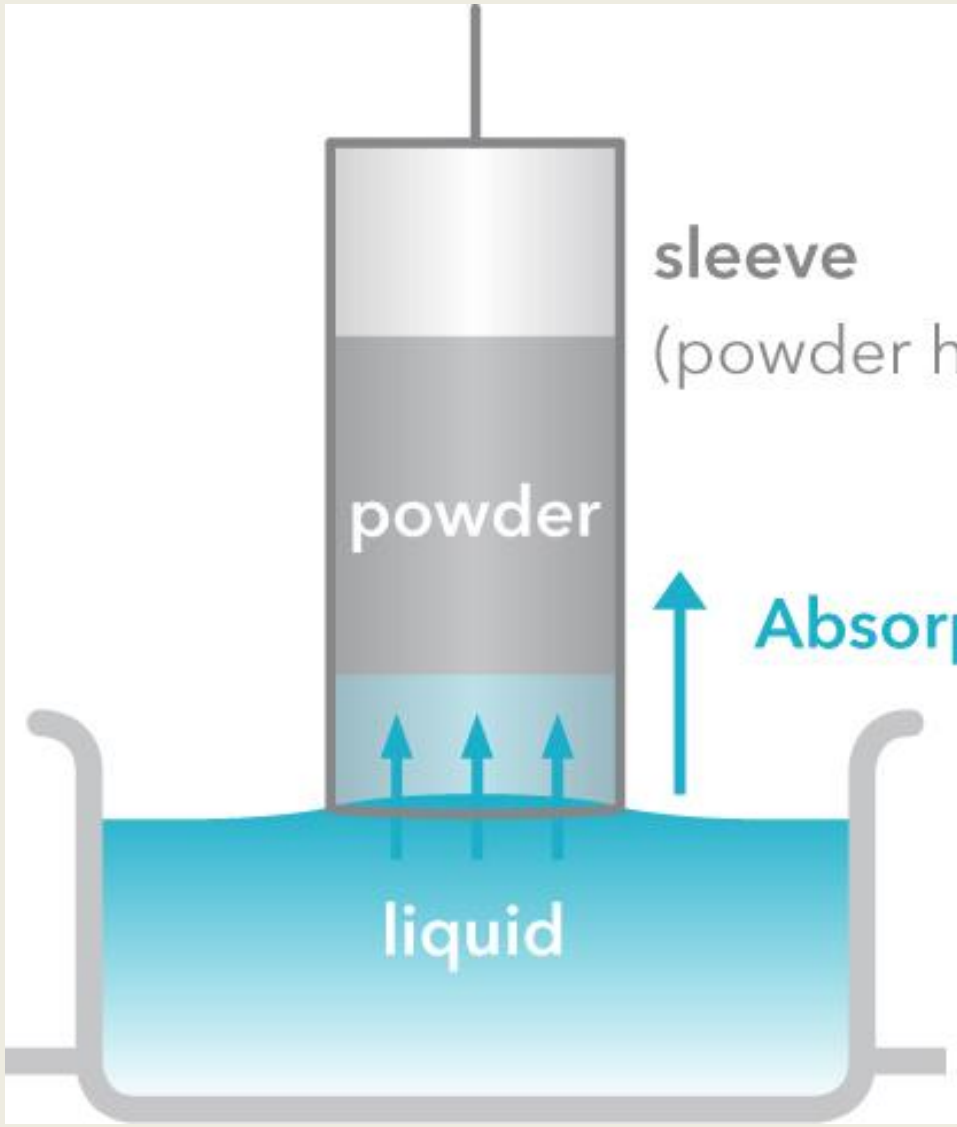


Wettability

Enslin apparatus



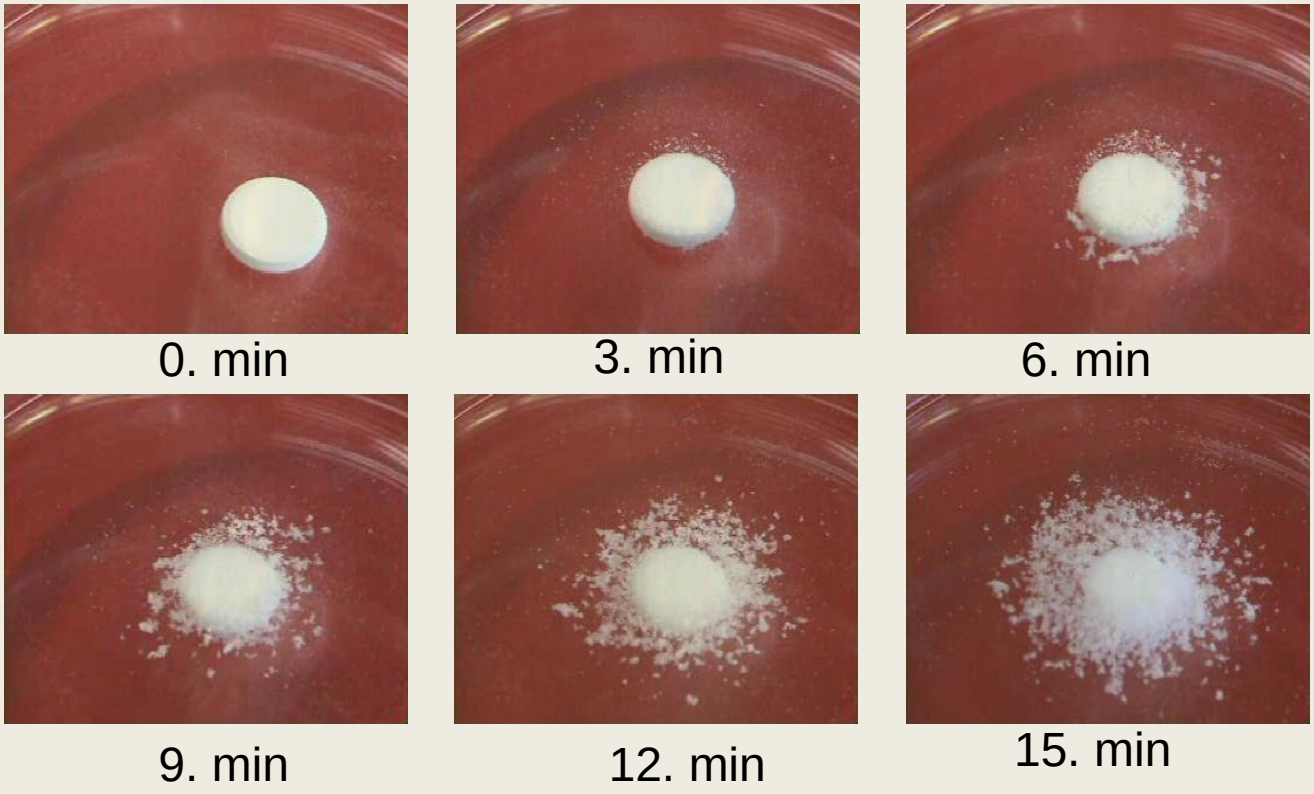
Wettability



Disintegration

Disintegration

- Disintegrating preparations



Disintegration

- Disintegrating preparations

0. min

1. min

2. min

3. min

4. min

