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Physical Pharmacy I
Solid state

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* كل الـ material تتغير من phase لـ phase آخر بنحكي انه صار phase change
وهذا الـ phase change بيصير at specific temperature، الـ solid بيتحول لـ liqued
على الـ melting point والـ liqued يتحول completely لـ gas على الـ boiling point.

Solid state

- Solid particles are made up of molecules, atoms or ions that are held in close proximity to each other.

• طبعاً هذا كله بسبب الـ very strong intermolecular forces يلي بين جزيئات الـ Solid.

- They are much denser than both gases and liquids due to the presence of very strong forces between molecules, atoms or ions.

* الـ physical form للـ solids، مثل الـ (packaging of molcules) size and shape) influence how the particls behave
مثلاً الـ size بأثر على الـ rate of dissolution، ومثلاً الـ shape بأثر على الـ powder flow، ومثلاً الـ packaging بتأثر على الـ density والـ solubility والـ melting point.

- Solids are unique because their physical form (the packing of molecules and the size and shape of particles) can have an influence on the way the material will behave.

وهذا المصطلح موجود فقط في الـ Solid Bhase.

- Solids may be **crystalline** or **amorphous** (or a combination of both).

* أغلب الأدوية هي organic molcules with low molculer weight.

molcules are orderd in a repeating pattern.

Solid state

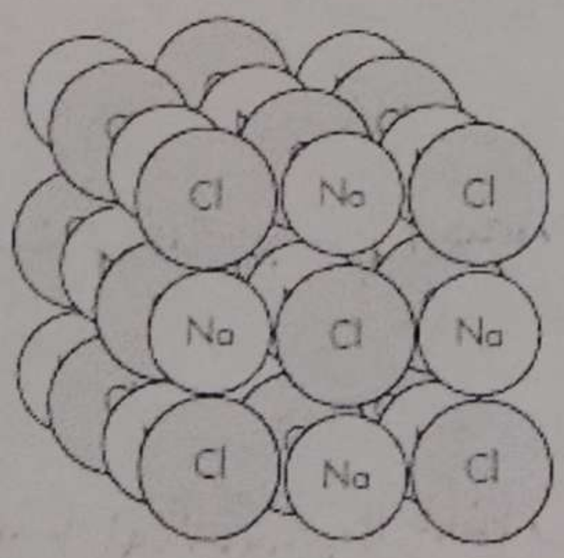
- Crystalline materials are those in which the units (i.e. molecules, ions or atom) are packed in a defined order and this same order repeats over and over again throughout the particle.
- The forces of interaction between units include:
  - **metallic bonds**
  - **covalent bonds (ex. Diamond)**
  - **ionic bonds (between ions in salts such as NaCl crystals)**
  - **hydrogen bonds (between molecules),**
  - **van der Waal's forces**

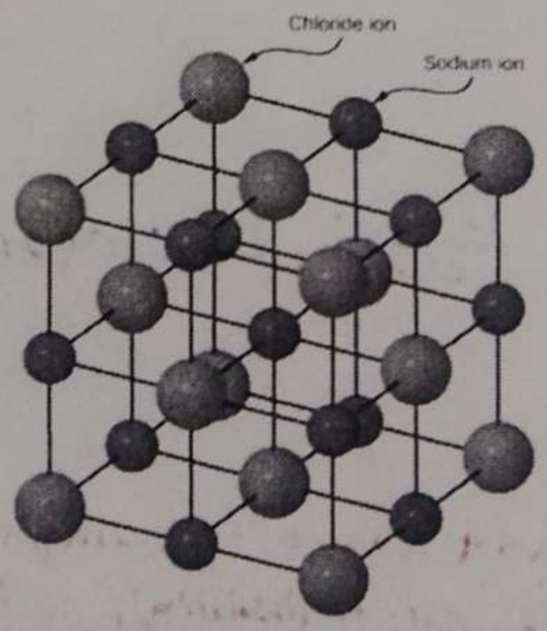
* نتشبه لنقطة مهمة إنه مكونات units وصنف نوع الـ units بتكون القوى مثلاً" الـ metallic ما بتكون بين الـ molecules بل بين الـ atoms (intra) وإنما بين (inter).

