Pharmaceutical Technology 3.

- **Dr. Széchenyi Aleksandar**
- **Dr. Nagy Sándor**
- **Ámanné Dr. Takácsi-Nagy Anna**
- **Dr. Pál Szilárd**

Important notes

Conditions for acceptance of the semester

- Students must fulfil requirements determined by the Code of Studies and Examinations
- Attendance of the lectures according to the Code of Studies and Examinations
  - 3 absences are allowed
  - In case of 4 or more absences the course is rejected!

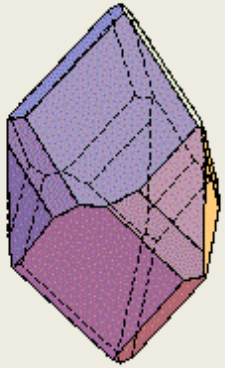
Important notes

- During the semester students have to write three tests and they have to reach 60% after average calculation.
- After two test if students reach average 60% taking into account both tests, writing the third test is not compulsory.
- Summarized average of all three tests has to be above 60%. In case of confirmed absence from the test, re-take chance is possible for the student.
- Missing the re-take assesment means 0%.

Important notes

- 1. test: October 1.
- 2. test: November 5.
- 3. test: December 3.

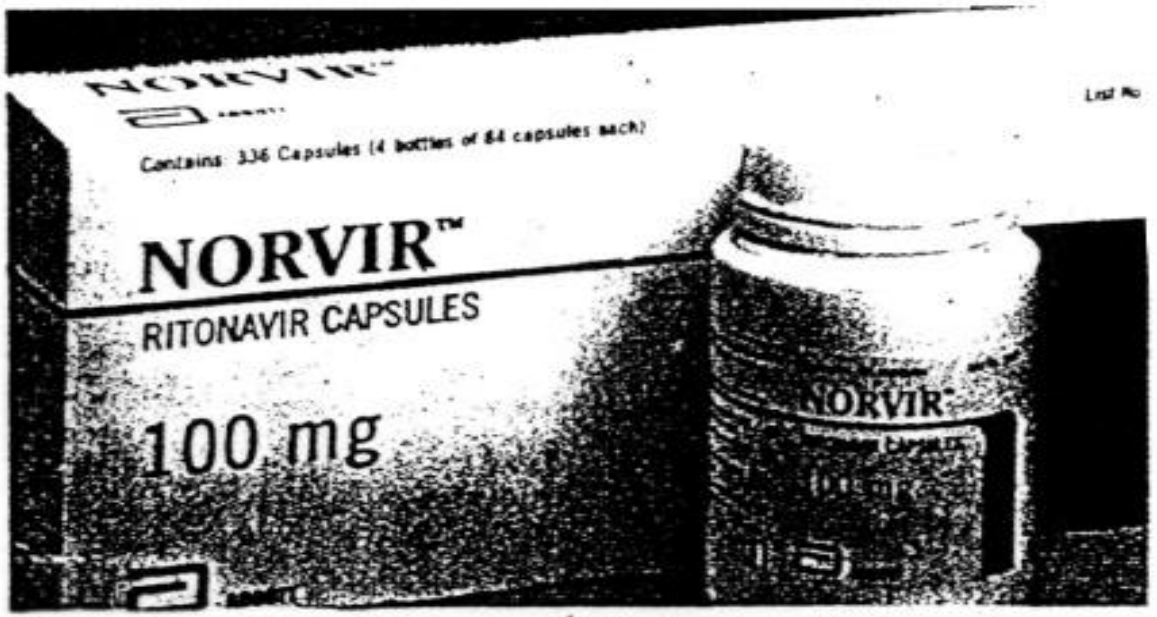
Crystallization



Institute of Pharmaceutical Technology and Biopharmacy

Manufacturing problems hit Abbott's HIV drug ritonavir

Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

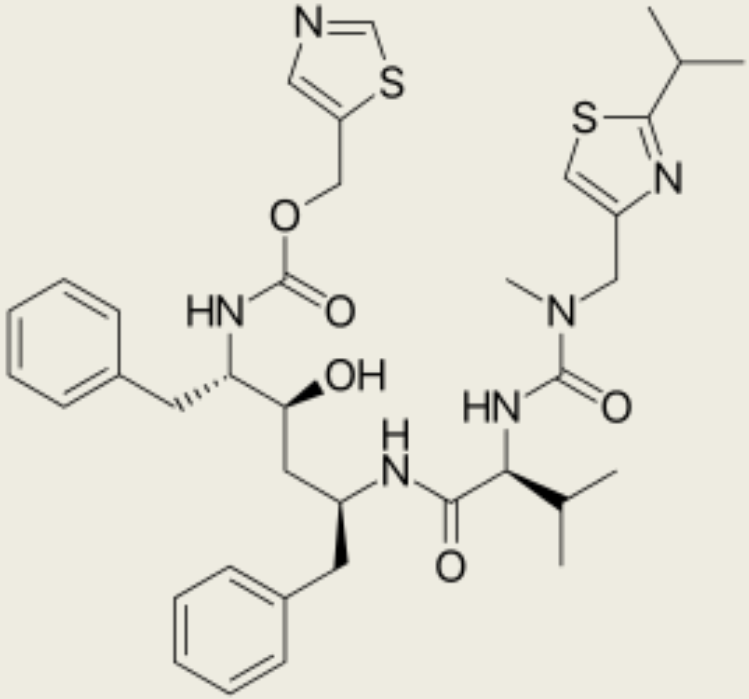


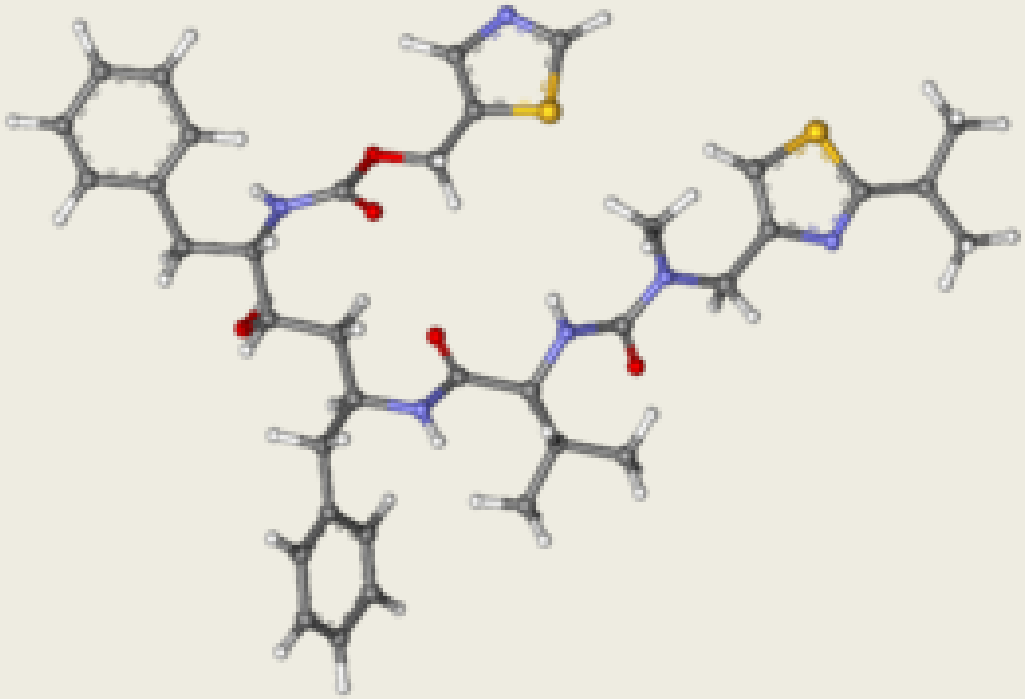
Capsules unlikely to be available from mid-August

The problem relates to "undesirable" crystal formation. Abbott says that a series of recent production batches of Norvir capsules failed the approved test for dissolution, and were not released for marketing. Investigation of the reason for the failure showed the presence of a new crystalline form of ritonavir which affects the way it dissolves, and possibly its absorption. Retained samples from a number of marketed batches of capsules were examined and there was no evidence of the unwanted crystalline form.

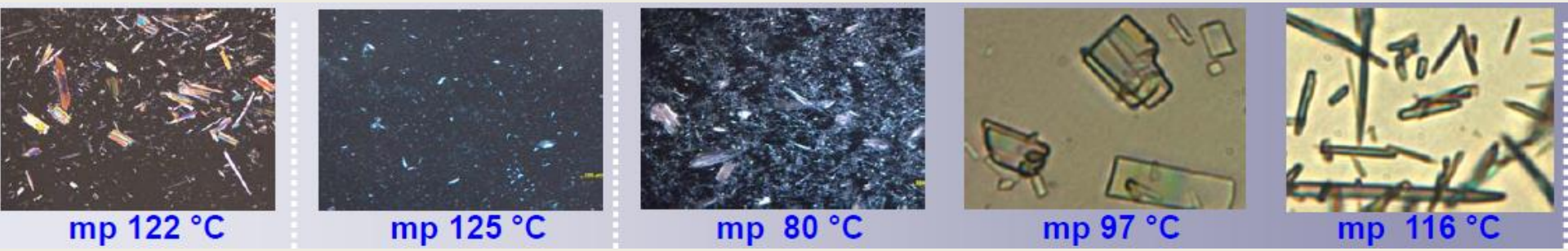
Mr Mark Haywood (managing director, Abbott Laboratories) said that teams were working round the clock to try to resolve the issue, but at present the company had no idea why the problem was occurring.

RITANOVIR





Form	Melting point, °C	ΔH_{fus}, J/g	Solid-state structure
I*	122	78.2	Monoclinic
II*	122	87.8	Orthorhombic
III	78–82	60.3	Monoclinic†
IV	116	59.8	Not assigned
V	97	32.0	Monoclinic†



Source: http://www.pnas.org/content/100/5/2180.long

Importance of crytals for pharmaceutical use

Solution **– the solubility can be changed what can lead to precipitation or to recrystallization**

Suspension **– the recrystallization and crystal growth can result in the change of particle size distribution.**

Ointment **– the recrystallization and crystal growth can result in the change of particle size distribution. The different size affects on the bioavailability too.**

Suppository **- the external phase may have recrystallization too. This process can effect to the melting point, (hardness –softness) consistency of the suppository and so to the drug-dissolution profile.**

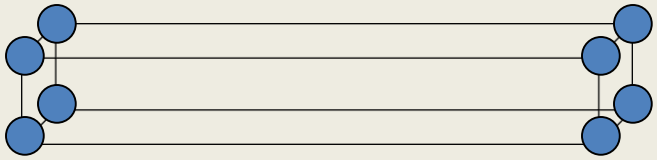
Microcapsules **- The isometric crystals are capable to form this type of drug delivery system.**

Tablet **- Not only the size of the crystals, but the form of the crystals also influences the future behavior of the dosage form.**

Crystals

Crystals

Crystals are solid particles in which the constituent molecules, atoms, or ions are arranged in some fixed and rigid, repeating three-dimensional pattern or lattice



The non-structured, semi-stable solid structures are called **amorphous materials**.

The crystals have (space) lattice structure, They are solid materials, that typical properties are: anisotropic, homogeneous, discontinuum.

Crystals

The three basic properties of the crystals:

1. The parallel directions are equals with each other. In these directions the properties of the lattice is homogeneous in each physical and chemical behavior.

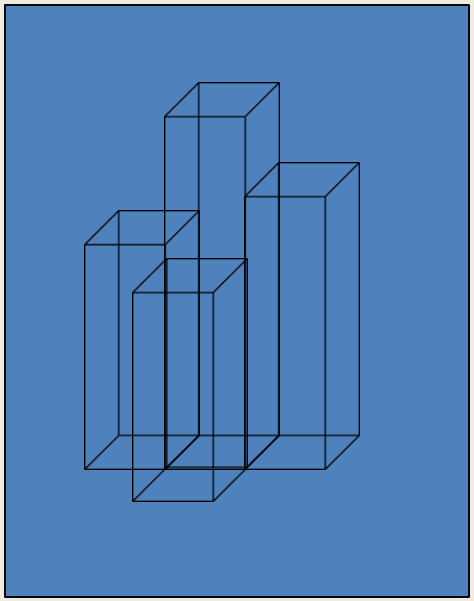
2. The physical and chemical behaviors of the lattice in each non-parallel direction are different. The anisotropic behavior is a direction-dependent property.

3. The building blocks of the lattice are located in periodic order, this means the discontinuous property of the crystal. (the material is not a continuous in the space)

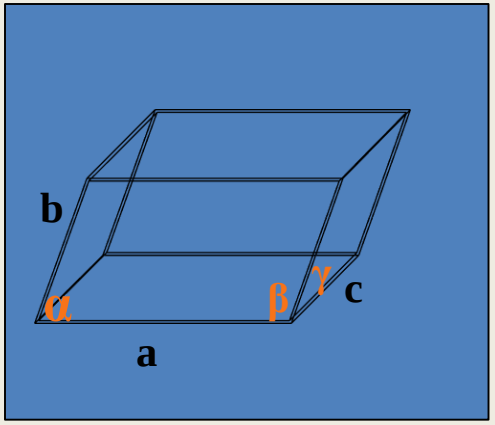
Classification of crystals

Classification of crystals

<u>Habit</u> of the crystals
(microscopic examination)

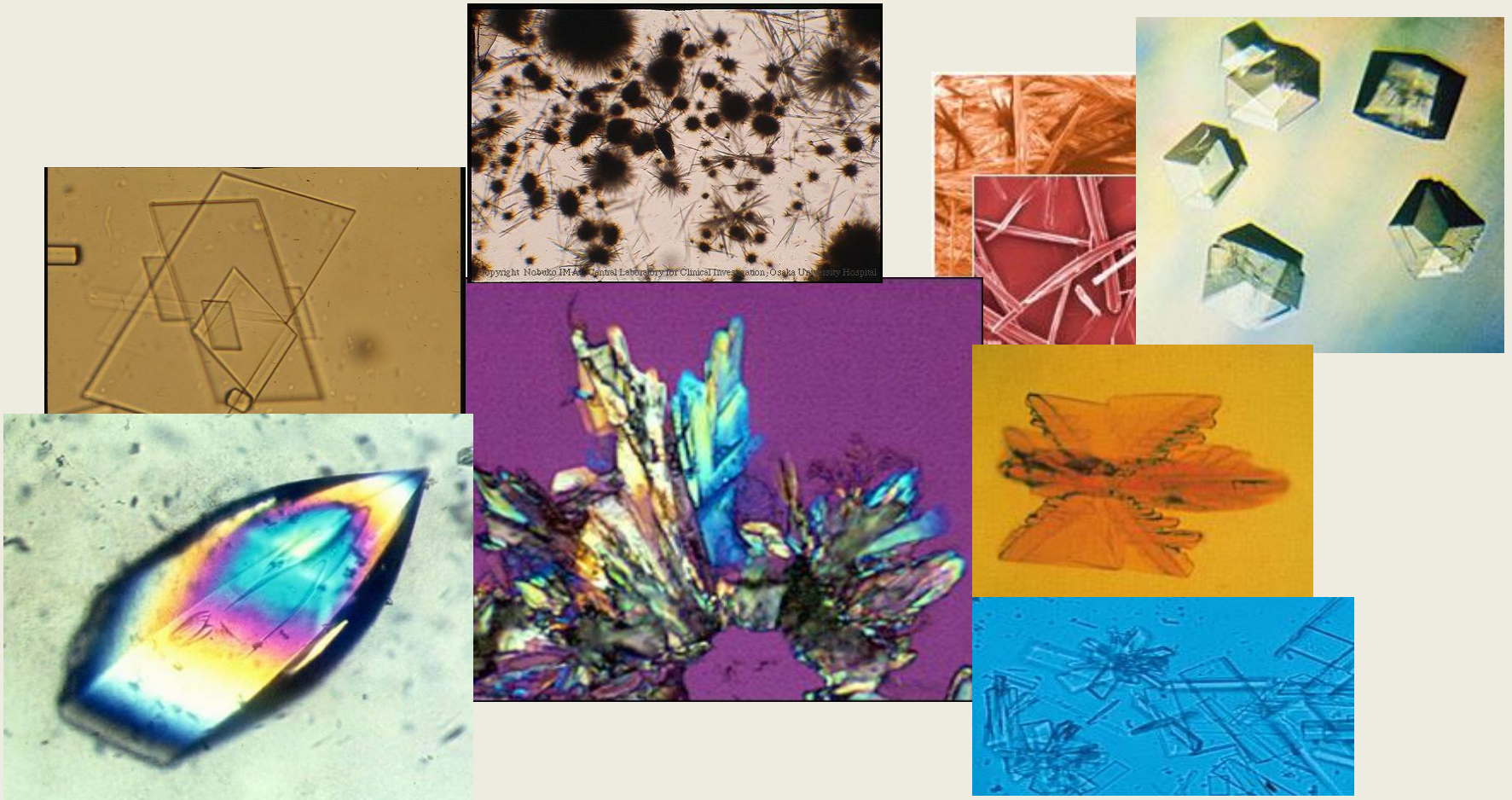


<u>Structure</u> of the crystals
(X-ray diffraction)