5. min

Disintegration

- Disintegrating preparations

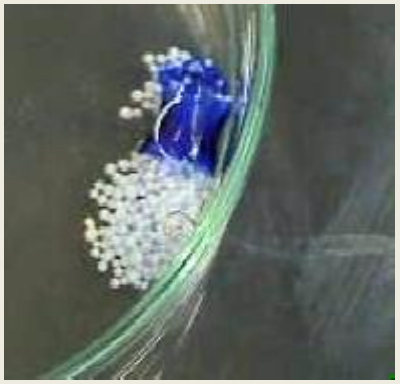

0. min


1. min


2. min

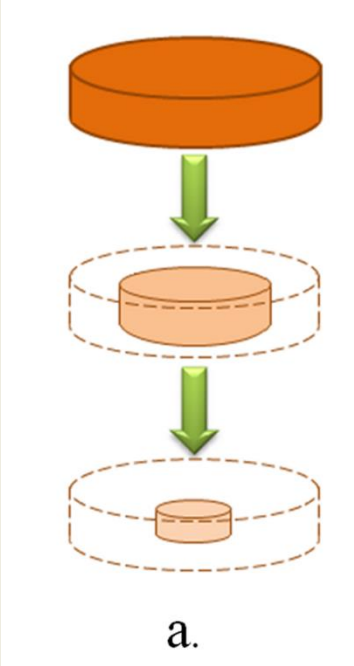

3. min

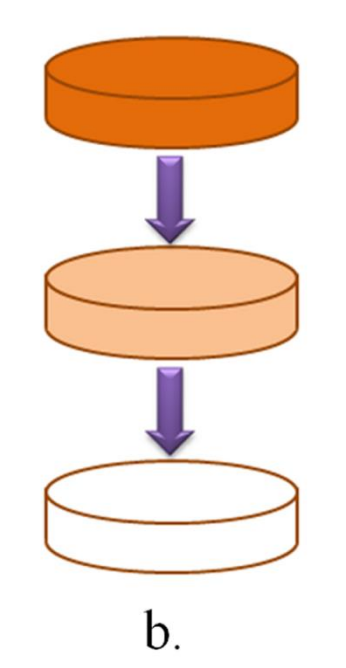

4. min


5. min

Disintegration

- Non-disintegrating preparations