* إذا كانت المادة solid لكن الـ molecules غير مصفوفة in a repeating pattern تسمى المادة إنها amorphous.

* عشان الـ molcules تكون صف (pattern) لازم تكون perfectly aligned with each other.

Ionic crystals



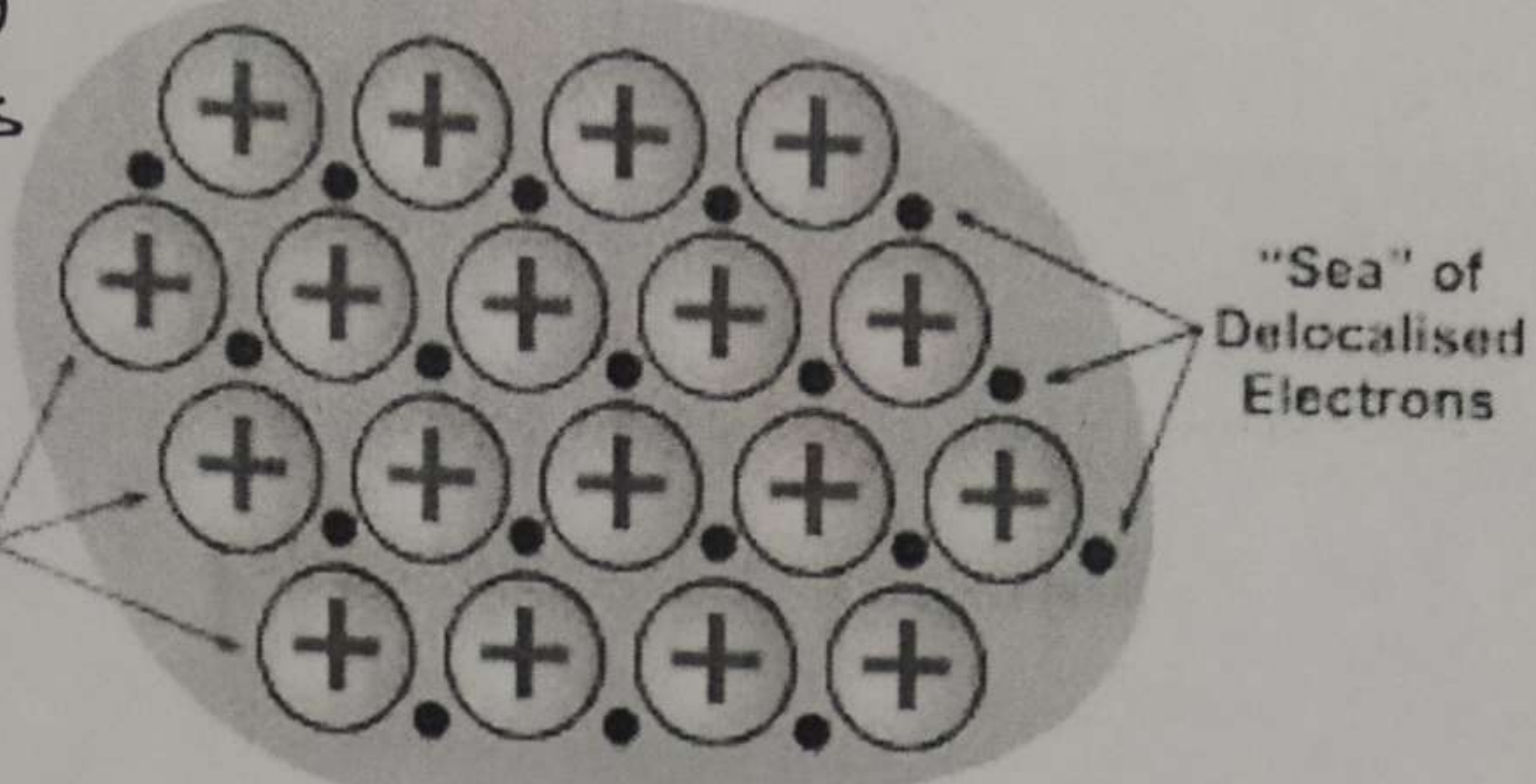


Space lattice of sodium chloride crystal. Each sodium ion is octahedrally surrounded by six chloride ions and each chloride ion is octahedrally surrounded by six sodium ions.