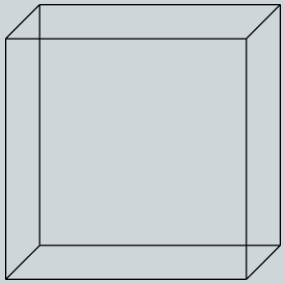
Classification of crystals

➔ **based on their habits**



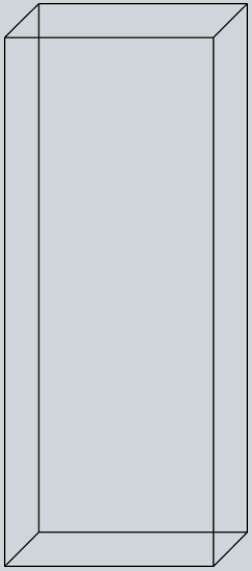
Classification of crystals

➔ **based on their habits**

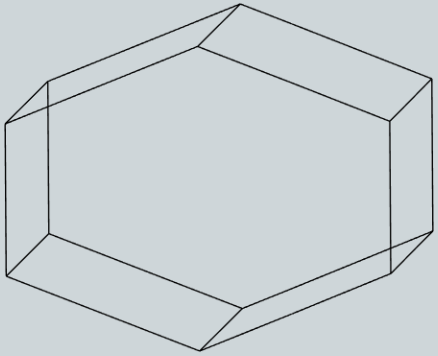


isometric

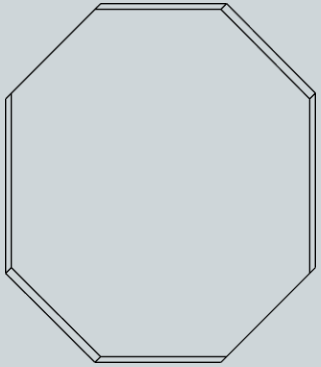
pin



column



table

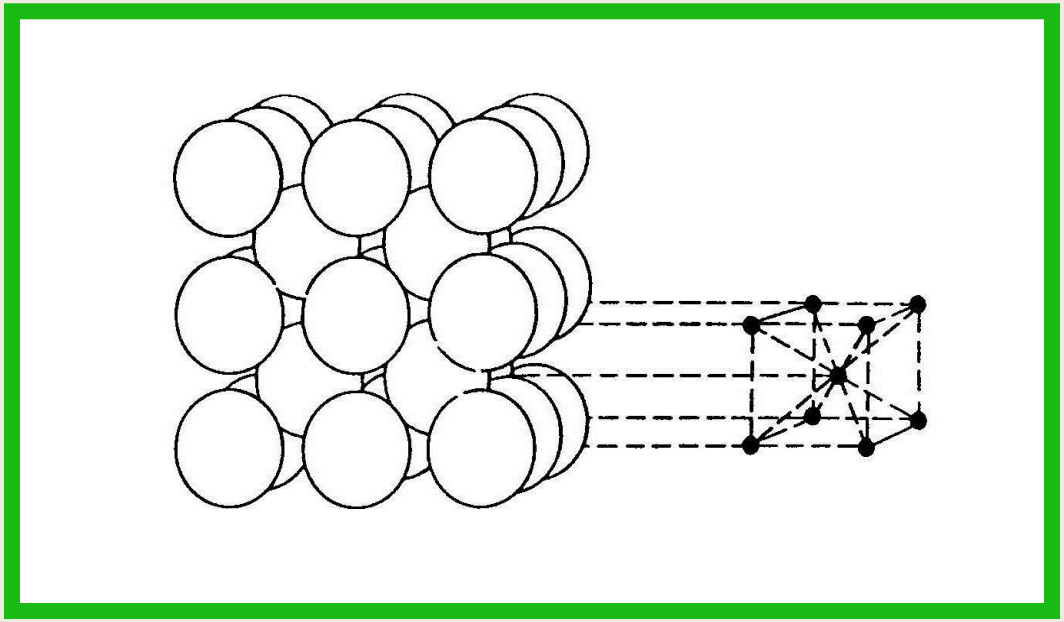


plate

Classification of crystals

➔ **based on their structure**

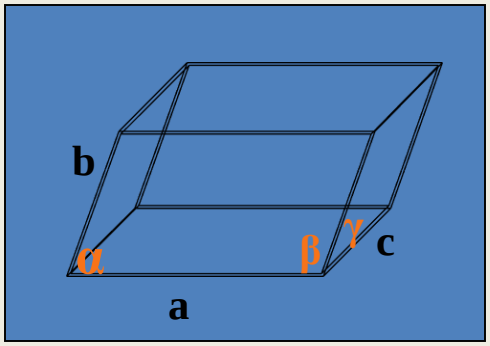
The term of unit cell is originated by *Bravais*. The unit cell is the smallest part of the lattice that can characterize the whole space lattice because the whole space lattice can be built up from it with the shifting of the unit cell into each direction (in 3D).

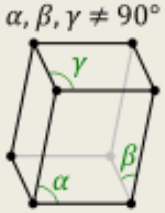


Classification of crystals

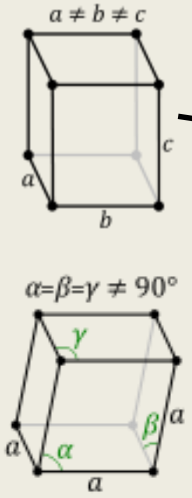
➔ based on their structure

➔ The 7 lattice system





triclinic	**a ≠ b ≠ c**	**α ≠ β ≠ γ ≠ 90° ≠ 120°**
monoclinic	**a ≠ b ≠ c**	**α = γ = 90°, β ≠ 90°**
orthothrombic	**a ≠ b ≠ c**	**α = β = γ= 90°**
tetragonal	**a = b ≠ c**	**α = β = γ= 90°**
rhombohedral	**a = b = c**	**α = β = γ ≠ 90°**
hexagonal	**a = b ≠ c**	**α = β = 90°, γ= 120°**
cubic	**a = b = c**	**α = β = γ= 90°**



Classification of crystals

➔ **based on their structure**

➔ **Euler-law**

$$s + p = e + 2$$

s	side(s) of the crystal
p	peak(s)
e	edge(s)

Crystallization

A process whereby solid crystals are formed from another phase, typically a liquid solution or melt.

Crystallization

Why is Crystallization Important?

Crystallization touches every aspect of our lives from the foods we eat and the medicines we take, to the fuels we use to power our communities. The majority of agrochemical and pharmaceutical products go through many crystallization steps during their development and manufacture. Key food ingredients, such as lactose and lysine, are manufactured using crystallization and the unwanted crystallization of gas hydrates in deep sea pipelines is a major safety concern for the petrochemical industry.

Crystallization

What can be the purposes of the crystallization process?

1. **Production of crystals with proper form, habit, particle size and crystal water content.**

The reproducable parameters of the crystallization is the basis of manufacture of proper medications.

2. **Purification and separation**

Crystallization

What kind of options are?

Crystallization can be made by:

a.) gas phase (desublimation)

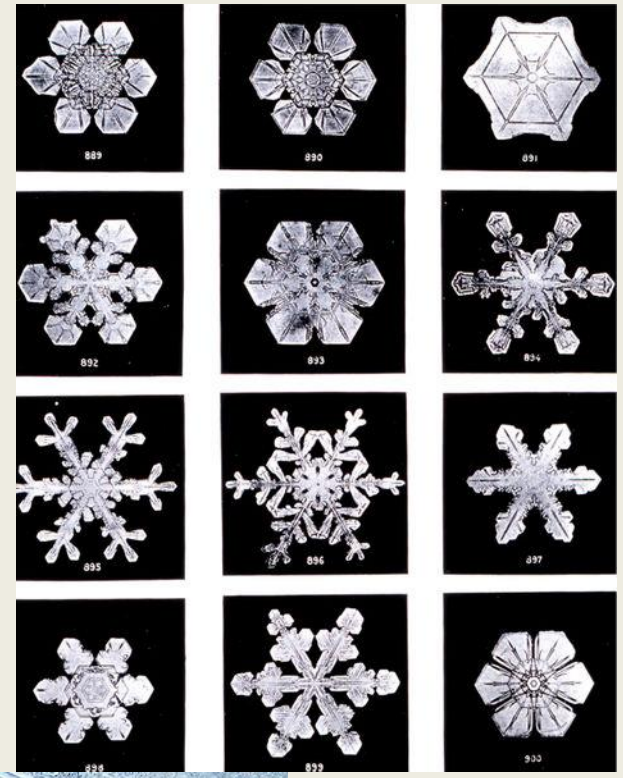
b.) liquid phase

b.1.) melt-crystallization (mono-component systems**)**

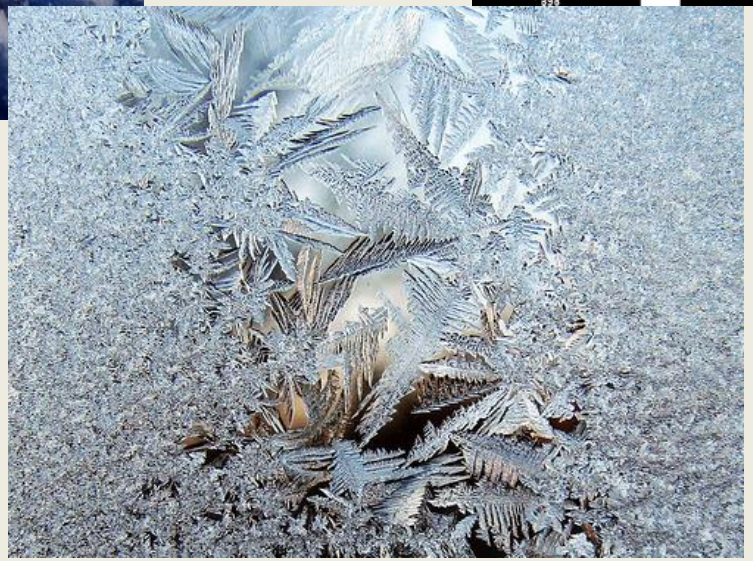
b.2.) solution-crystallization (multi-component systems**)**

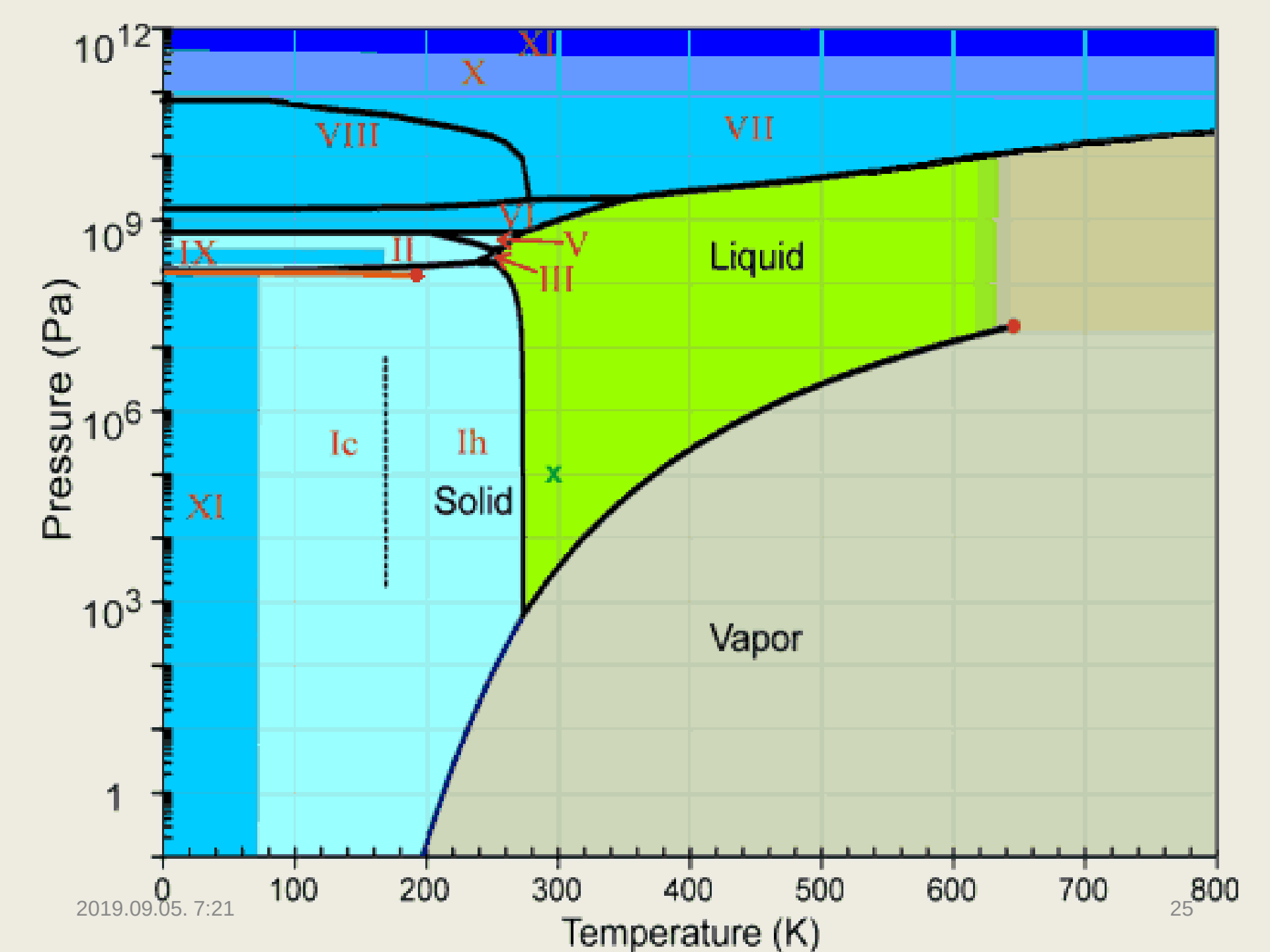
Crystallization

➔ melt-crystallization



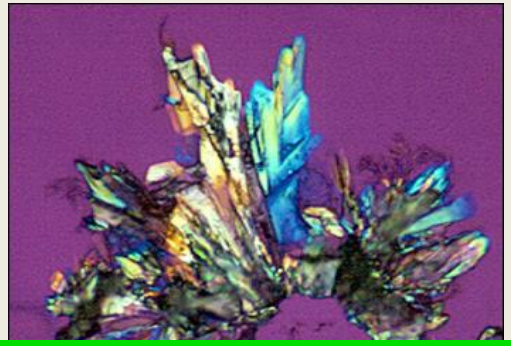
Ice and snowflakes



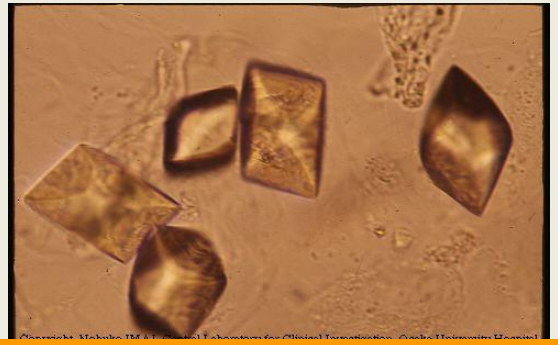

10^{12}
10^{9}
10^{6}
10^{3}
1
Pressure (Pa)
XI
X
VIII
VII
VI
V
III
IX
II
Liquid
Ic
Ih
Solid
XI
x
Vapor
0
100
200
300
400
500
600
700
800
Temperature (K)