Swelling

Swelling

Swelling (ξ)

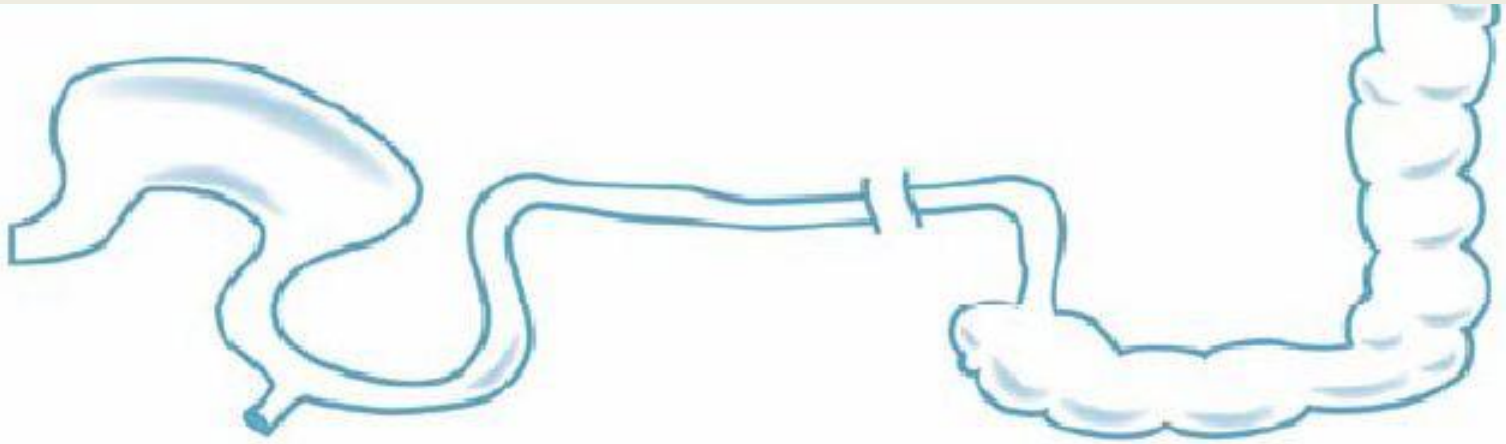
$$\zeta = \frac{V_t}{V_0}$$

V_t volume measured in ‘t’ time

V_0 initial volume

Hydrophil matrix tablets


pH



	Stomach	Jejunum	Ileum	Colon	
pH	1.4-2.1	4.4-6.6	6.8-8.6	5-8	fasting
	3-7	5.2-6.2	6.8-8.0	5-8	fed