- **Ionic bond:** NaCl, CsCl, ZnS
- **High melting point**
- **Hard and brittle** → the material have alow resistance to impact.

Metallic Crystals

* ال metal تعتبر neutral لكن usually بنقدر نشوفها كـ grid of metal cations لأنه ال valance electron تبعها completely delocalized ما بتخص ذرة بعينها فالإلكترونات بتتحرك بحرية وهذا الإشي بخلي ال atoms يتجاذبوا و يتقربوا من بعض من خلال التجاذب بين ال nuclei وال electrons.



single metal

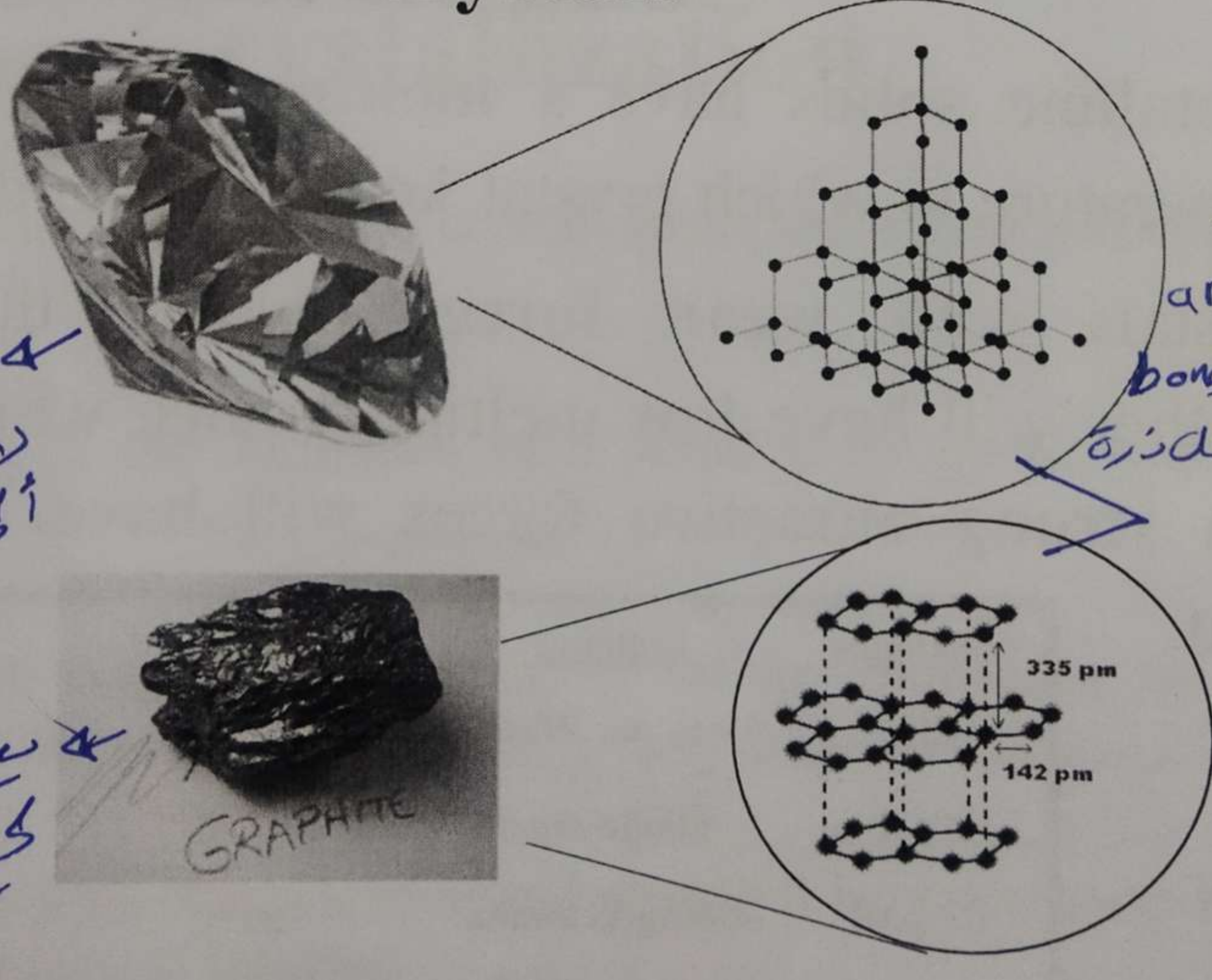
- **Fe, Cu, Zn**
- **Metallic bonds**
  - Electrons are not bonded to any particular atom and are free to move about in the solid
- Good conductors (موصلات ممتازة للكهرباء)
- Hard
- deformable and ductile