Crystallization

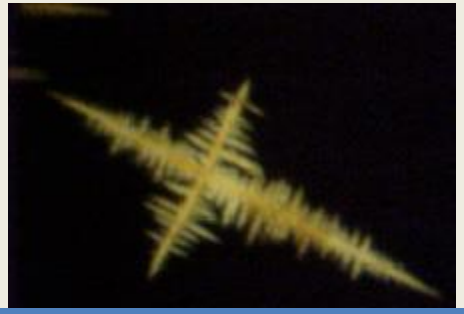
➔ melt-crystallization



anti-AIDS drug zidovudine



Sulfamethoxazole
Thymidilate-syntase inhibitor

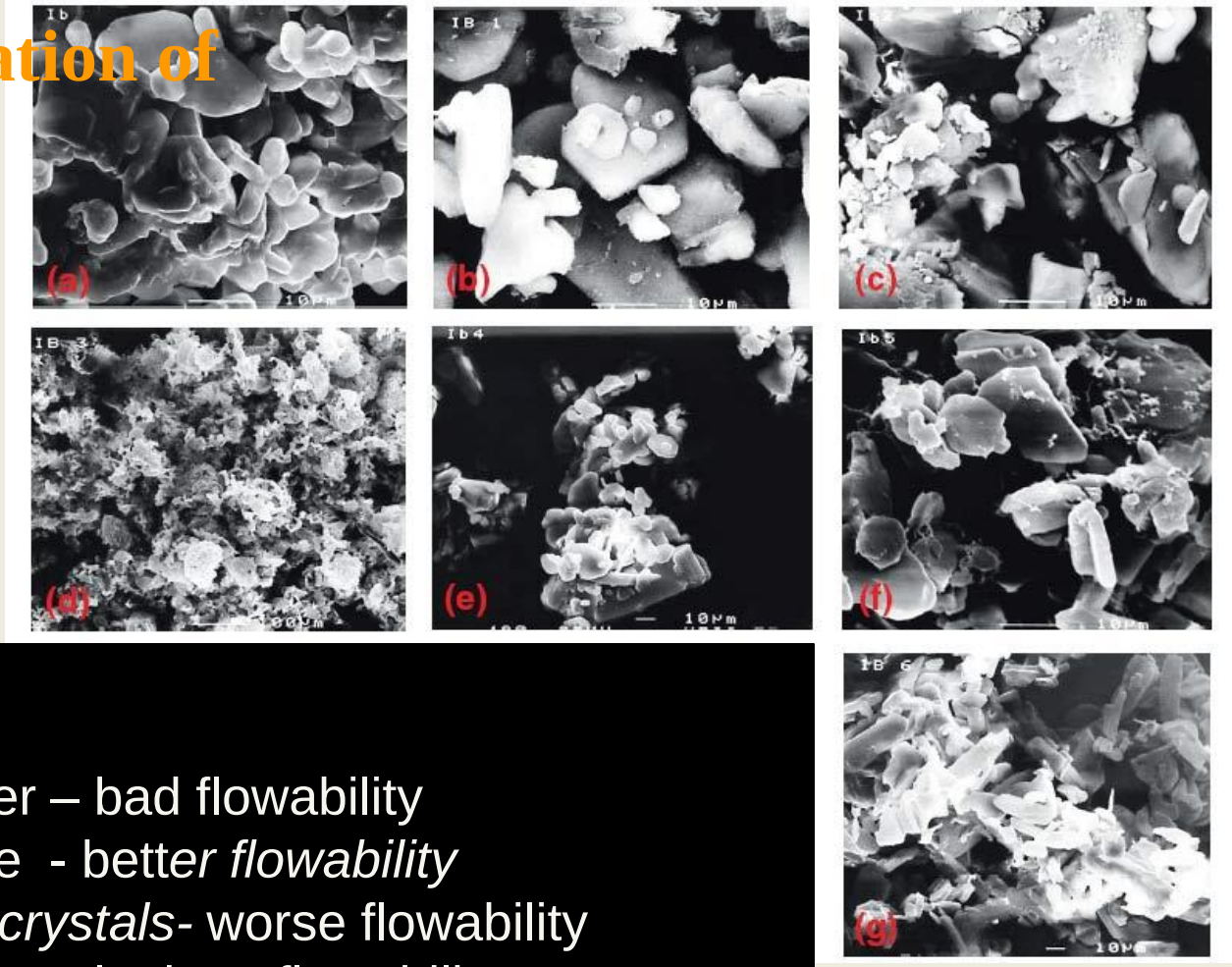


inzulin

Crystallization

➔ **Recrystallization of**

Ibuprofen



a.) initial powder – bad flowability
b.) agglomerate - bett*er flowability*
c.) flat and big crystals- worse flowability
d.) spherical crystals- best flowability

Crystallization

Recrystallization – technical parameter

Table I: Density, flow, and compressibility of raw and treated ibuprofen.

Sample	Fluff density (g/cm^3)	Tap density (g/cm^3)	Angle of reprose θ (°)	Flow rate (g/s)	Carr's index (%)	Hausner ratio	Cohesion flow index (gmm/g)
Ib	0.294	0.526	54.3	0.192	44.1	1.79	−104
Ib1	0.417	0.571	38.9	7.33	27.0	1.37	−43
Ib2	0.526	0.678	40.1	4.51	22.4	1.29	−34
Ib3	0.378	0.455	36.3	5.71	17.1	1.2	−14
Ib4	0.385	0.40	37.0	4.0	3.8	1.04	−23
Ib5	0.286	0.408	40.0	6.6	30.0	1.43	−43
Ib6	0.385	0.40	36.0	5.67	3.8	1.04	−18

The Carr index

Carr's Compressibility Index is an indication of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr.

The Carr index is calculated by the formula:

$$C = 100\frac{V_T - V_B}{V_T}$$

V_B is the volume that a given mass of powder would occupy if let settled freely, and V_T is the volume of the same mass of powder would occupy after "tapping down"

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner

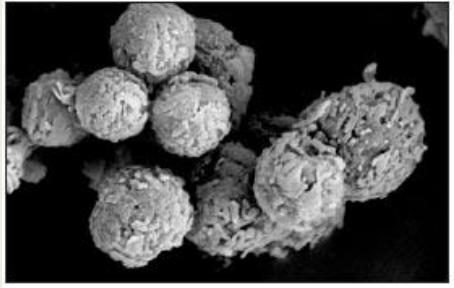
The Hausner ratio is calculated by the formula:

$$H = \frac{\rho_T}{\rho_B}$$

Where ρ_B is the freely settled bulk density of the powder, and ρ_T is the tapped bulk density of the powder.

The Hausner ratio is not an absolute property of a material; its value can vary depending on the methodology used to determine it.

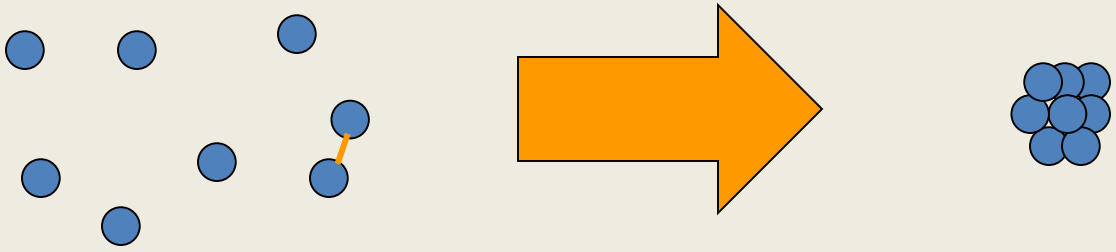
Crystallization



Spherical crystals

Spherical agglomeration (SA)

Small crytal particles are obtained by precipitation. The saturated solution of the API is poured into a solvent mixture what is a weak solvent of the API.
The cohesion have to be more higher between the two solvent than the cohesion developed between the solvent and the API. This can ensure the proper wettability of the formed new crystals. (bridge liquid, BL)



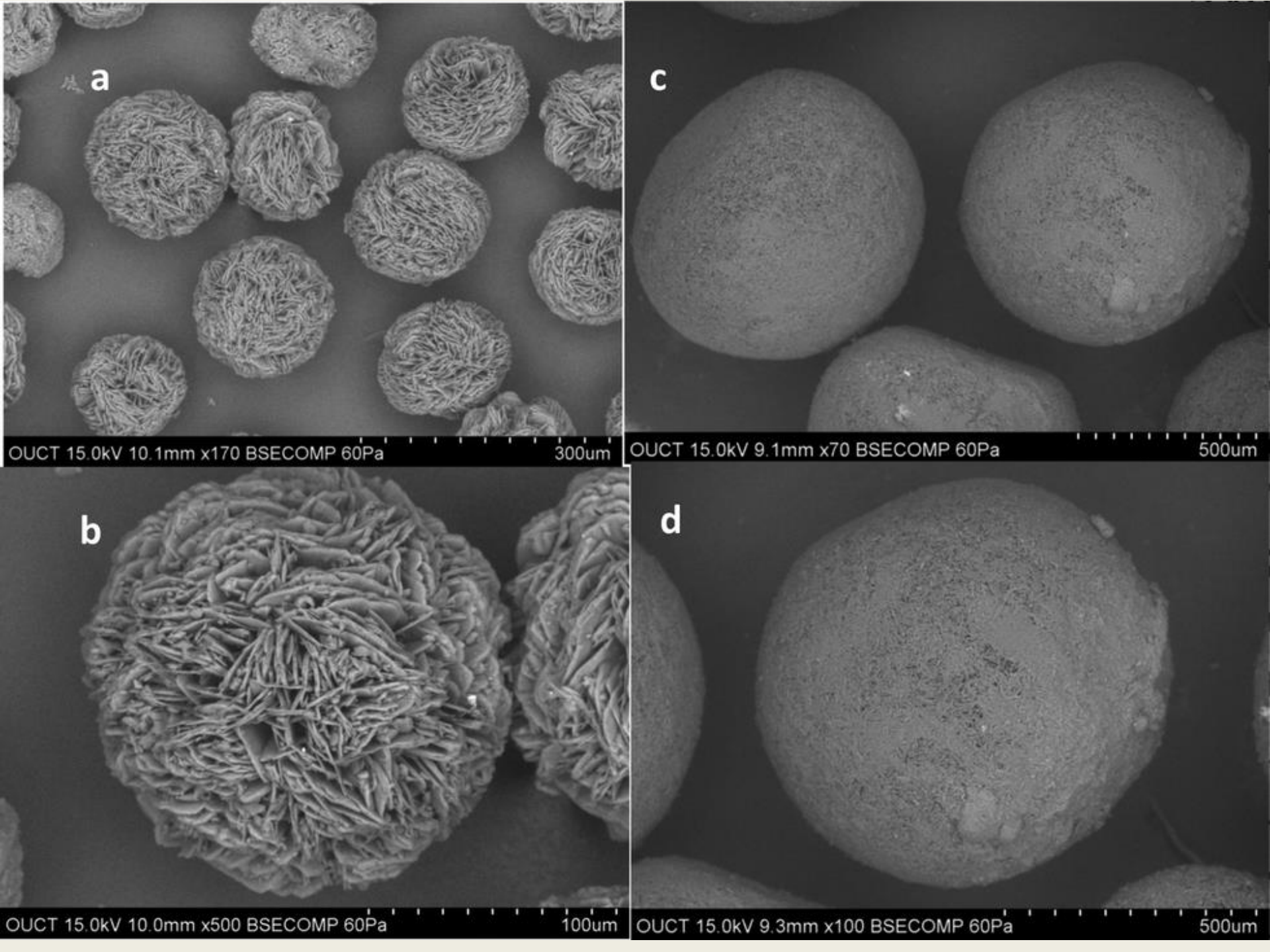
Crystallization

Spherical crystals

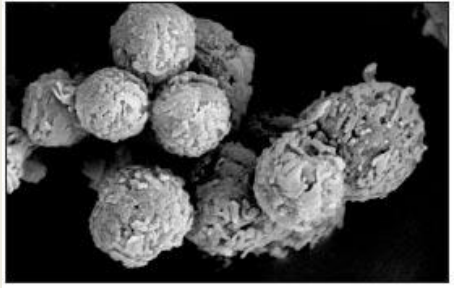
Spherical agglomeration (SA)

Drug	Method	Solvent used
Roxythromycin	SA	Methanol, chloroform, water
Aminophylline	SA	Ethanol, chloroform, water
Naproxen	SA	Acetone ethanol, chloroform, water
Aspirin	SA	Acid buffer, methanol, chloroform
Salicylic acid	SA	Water, ethanol, chloroform
Aspartic acid	SA	Water, methanol
Ibuprofen	SA	Water, ethanol
Acetyl salicylic acid	SA	Ethanol, water, carbon tetrachloride
Ascorbic acid	SA	Water, ethyl acetate, chloroform
DCP	SA	Water, phosphoric acid solution, citric acid
Tranilast	SA	Ethanol, acetone, water, chloroform, DCM
Celecoxib	SA	Acetone, water, chloroform
Mefenamic acid	SA	DMF, water, carbon tetrachloride/ chloroform
Nabumetone	SA	Ethanol, water, cyclohexane/n-hexane
Aceclofenac	SA	Acetone, water, dichloromethane

Research J. Pharm. and Tech.2 (2): April.-June. 2009,


a
OUCT 15.0kV 10.1mm x170 BSECOMP 60Pa
300um
c
OUCT 15.0kV 9.1mm x70 BSECOMP 60Pa
500um
b
OUCT 15.0kV 10.0mm x500 BSECOMP 60Pa
100um
d
OUCT 15.0kV 9.3mm x100 BSECOMP 60Pa
500um

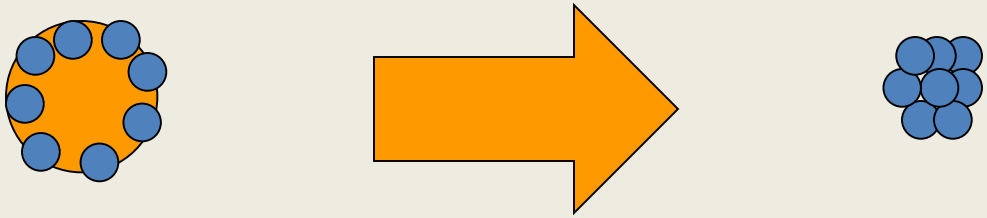
Crystallization



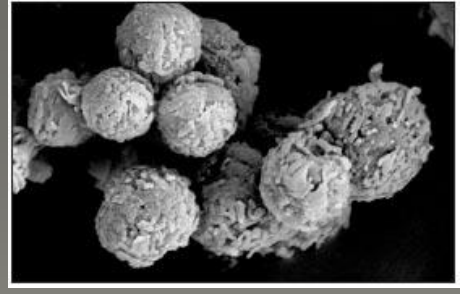
Spherical crystals

Emulsion solvent diffusion (ESD) method

Contrast to the SA-method, here is more important the cohesion between the API and the solvent than the cohesion between the two solvents.
The API have to be dissolved in the proper solvent. This solution have to be dispersed (emulsified) in the other solvent that can dissolve the API and its solvent very poorly.
The solvent of the drops is diffused into the external solvent, so the drop will be more and more concentrated until the point called supersaturated state. When it is reached, than the spontanious nucleation occures.



Crystallization



Spherical crystals

Emulsion solvent diffusion (ESD) method

Drug	Method	Solvent used
Ibuprofen	ESD	Ethanol, water with sucrose, fatty acid ester
Acebutalol HCl	ESD	Water, ethanol, Isopropyl acetate

Research J. Pharm. and Tech.2 (2): April.-June. 2009,

Crystallization

➔ **Recrystallization**

➔ **Purification**

The purification is possible, because a crystal can be made up from its own elements and it contains no any foreign material.

(„foreign materials” is possible on the surface of the crystals or in crystals in their inclusion form)

Crystallization

➔ **Recrystallization**

➔ **Purification**

$$E_A = \frac{m_{Ak}}{m_{Aa}}$$

$$E_B = \frac{m_{Bk}}{m_{Ba}}$$

$$\alpha = \frac{E_A}{E_B}$$

E_A the factor of the component A

E_B the factor of the component B

m_k The amount of the A or B in the crystal

m_a The amount of the A or B in the ‘mother liquid’

α separation factor

Crystallization

The crystallization is a two step process.
The crystallization process consists of two major events, nucleation and crystal growth.

These processes happen at the same time.

Crystallization

Solubility equilibrium curve

The driving force of the crystallization is the supersaturated state of the solution.