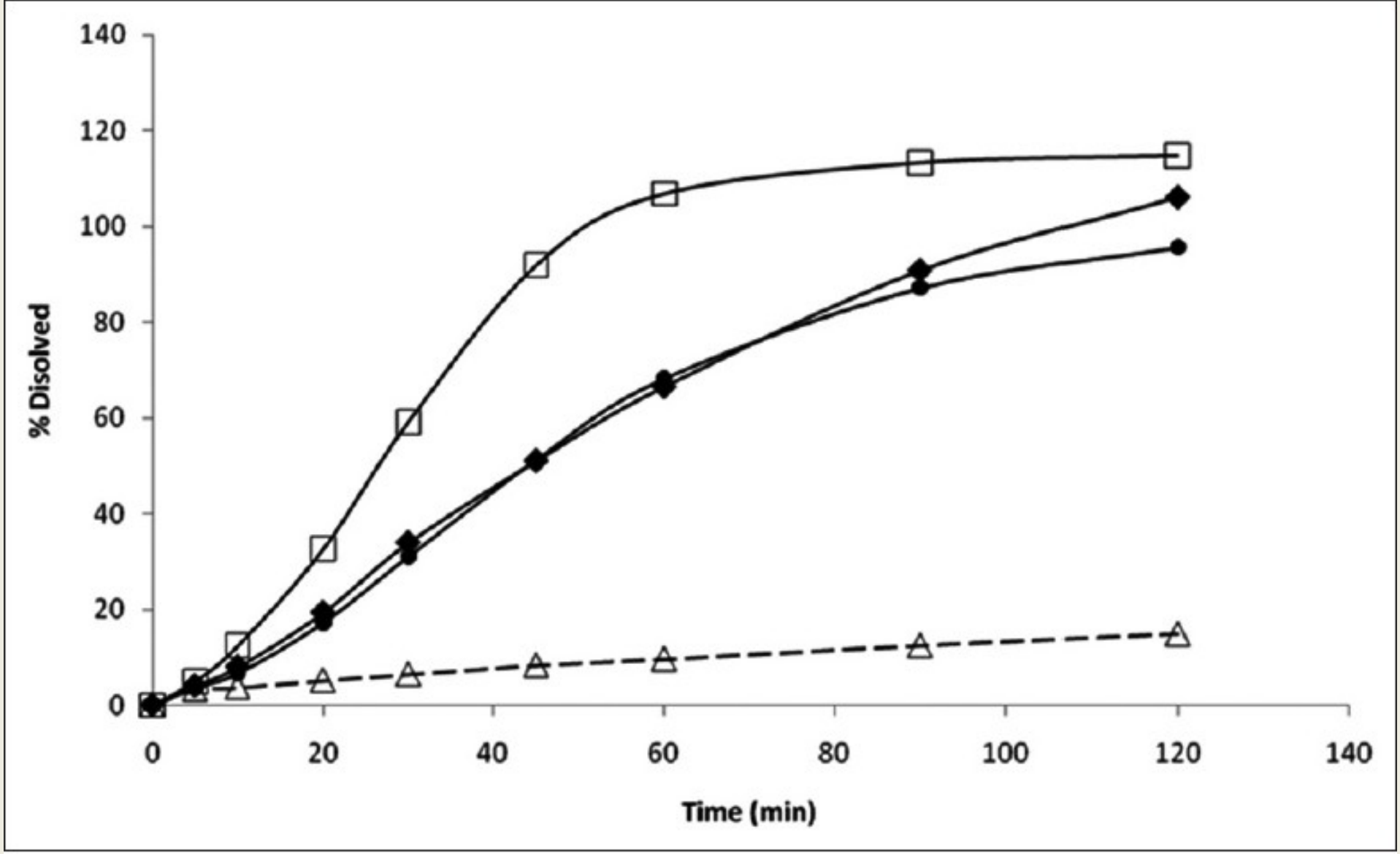


Fig. 2: Dissolution profiles of ibuprofen (IBP) suspension at 25 rpm. IBP release patterns at pH 7.2 (-□-), pH 6.8 (-◆-), pH 4.5 (-●-) and pH 1.2 (-△-)