* ال metal مش brittle زي الأملاح يلي بتكون فيها ال ions.

deformable → * can be shaped by physical force. (زي لما بنطرق الحديد و بنشكله مثلا).

ductile → can be shaped by stretching. (مثلا بنقدر نعمل منها أسلاك زي أسلاك النحاس).

Covalent crystals



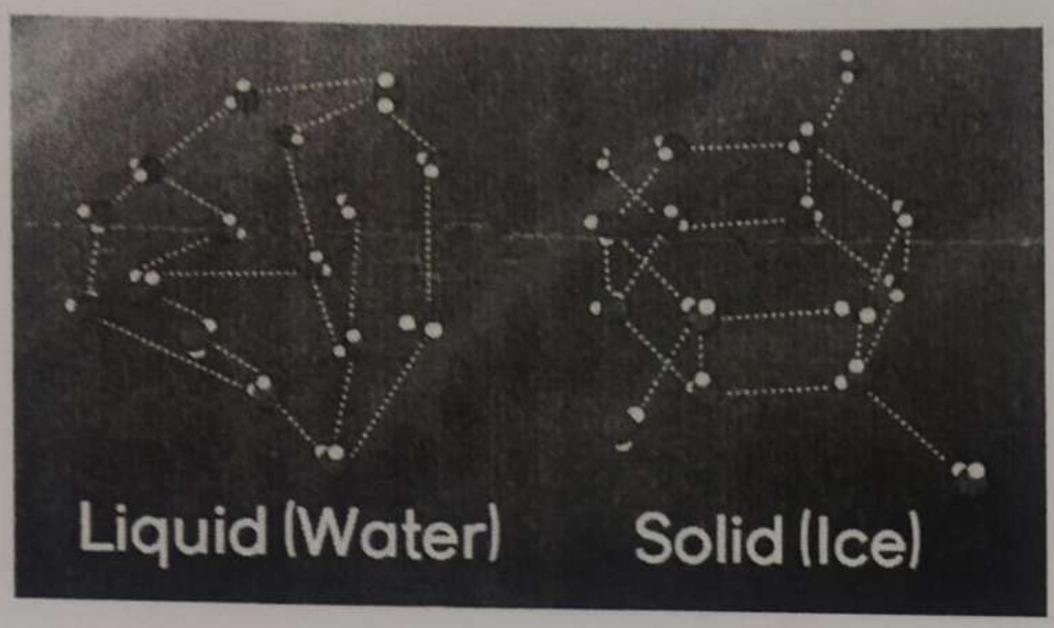
* لكن هون أقوى بكثير لأنه عدد ال covalent bonds أكبر.

* بينما هون ال interaction كثير ضعيف

* الفرق هو ال arrangment وعدد ال bonds يلي عاملها كل ذرة كاربون.

- Diamond, quartz, graphite
- Covalent bonds
- Very hard and brittle

Molecular crystals



The structure of solid benzene

- Molecules not atoms
- Hydrogen and Van der Waals bonds
- Low melting point, soft

Solid state

- Crystalline solids have a **melting point** which is the temperature at which crystal lattice breaks down.
- Crystals with **weak forces** holding the molecules together will have **low** melting points, whereas crystals with **strong** attractive forces will have **high** melting point.