The supersaturation state can be reached by different ways. (cooling, evaporation, interchange of the solvent)

Crystallization Gibbs-phase rule

F freedoms
C components
P phases

$$F = C - P + 2$$

The equilibrium of the gas-fliud-solid phases is influenced by the ***temperature, pressure*** and the ***concentration.***

$$F = C - P + 1$$

During the drug crystallization, the pressure (p) is constant

Crystallization Solubility curve

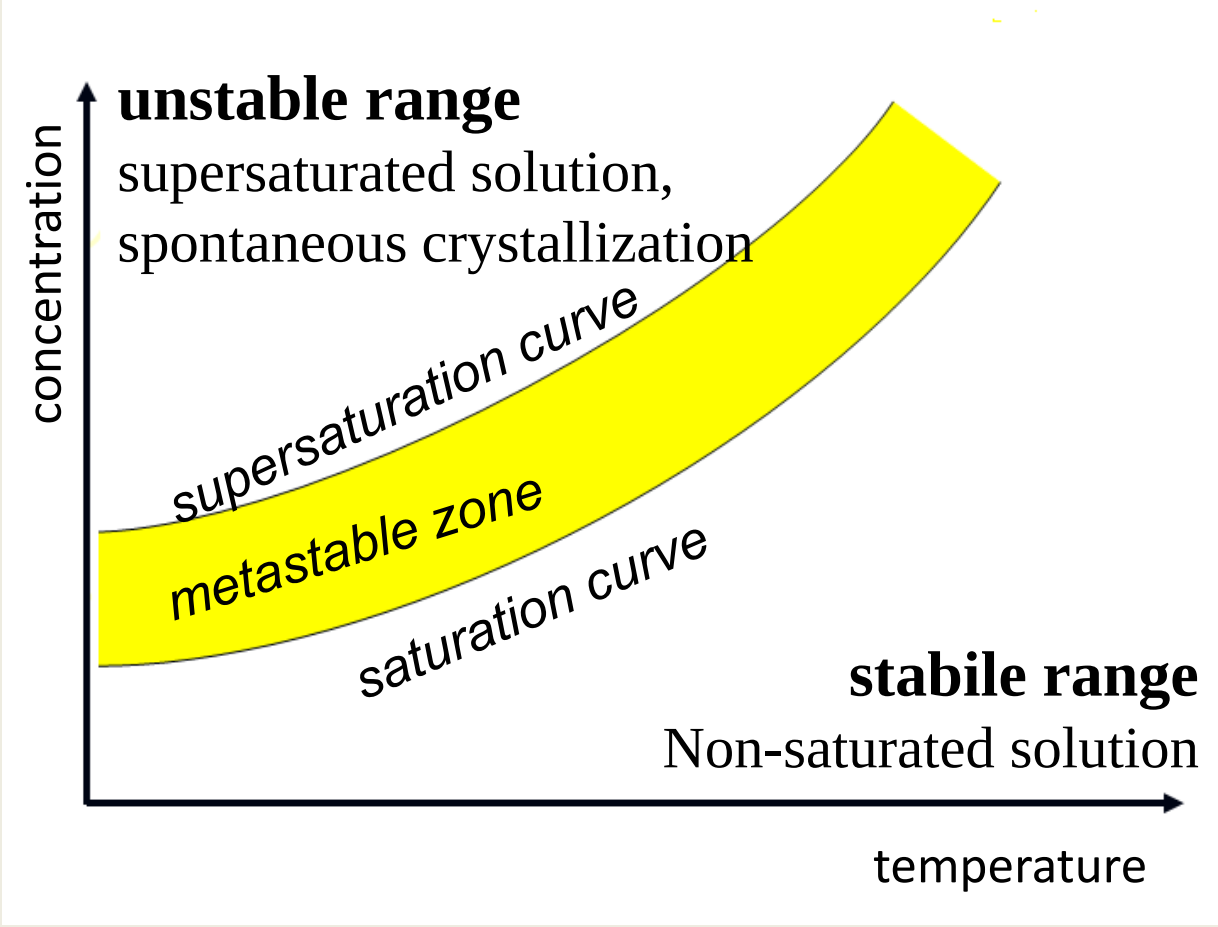
If the solubility curve is

➔ linear (horizontally) – the the solubility is independent by the temperature:

evaporation

➔ non-linear: The solubility is dependent by the temperature:

cooling

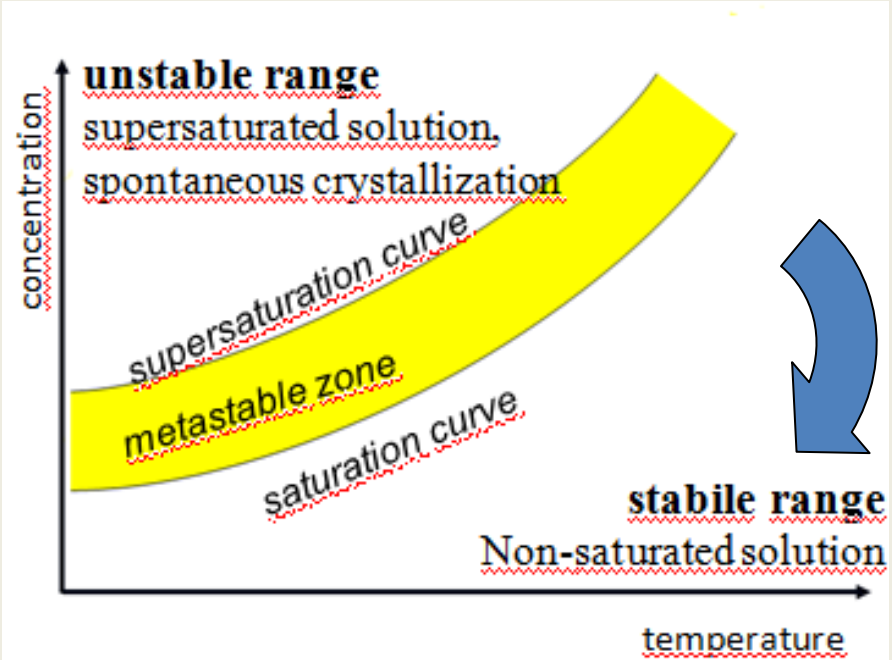


Crystallization Solubility curve

➔Crystallization and the temperature

The <u>stabile range</u> is the non-saturated region of the graf.

Here is an equilibrium among the precipitation and the dissolution process.



Crystallization Solubility curve

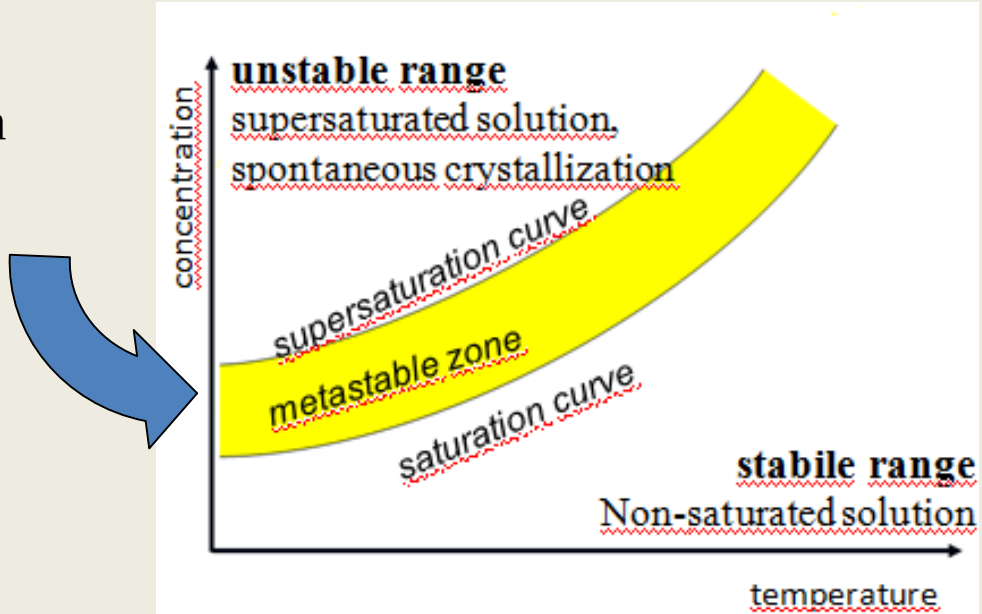
➔Crystallization and the temperature

The metastable zone (Ostwald-Miers)

Here is not any nucleation process, but crystal growth is possible.

The supersaturated curve is dependent by the temperature, the coolig speed, evaporation and by the stirring (rpm).

Unstable supersaturated solution

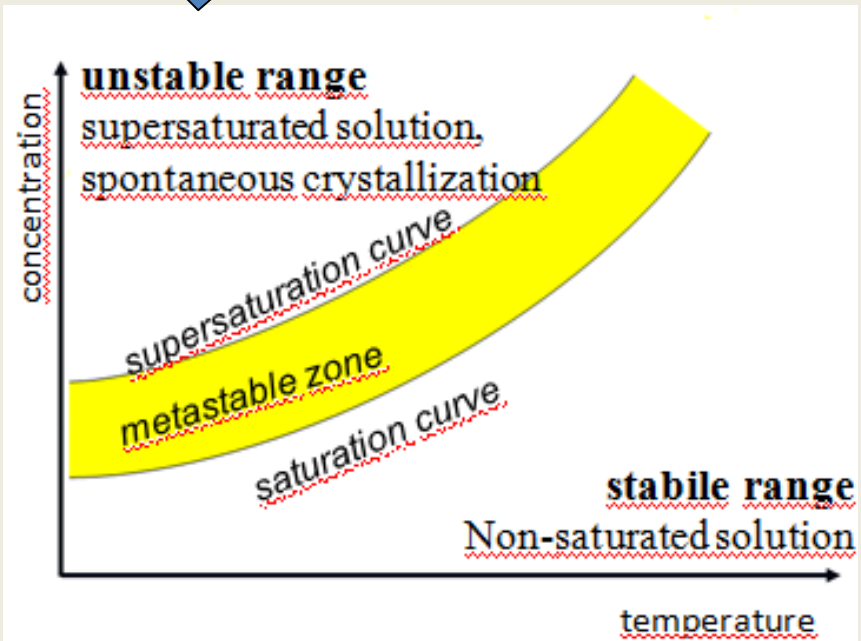


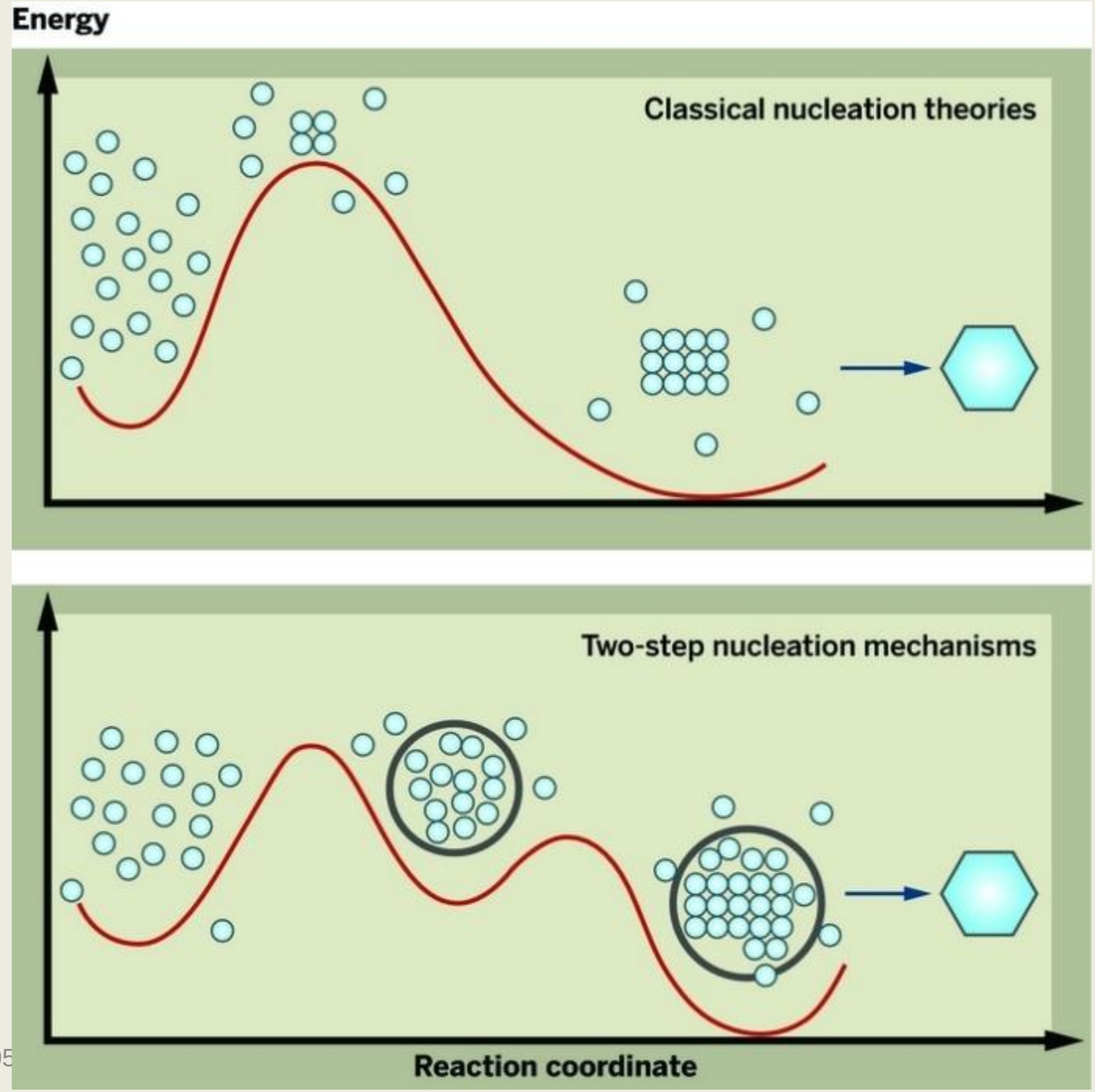
Crystallization of sodium acetate

Crystallization Solubility curve

➔Crystallization and the temperature

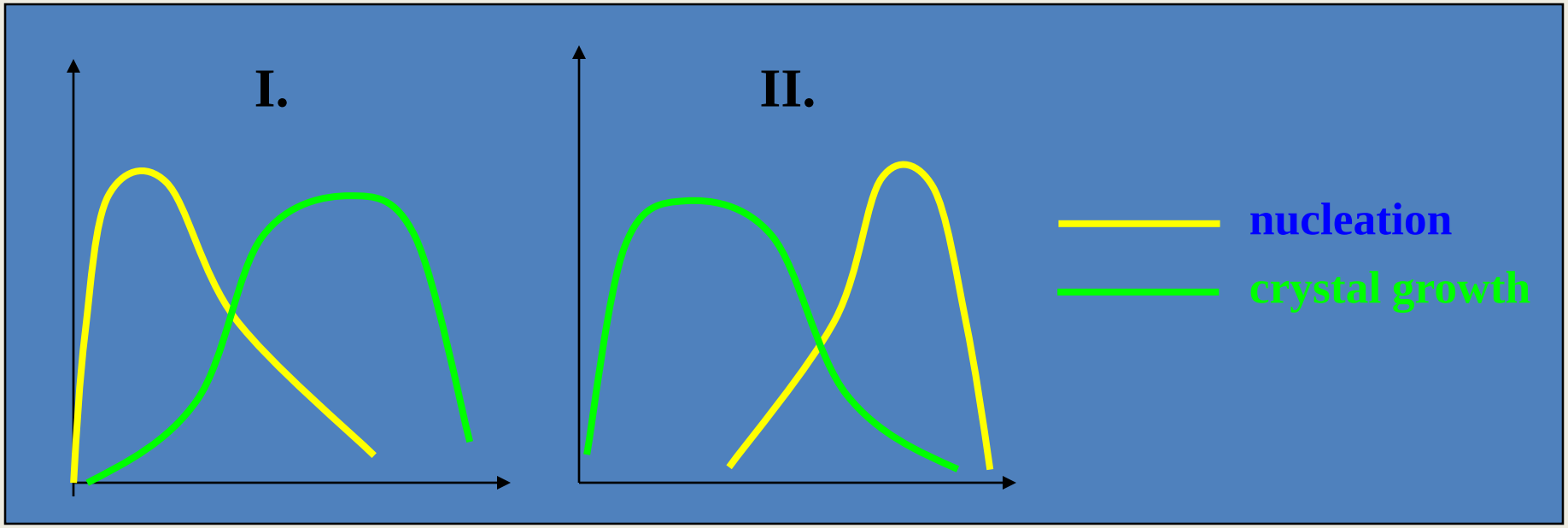
The <u>unstable region:</u> here is possible the spontan crytal formation, the nucleation and the crystal growth processes too.