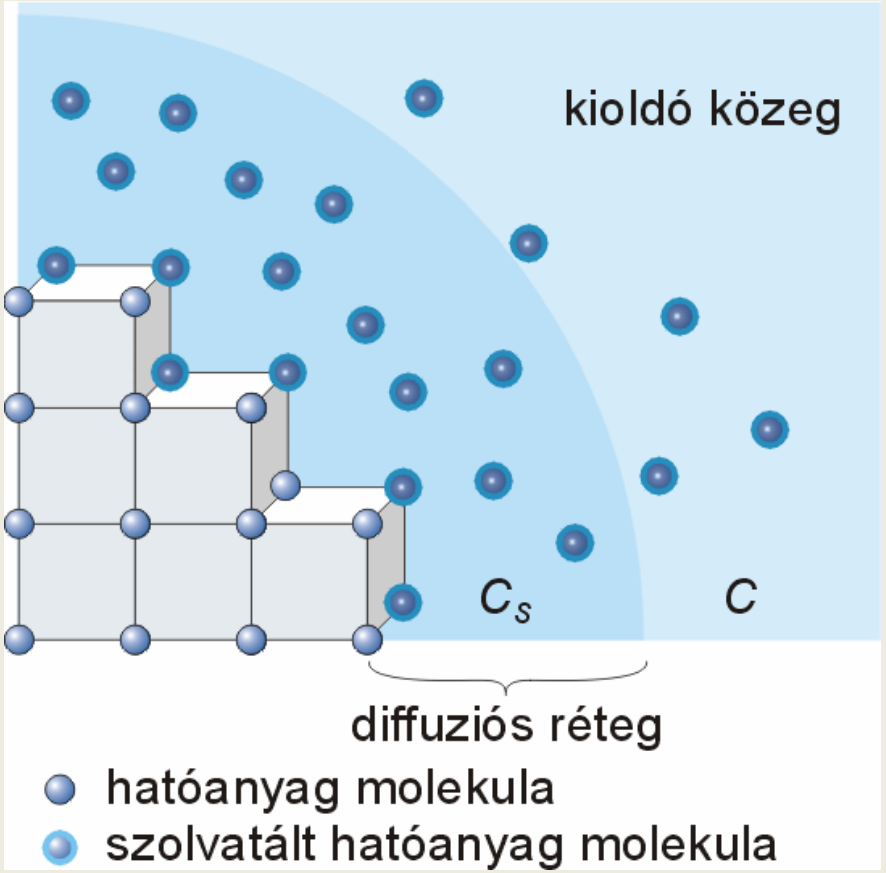
Dissolution

Dissolution

Crystal dissolution

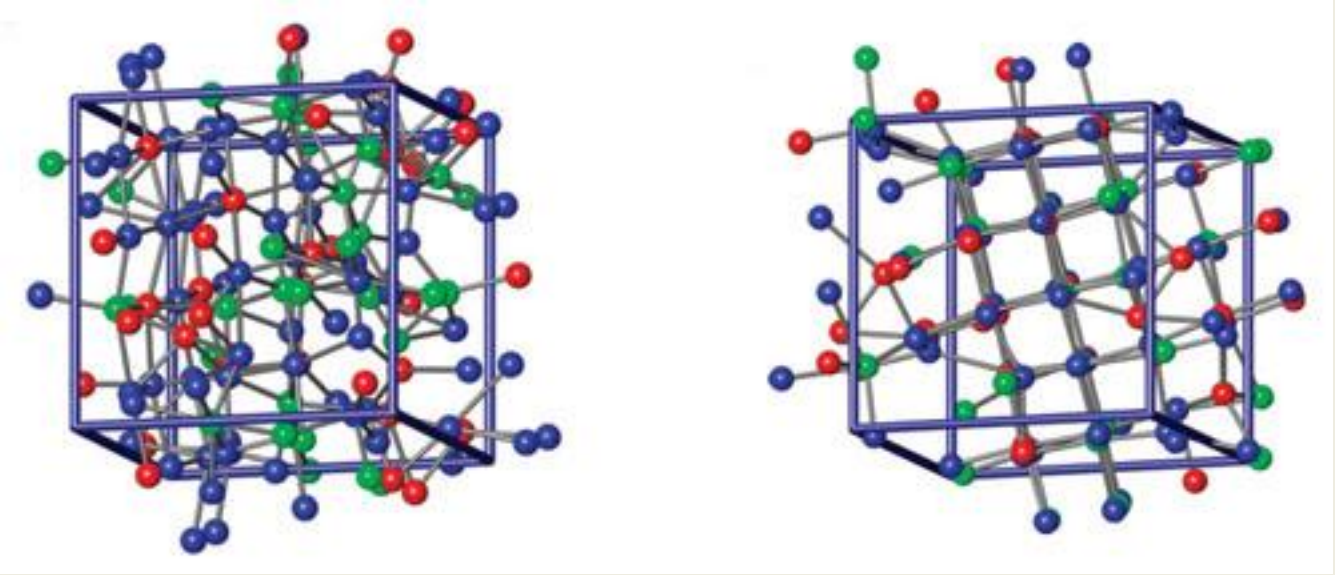
Dissolution occurs according to the concentration fradient from the outer part of the crystal to the deeper layers ($\Delta C = Cs - C$).

Finally dynamic balance develops.



Dissolution

Amorf szubsztancia oldódás



Dissolution

Solubility

- **Two types:**
  - Real or. intrinsic solubility measured in ion-exchanged water, thus its value is independent from the pH and the ionic strength
  - In different solutions with different pH (buffers) the apparent solubility is determined, which depends on the pH and the ionic strength.