Substance	Bonding	MP
CH_4	van der Waal's	-182°C
CH_3F	dipole-dipole	-141°C
CH_3OH	hydrogen bonds	-93°C
Al	metallic	660°C
AlF_3	ionic	1291°C
C	covalent	3550°C

Crystallization

- Crystals are produced by inducing a change from the liquid or gas state to the solid state by either:

Crystallization from melt

- Cooling of a molten sample to below its melting point.

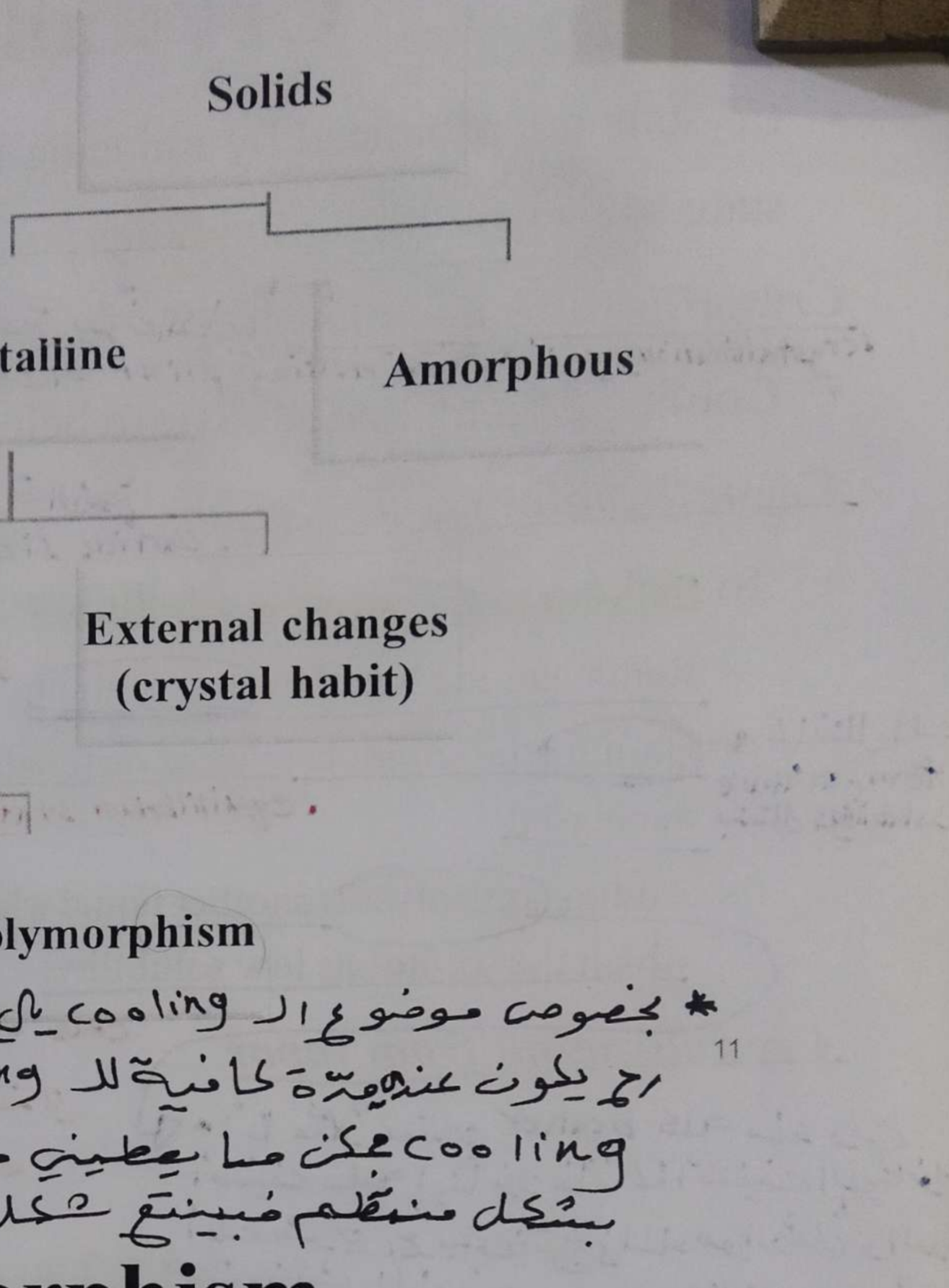
Crystallization from solution

- To make a supersaturated solution by:
  - Removing the liquid by evaporation
  - Cooling the solution, as most materials become less soluble as temperature is decreased
  - Adding antisolvent (another liquid which will mix with the solution, but in which the solute has low solubility)