Energy
Classical nucleation theories
Two-step nucleation mechanisms
Reaction coordinate

Crystallization

Curve of the nucleation and crystal growth



I. $v_{nucleation} > v_{crytal\ growth}$ …… a lot of smal crystals

II. $v_{nucleation} < v_{crytal\ growth}$ ….. …..a few huge crystals

Crystallization

Crystal growth

- **Diffusion from the solution to the surface of the formed crystals**
- **The incorporation of the material into the crystal**

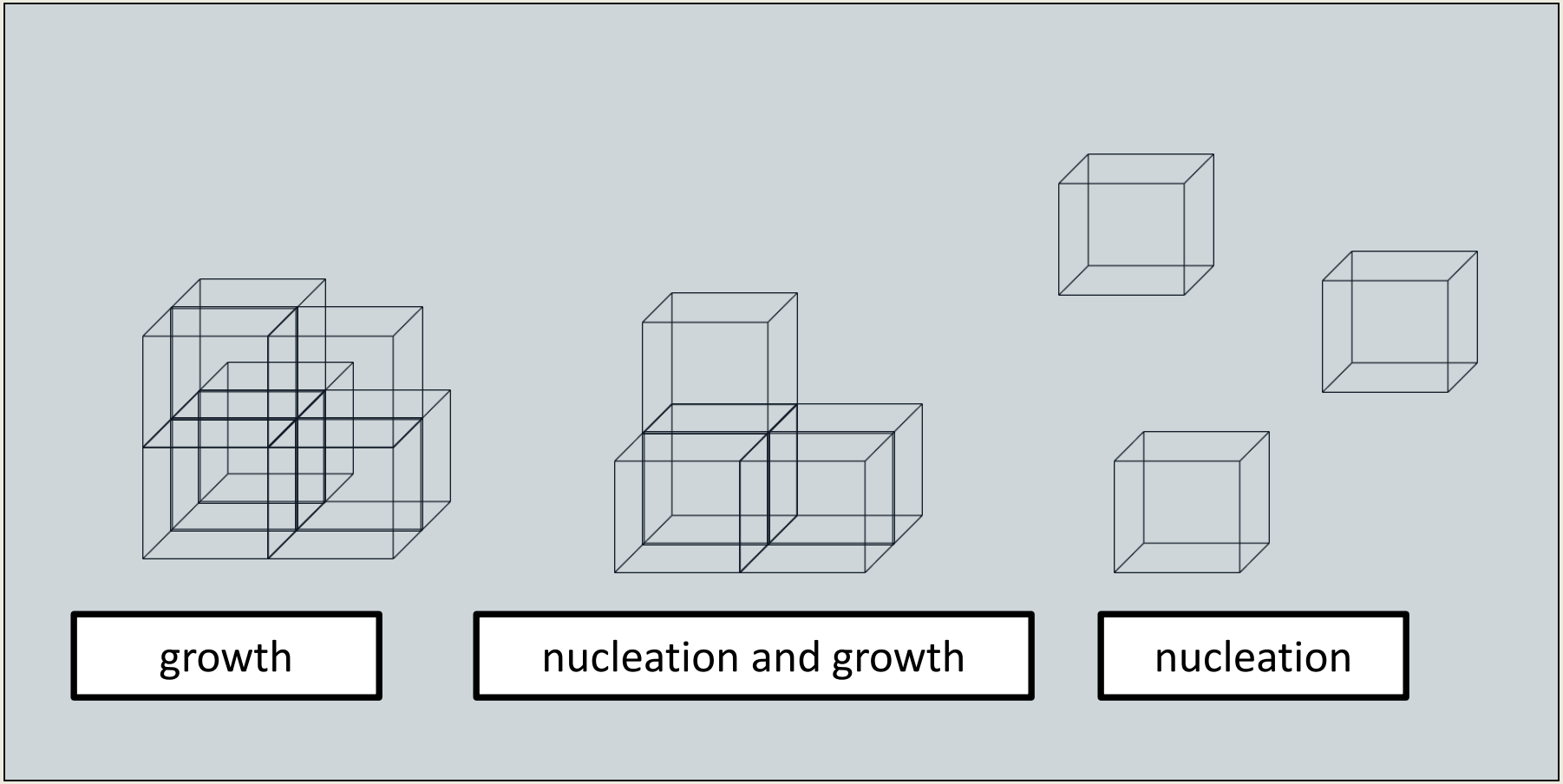
$$\frac{dm}{dt} = k_1 A(c - c_f)$$

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

m	mass
t	time
k	rate constant
A	surface area
c	concentration of the solution
$\mathbf{c_f}$	concentration on the surface of the crystal

Crystallization

The unit cell and the crystal



Crystallization equipments

Crystallization equipments

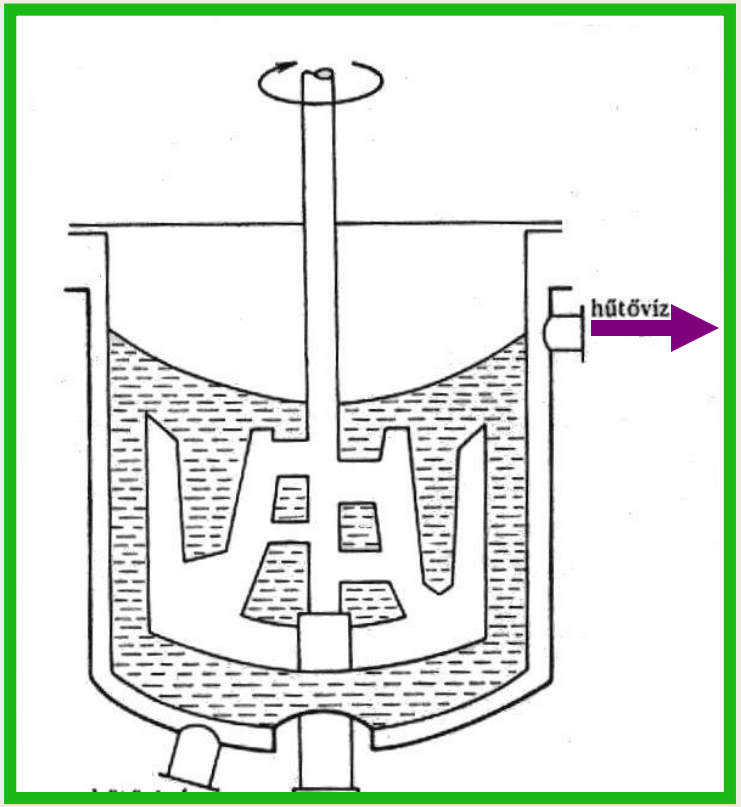
- with spontaneous crystallization (too slow, this method is not applied in the ‘industry’)
- with cooling
- with evaporation (evaporators)
- with vacuum

Crystallization equipments

➔ Crystallization with evaporation or with cooling

Duplicator – for crystallization

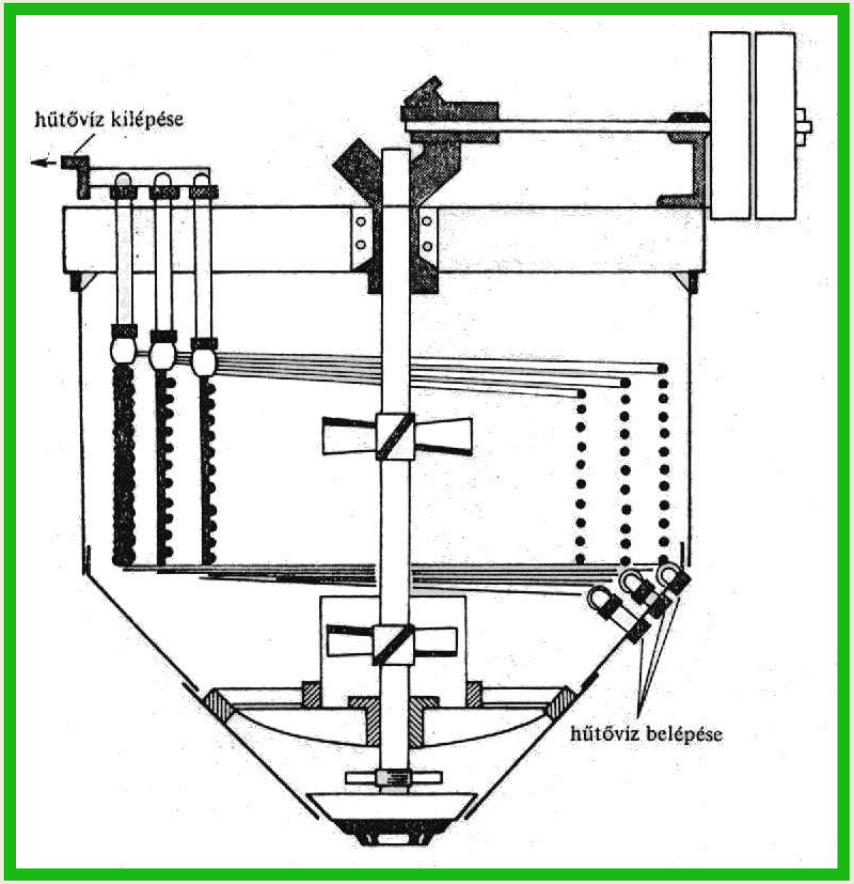
It is capable for those type of materials that can be crystallized by cooling.



Crystallization equipments

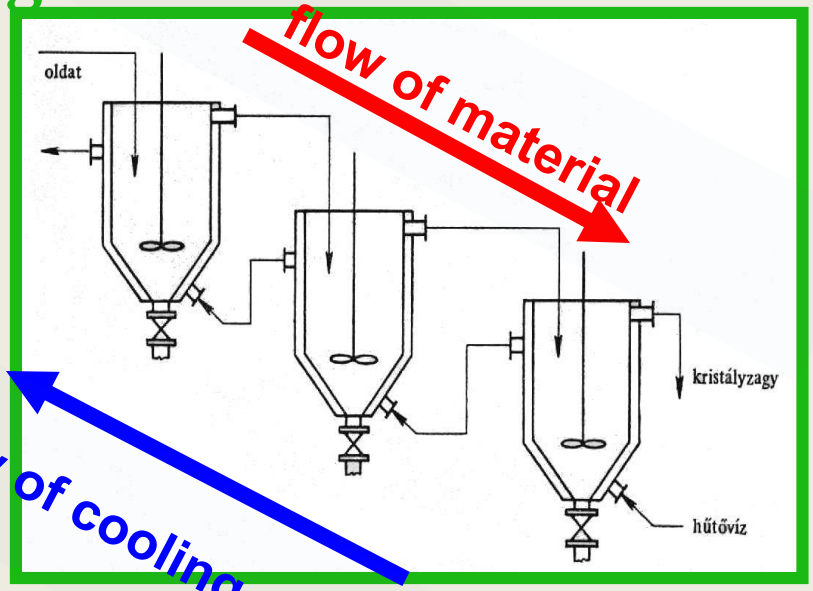
➔ Crystallization with evaporation or with cooling

Shell-tube crystallizer



Crystallization equipments

➔ Crystallization with cooling



Multiple mould/crystallizer

continuous mode

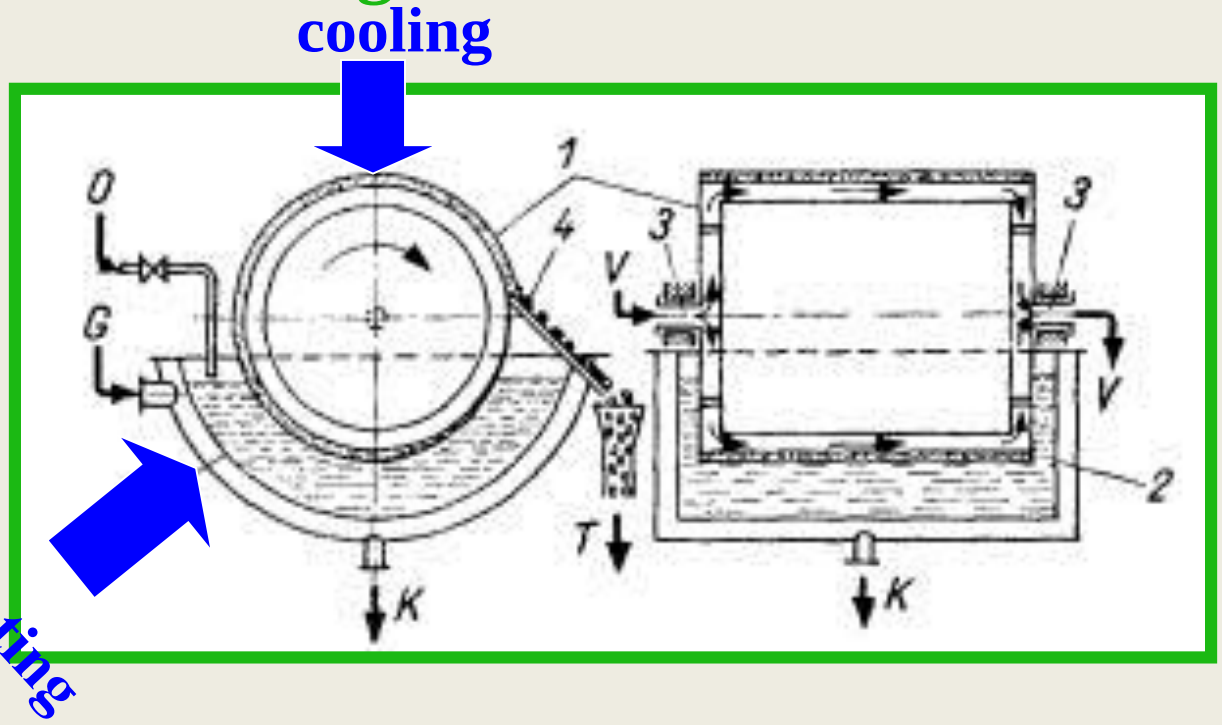
The counterflow is better: effectiveness, energy-saving

Crystallization equipments

➔ Crystallization with cooling

Rotary-drum crystallizer

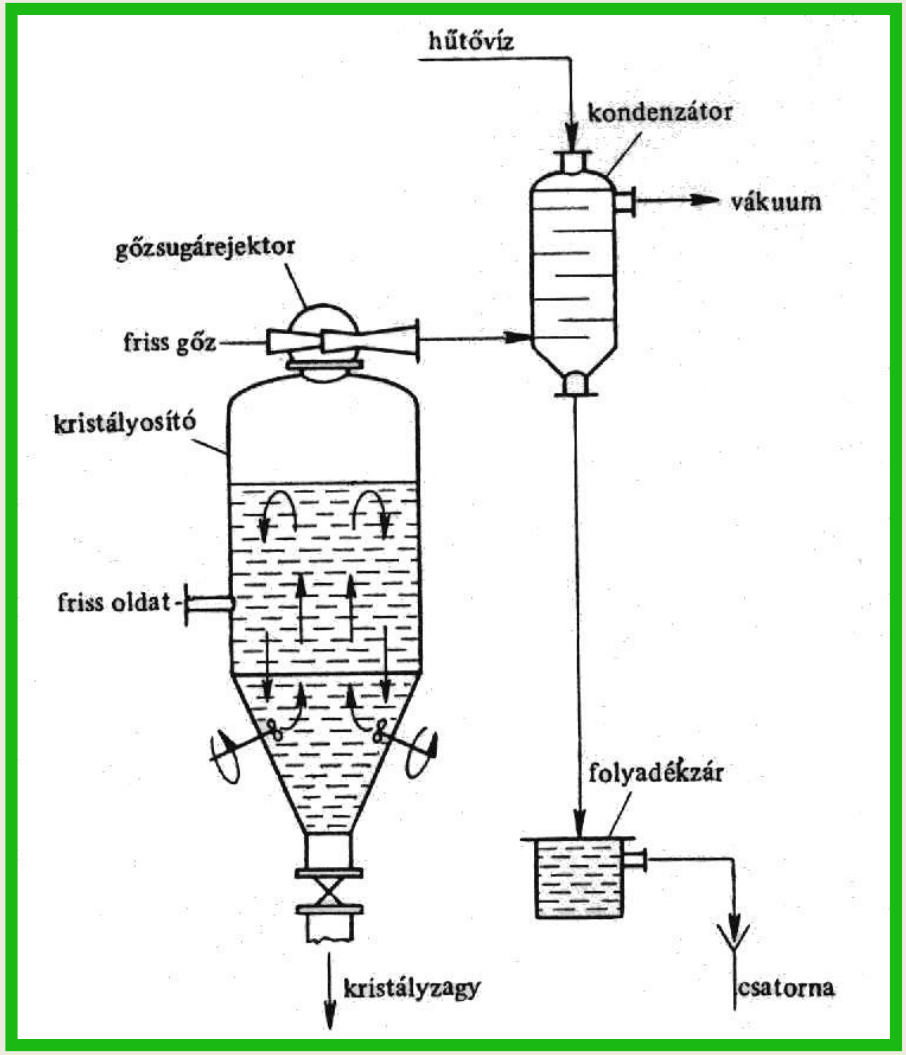
continuous mode



Crystallization equipments

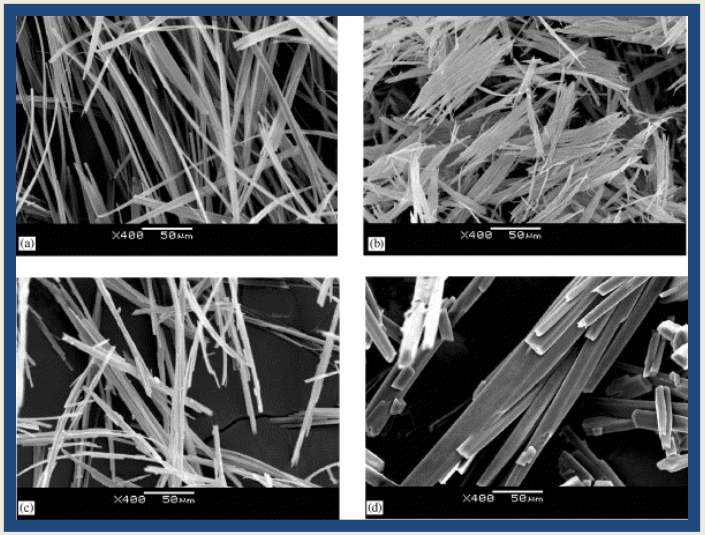
➔ Crystallization with vacuum

Vacuum crystallizer



Elimination of the solvent

Polymorphism of the crystals



Polymorphism of the crystals

Isotypic

If the crystals have ***similar external shape*** and ***internal structure.*** (NaCl, KCl).