Dissolution

Solubility

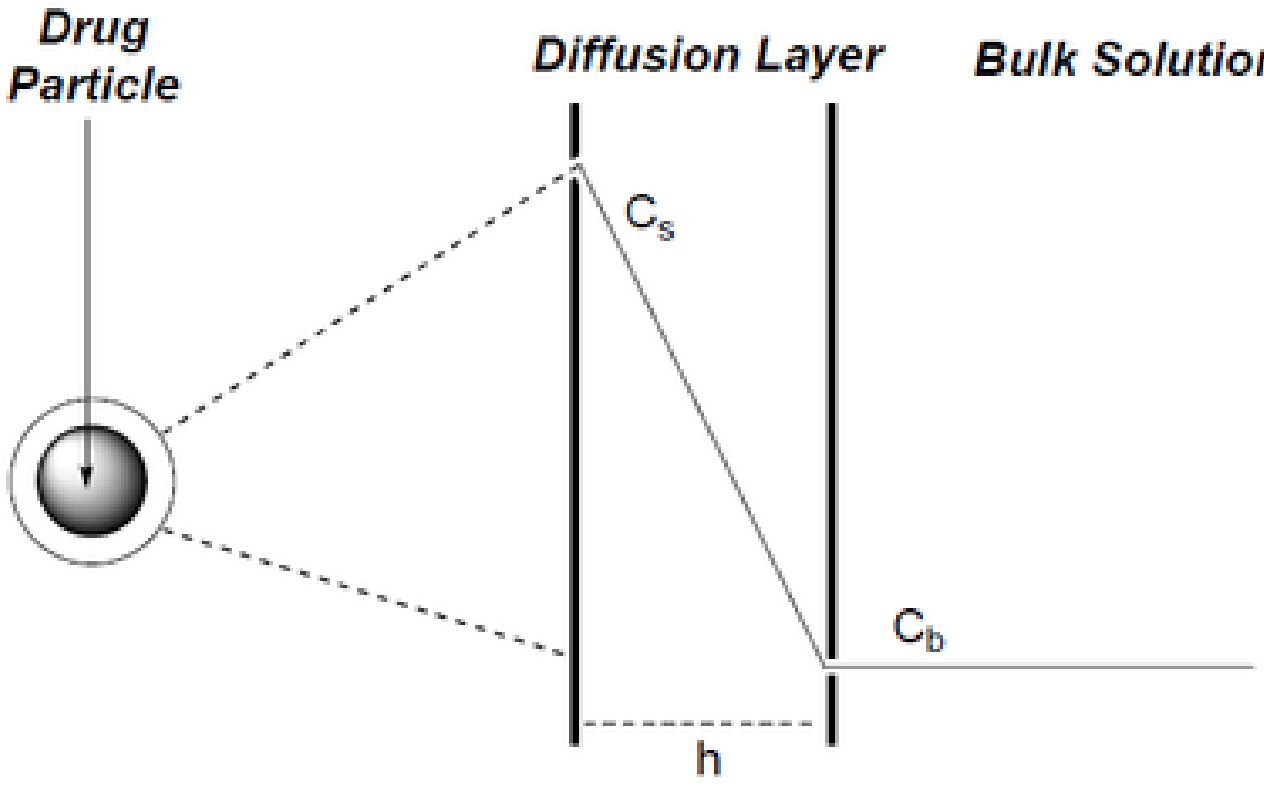
- **Solubility is determined by:**
  - **the API's**
    - **chemical character, functional groups**
    - **crystal structure**
  - **the medium's**
    - **pH,**
    - **ionic strength,**
    - **temperature,**
    - **buffer capacity**

Intrinsic Dissolution Rate (IDR)

- It is the rate of dissolution of a clean substance from a specific surface in ion exchanged water.

Dissolution

Noyes-Whitney equation



Scheme 1. Dissolution of drug particles according to diffusion layer model.

Dissolution

Brunner and Tolloczko equation

$$k = k_1 A$$

$$\frac{dm}{dt} = k_1 A(C_s - C)$$

k_1 dissolution rate constant

A area

Dissolution

Nernst and Brunner equation

$$K = \frac{DA}{V\delta}$$

$$\frac{dm}{dt} = k_2 K(c_s - c)$$

K	dissolution rate constant
A	area
D	diffusion constant,
δ	diffusion layer thickness,
V	volume of the dissolution medium
k_2	real dissolution rate constant for the API

Thank you for your attention!