Isomorphy

Those isotypic crystals in that the iones can substituated each other. (mixed crystal / mischcrystal)

Depend on:

a.) similar weight
b.) similar polarisation
c.) equal unit cell and same structure ($CaCO_3$,$NaNO_3$)

Polymorphism of the crystals

Polymorphy

The same chemical compound or element with different unit cell stucture because of the different ambient conditions.

1. enantiotrope (reversibile)
2. monotropic (irreversibile)

The differnet polymorphs of the APIs have different properties:

a.) solubility,
b.) dissolution rate,
c.) biopharmaceutical behaviour,
d.) bioequivalence

Polymorphism and bioavailability

Change in Physical Form

Low energy form (crystalline) is thermodynamically the most stable form but it is a less soluble form and hence less bioavailable. An amorphous form of drug substance is the highly soluble form and hence it is more bioavailable ; however, it is thermodynamically less stable.

Crystals are harder than amorphous solids.

Crystals are more brittle and tend to be less compressible than amorphous solids.

Crystals are more ordered than amorphous solids.

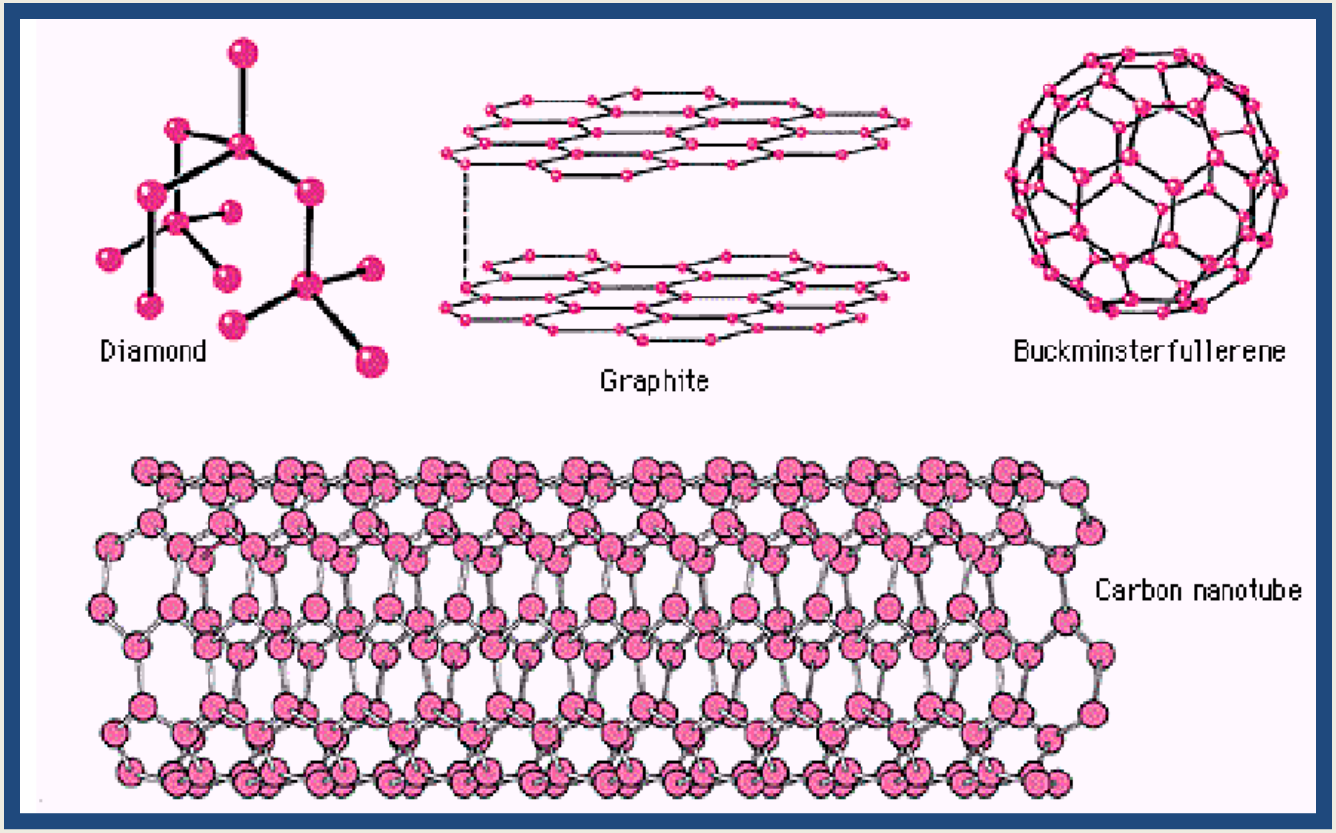
Crystalline form appears white or colored using cross polarisers, while the amorphous form is mainly invisible against the black background.

Semi-crystalline form appears birefringent (colored), but does not show well-defined extinction.

Polymorphy

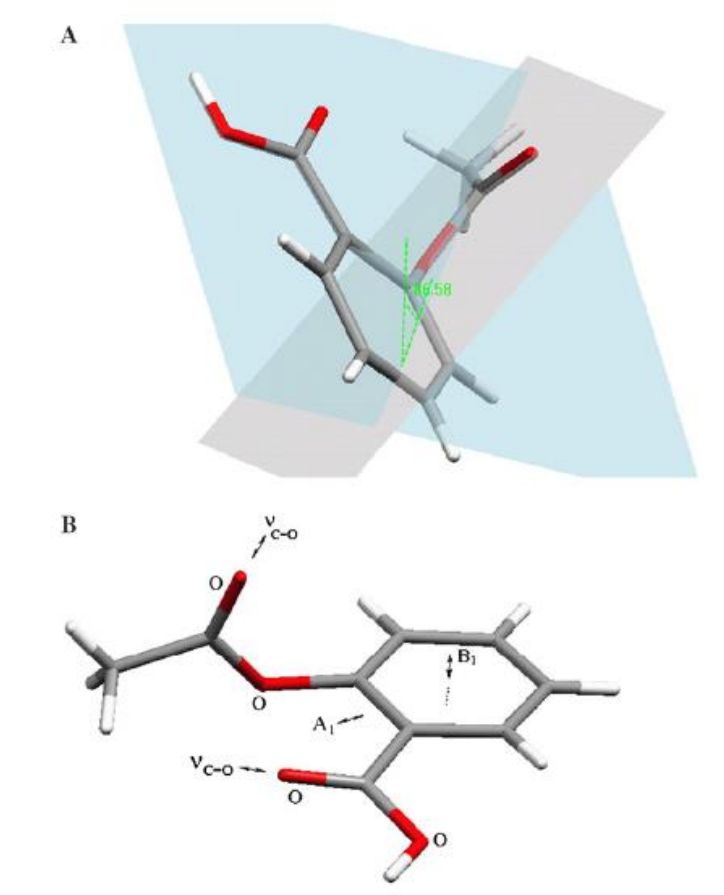
Allotropy is the polymorphy of the elements.

The allotrope forms of carbon.



Polymoprphism

ASA



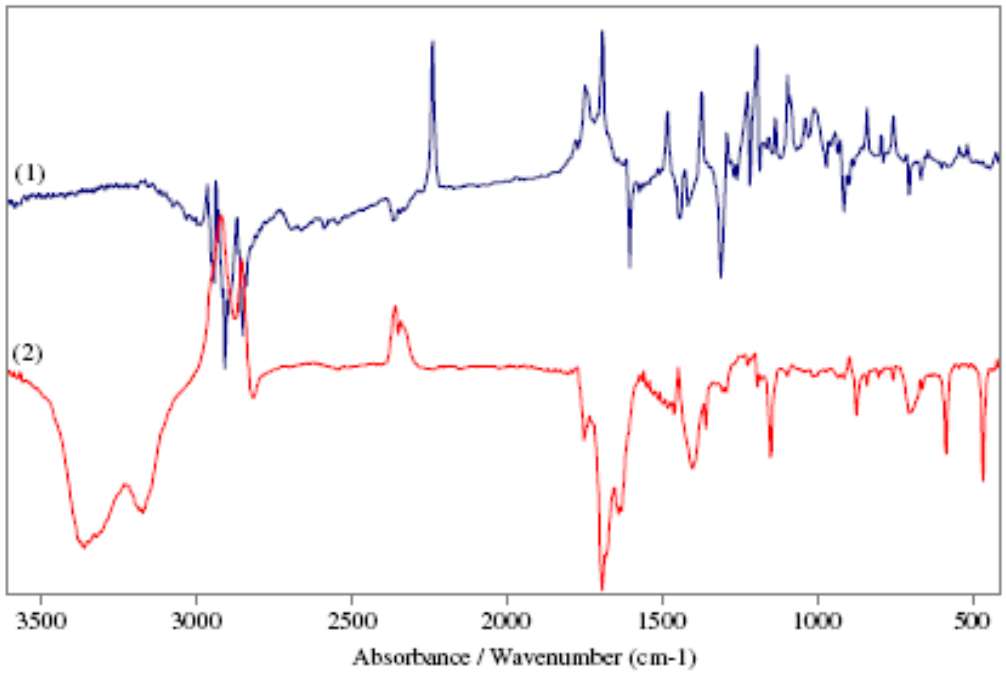


Fig. 1. Difference IR-LD spectra of Aspirin polymorphs: form I (1) and form II (2).

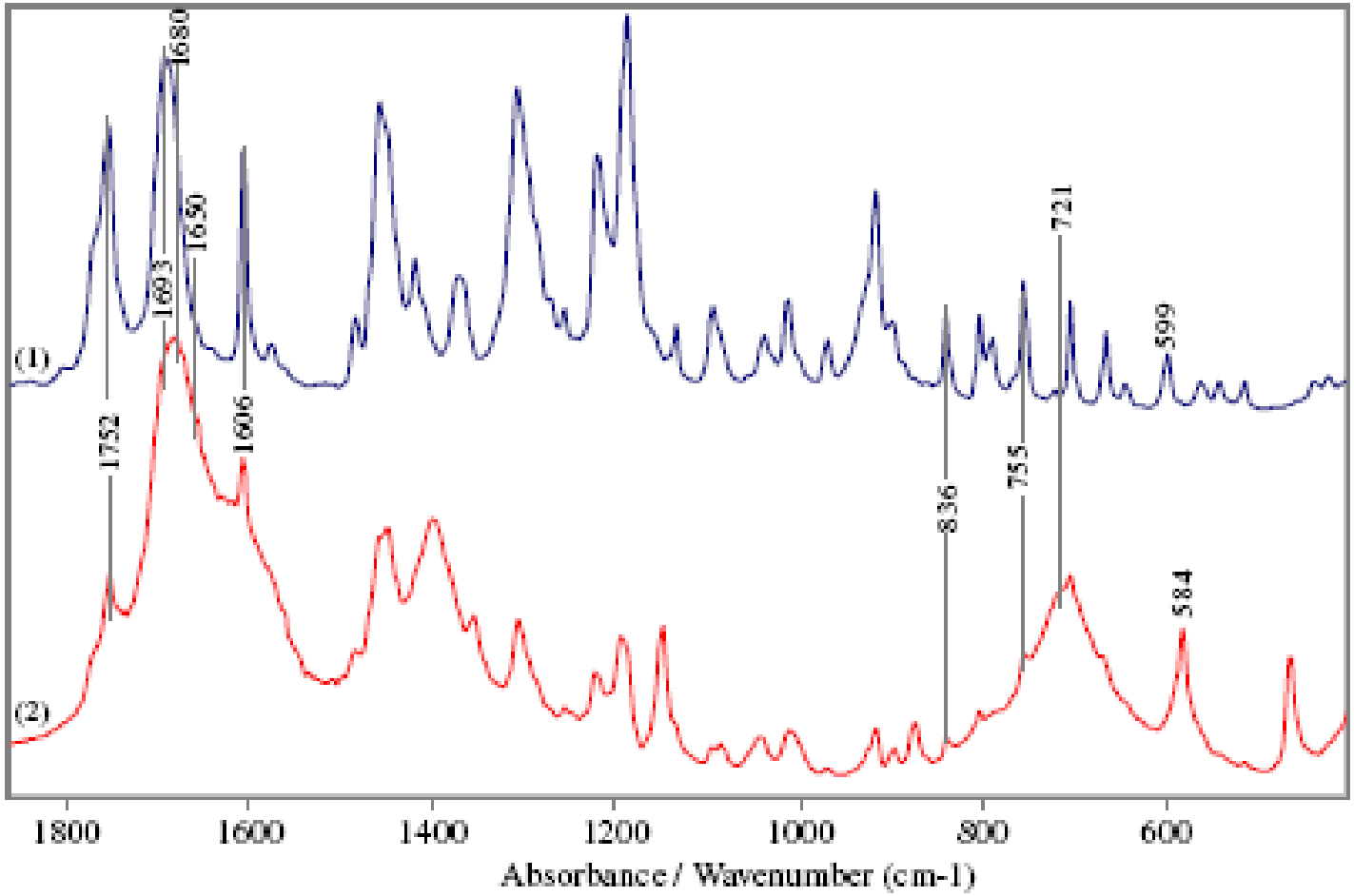


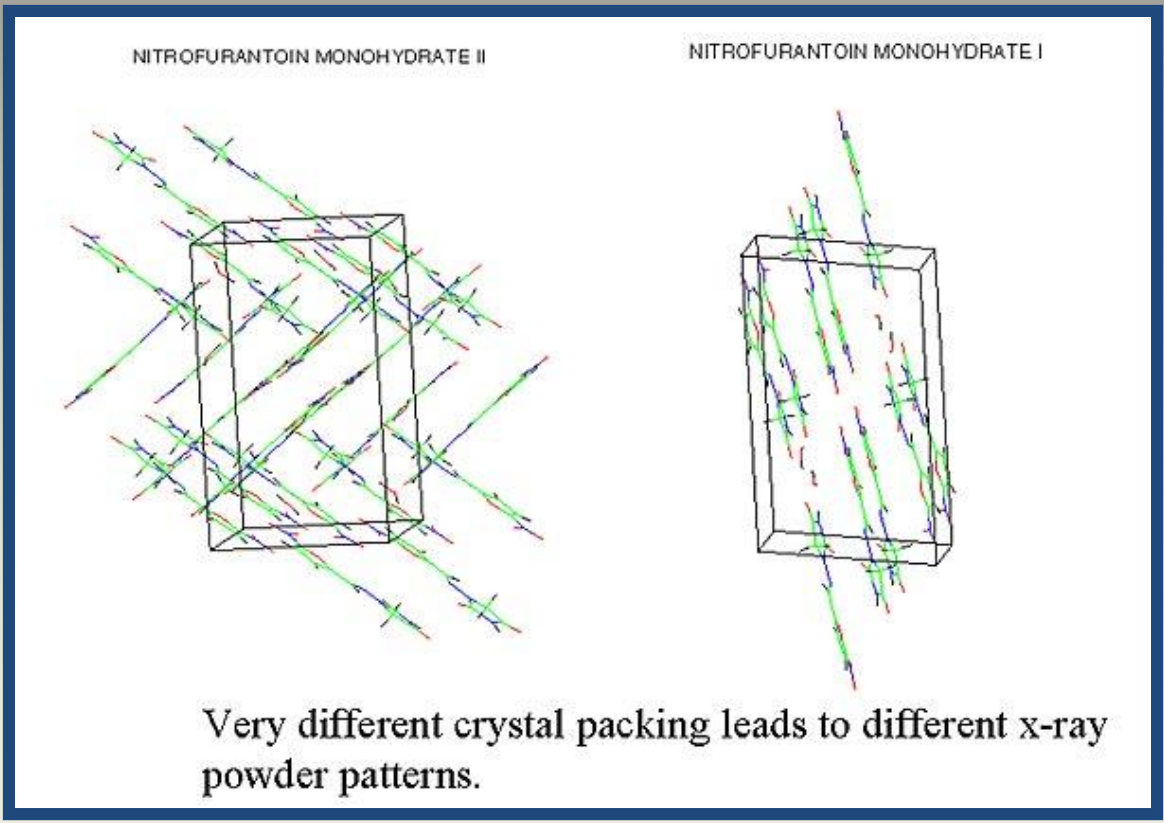
Fig. 2. 1800–400 cm^{-1} solid-state IR-spectra of form I (1) and form II (2) of Aspirin.

Polymoprphy

Nitrofurantoine- monohydrate

different physical-chemical behavior

(solubility, stability)

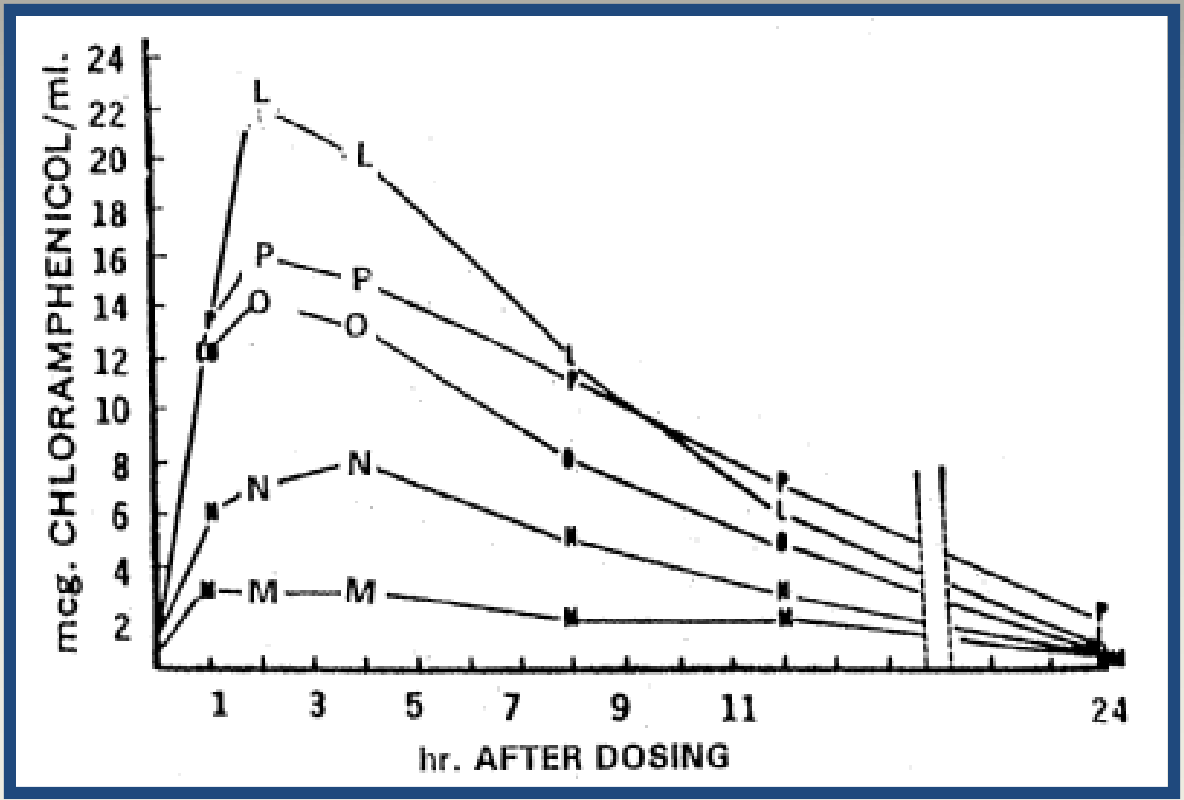


Polymoprphism

Plasma concentration of chloramfenikol-palmitate

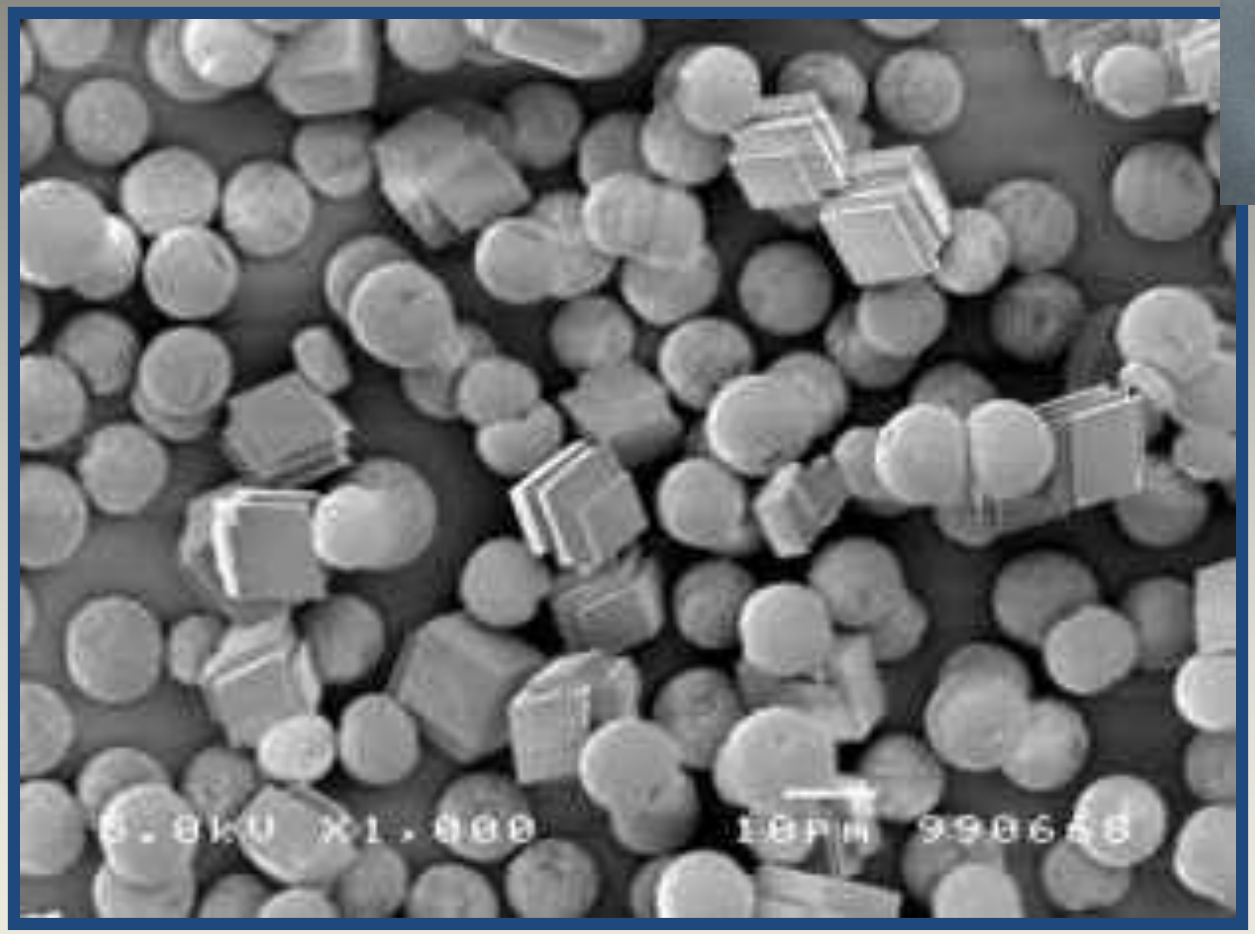
Suspension systems with different A:B ratios

M, 0%; N 25%; O, 50%, P; 75%; L, 100% B



Polymoprphism

Calcium-carbonate



Polymoprphism

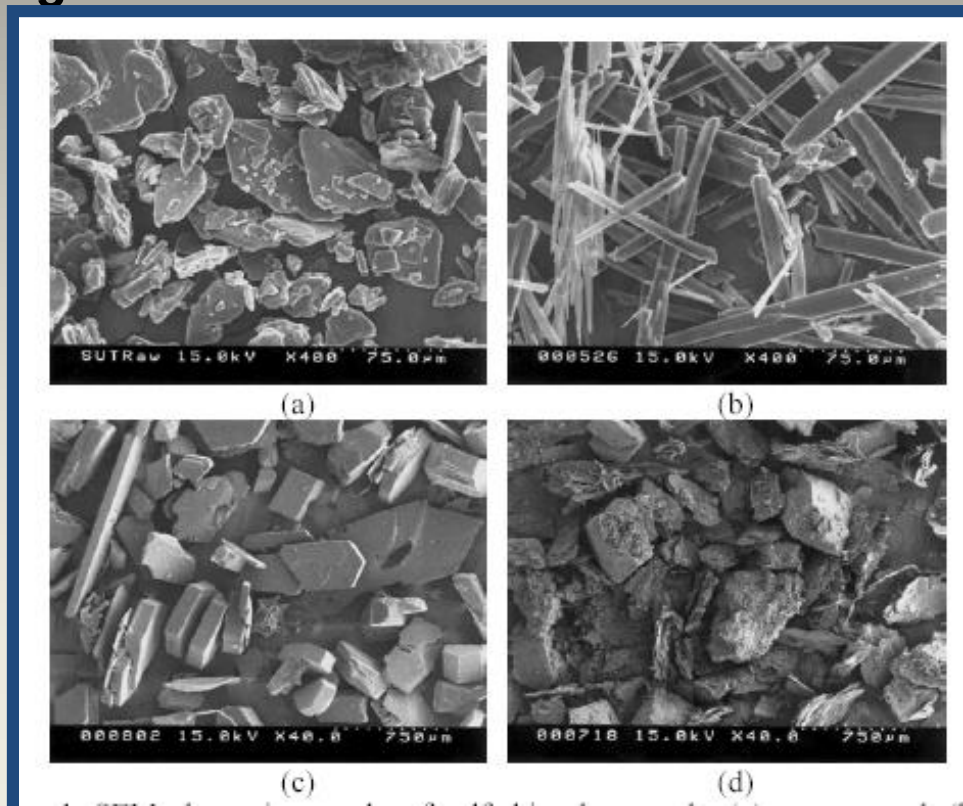
Sulfatiazole

a.) initial

b.) in metanol with fast dosing rate 30C°

c.) in metanol with slow dosing rate 35C°

d.) in acetone with slow dosing rate 40C°

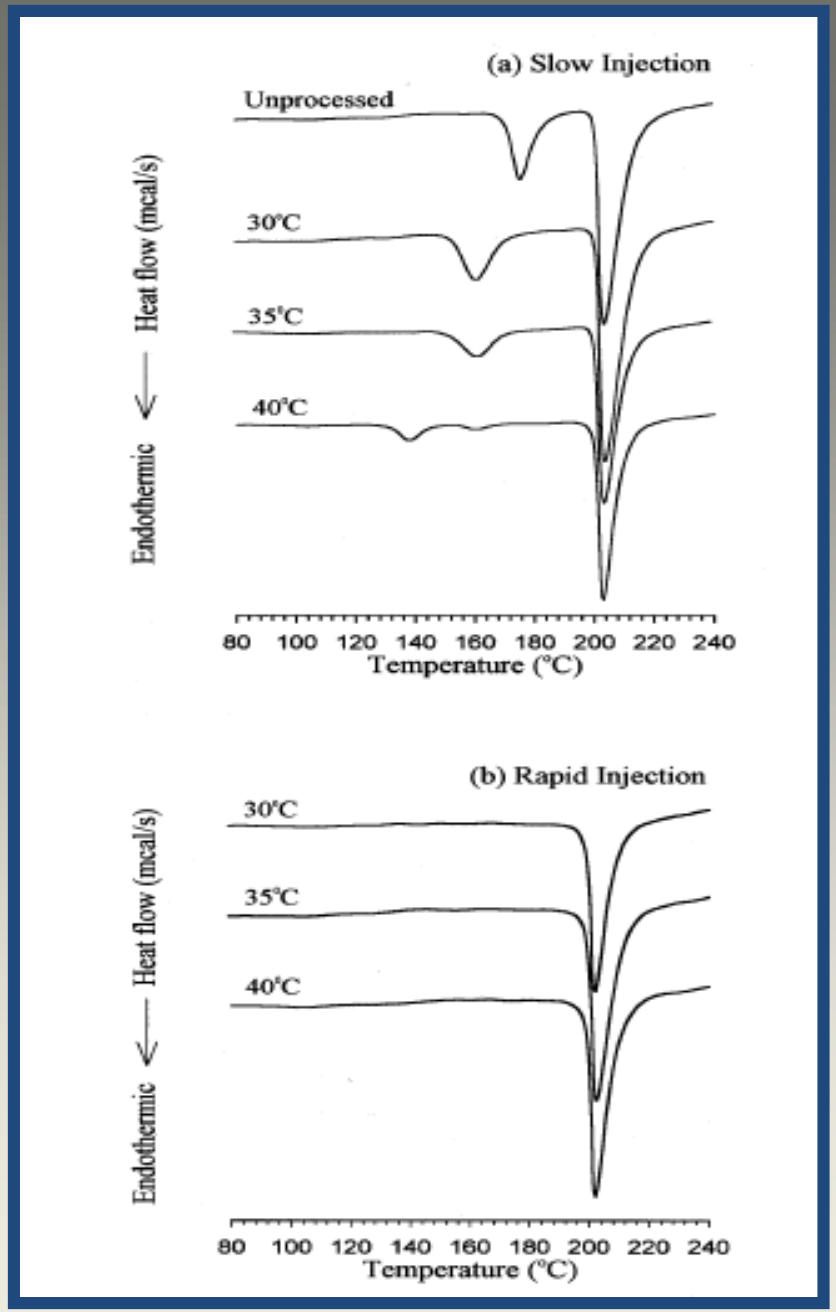


Polymoprphism

Sulfatiazole

DSC examination

(in acetone)



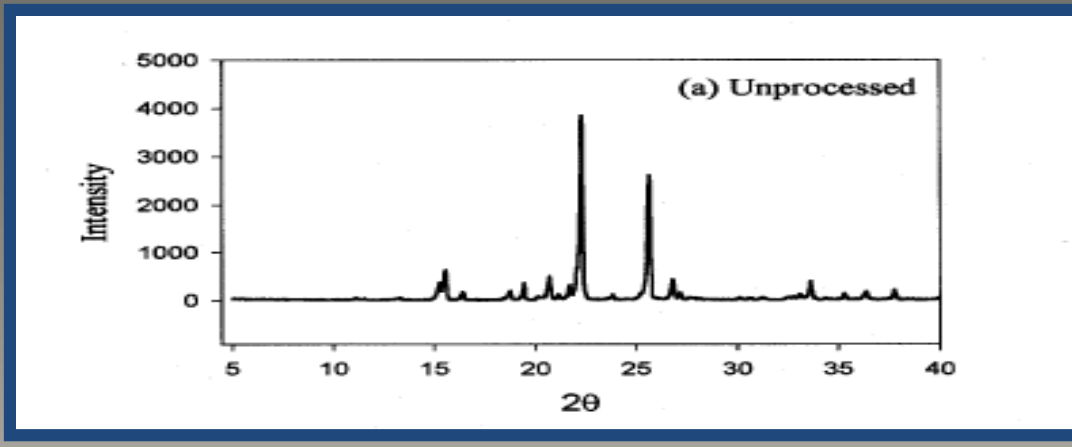
Polymoprphism

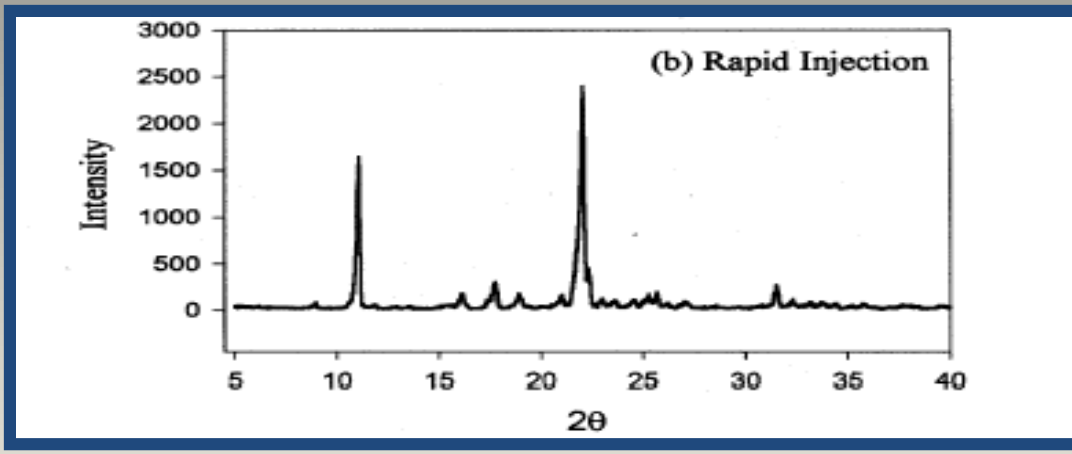
Sulfatiazole

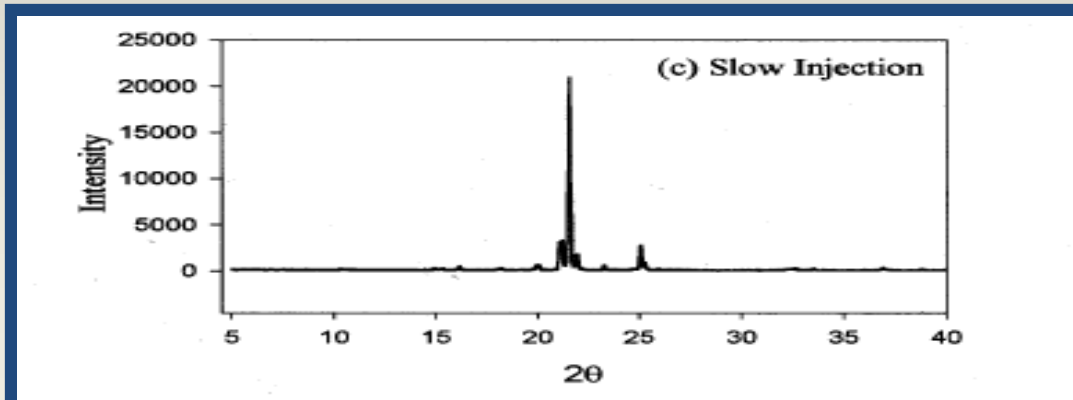
polymorphs

X-ray diffraction

ecatone







Examination of crystals

Examination of crystals

➔ ***Crystallographic examinations***

- **conductivity analysis (ETA)**
- **wettability**
- **adsorption**
- **particle size**
- **melting point, freezing point**
- **habit of the crystals with microscope**
- **X-ray diffraction**
- **Rietveld analysis (stucture examination)**
- **X-ray fluorescency**
- **NMR spectroscopy**
- **IR, NIR spectrophotomertry**
- **Raman spectrophotometry**
- **UV spectrophotometry**
- **Termoanalysis**

Examination of crystals

➔ *Crystallographic examinations*

➔ **termoanalysis**

- **termogravimetry (TG)…….. mass**
- **derivative termogravimetry (DTG)…….. mass**
- **termodialotometry (TD)…….... lenght**
- **differential termoanalysis (DTA)…….... temperature**
- **differential scanning calorimetry (DSC)… entalpy**
- **heated microscopic examinations…….temperature**

Examination of crystals

What kind of examinations we do with the crystals?

- **Particle size, ant their distribution**
  - **Surface area**
  - **Dissolution rate**
  - **Flowability**
  - **Tabletting behaviour**
- **Moisture content**
  - **External mousture (adsorbed water)**
  - **Internal moisture (crystal water)**
- **Stability**
- **Biopharmacy**
  - **Dissolution test**
  - **Absorption test**

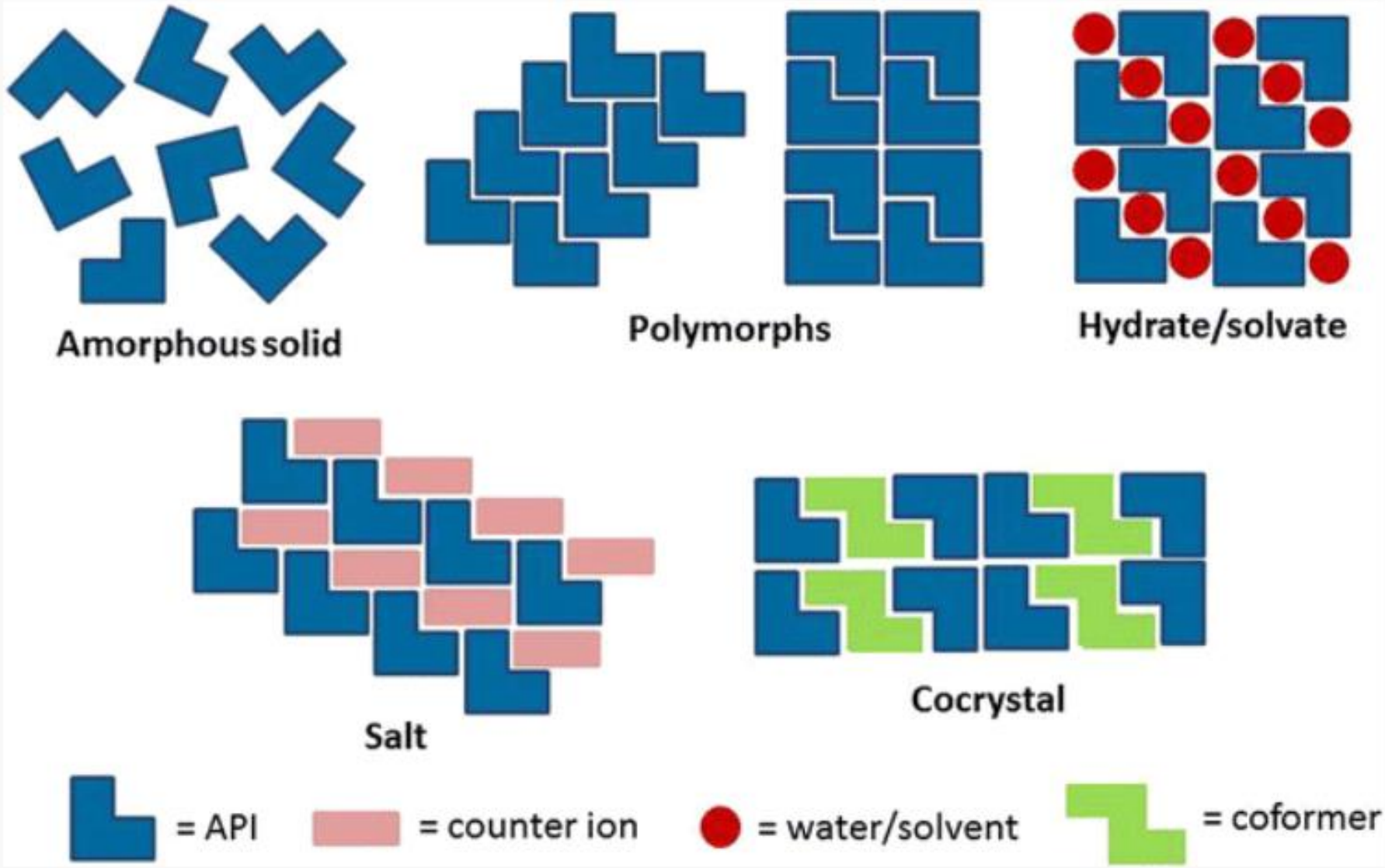
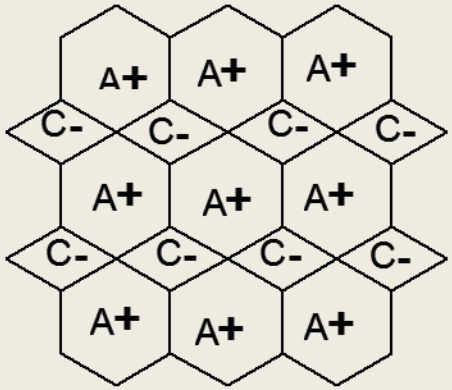
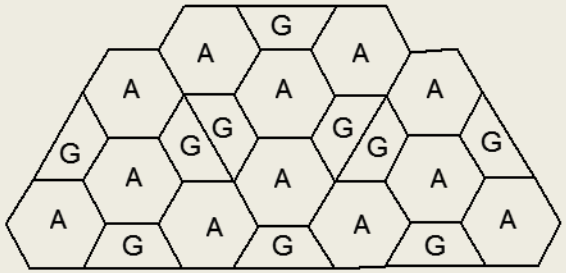


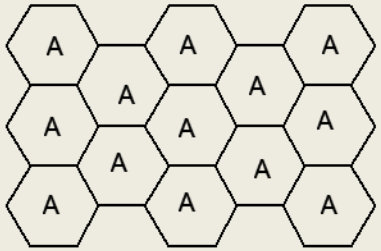
Figure 3:

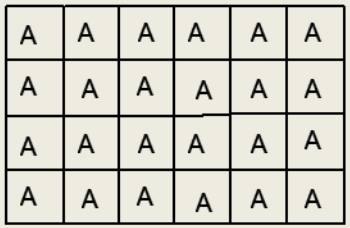
Most common solid forms of pharmaceuticals.

Co-Crystals









Salts **Co-crystals** **Polymorphs**

Crystalline Molecular Complexes:
Co- Crystal / Salt Continuum

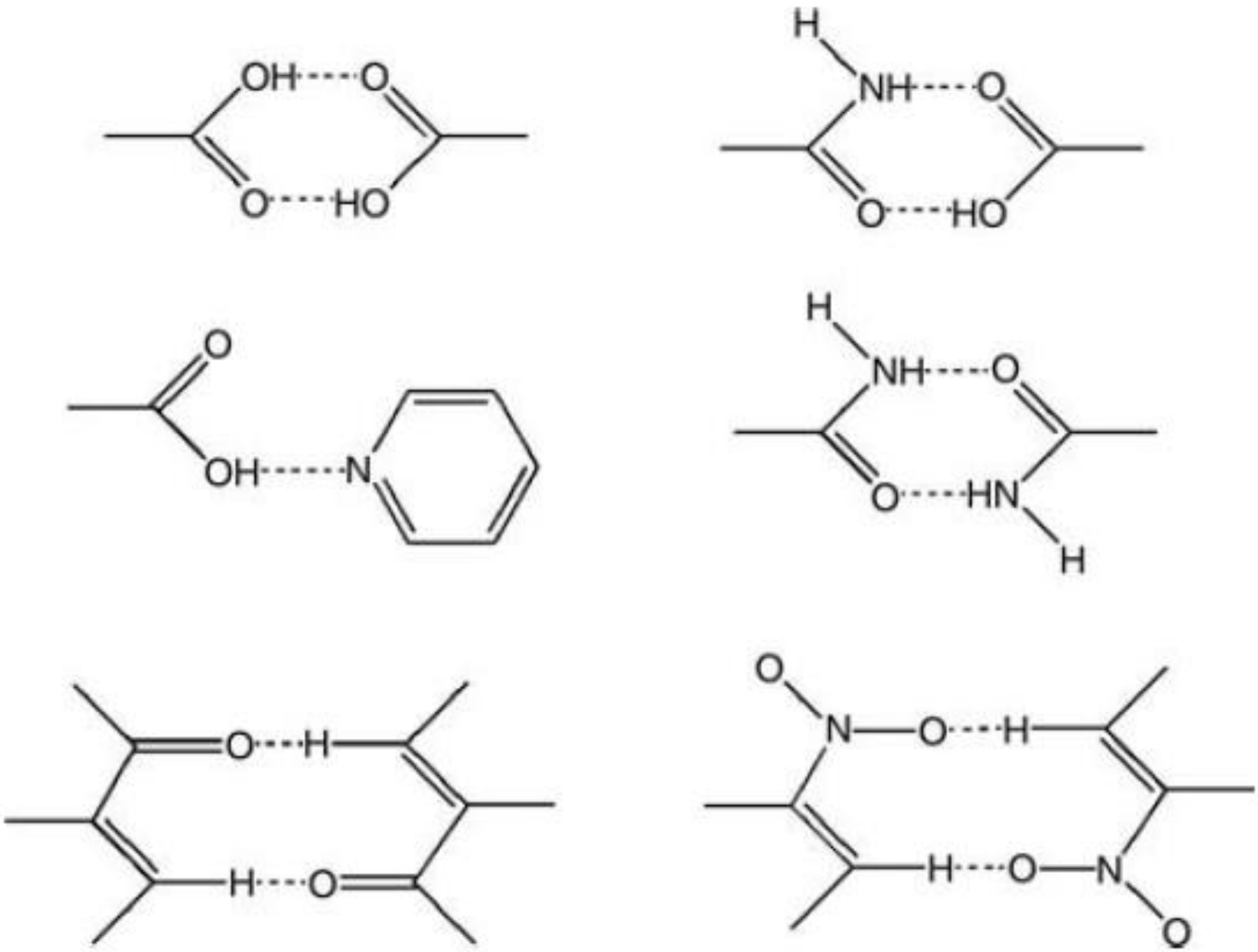
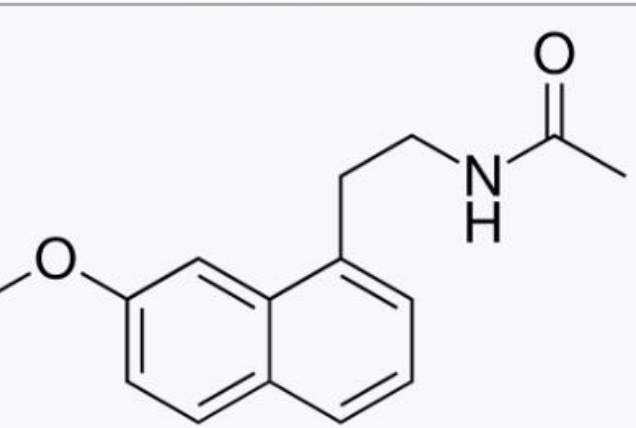
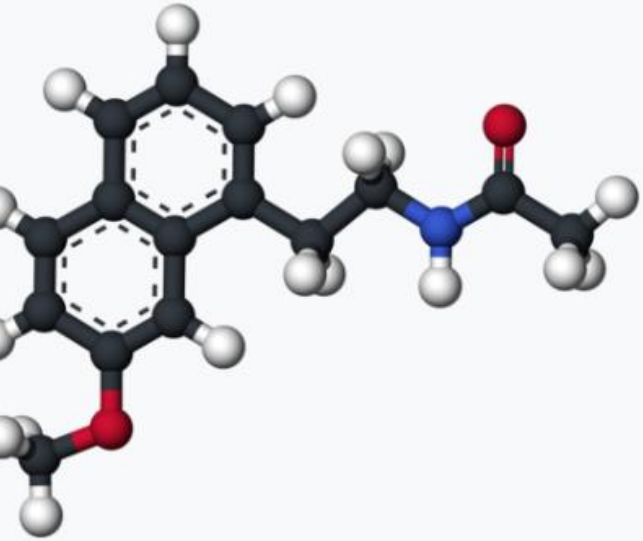


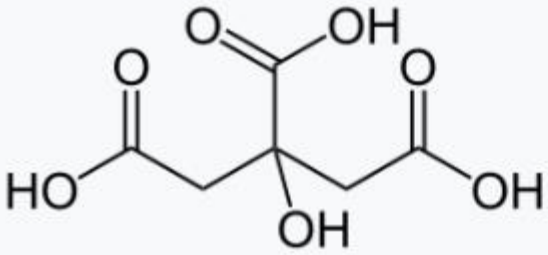
Fig. 1 Common synthons in supramolecular assemblies.

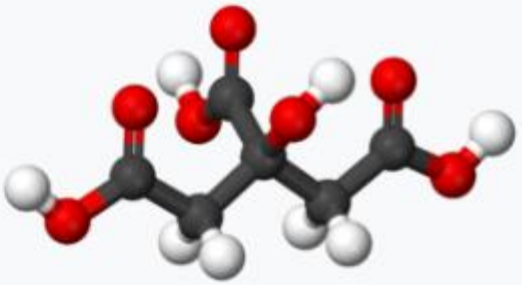
Agomelatine





Citric acid





- ASSIMIL 25 mg tablet

Benefits of cocrystalization

- Enhnanced solubility
- Modification of mechanical properties:
  - Hardnes
  - Stability
  - Flowability
- Purification:
  - Purifying cannabidiol from natural cannabis extract

Thank you for your attention.