Crystallization from vapor

Crystallization

- The processes by which a crystal forms are called *nucleation* and *growth*.
- Nucleation is the formation of a small mass on to which a crystal can grow.
- Growth is the addition of more solute molecules to the nucleation site.
- In order to achieve nucleation and growth it is necessary to have a **supersaturated solution**.



* بخصوص موضوع الـ cooling يلي تحت أنا مثلاً "لما أعمل slow cooling رح يكون عندي مدة كافية للـ packing ولكن لو كان عندي speed cooling ممكن هيك بعطيني فرصة أنه هذا الـ packing يصير بشكل منتظم فبينتج شكل ثاني.

Polymorphism

- The ability of material to exist in more than one **packing pattern** (leading to crystals with different **internal structure** = different **crystal lattice**) is termed polymorphism

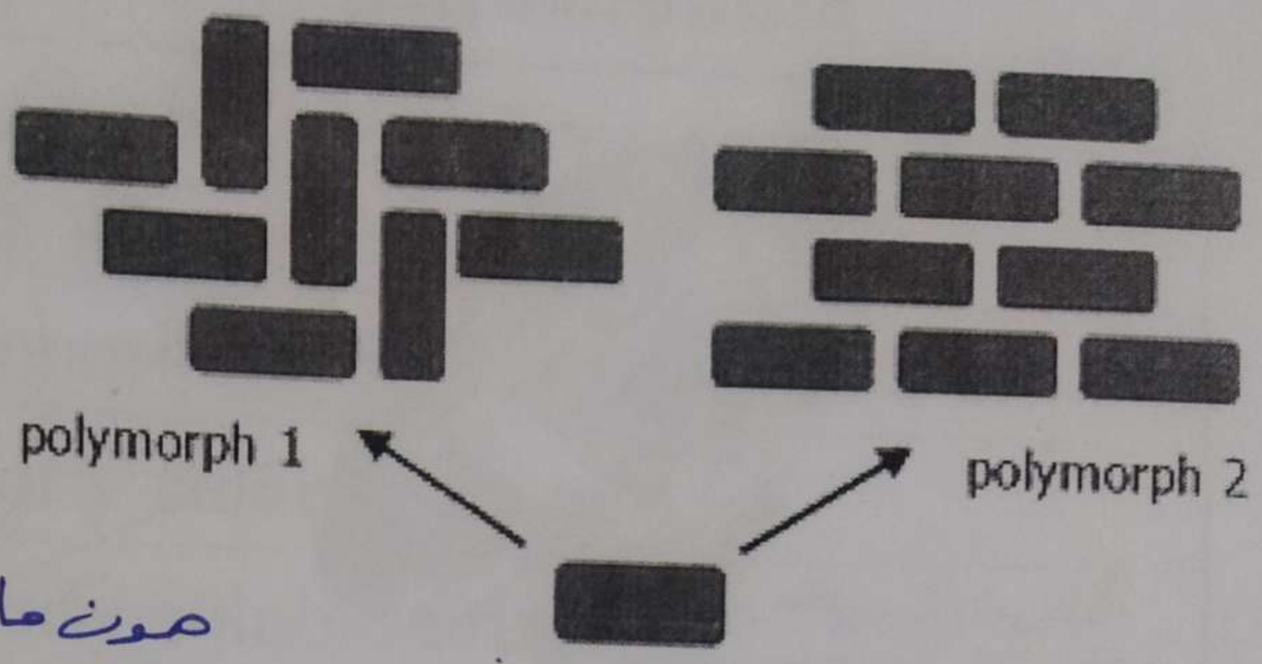
تنبيه

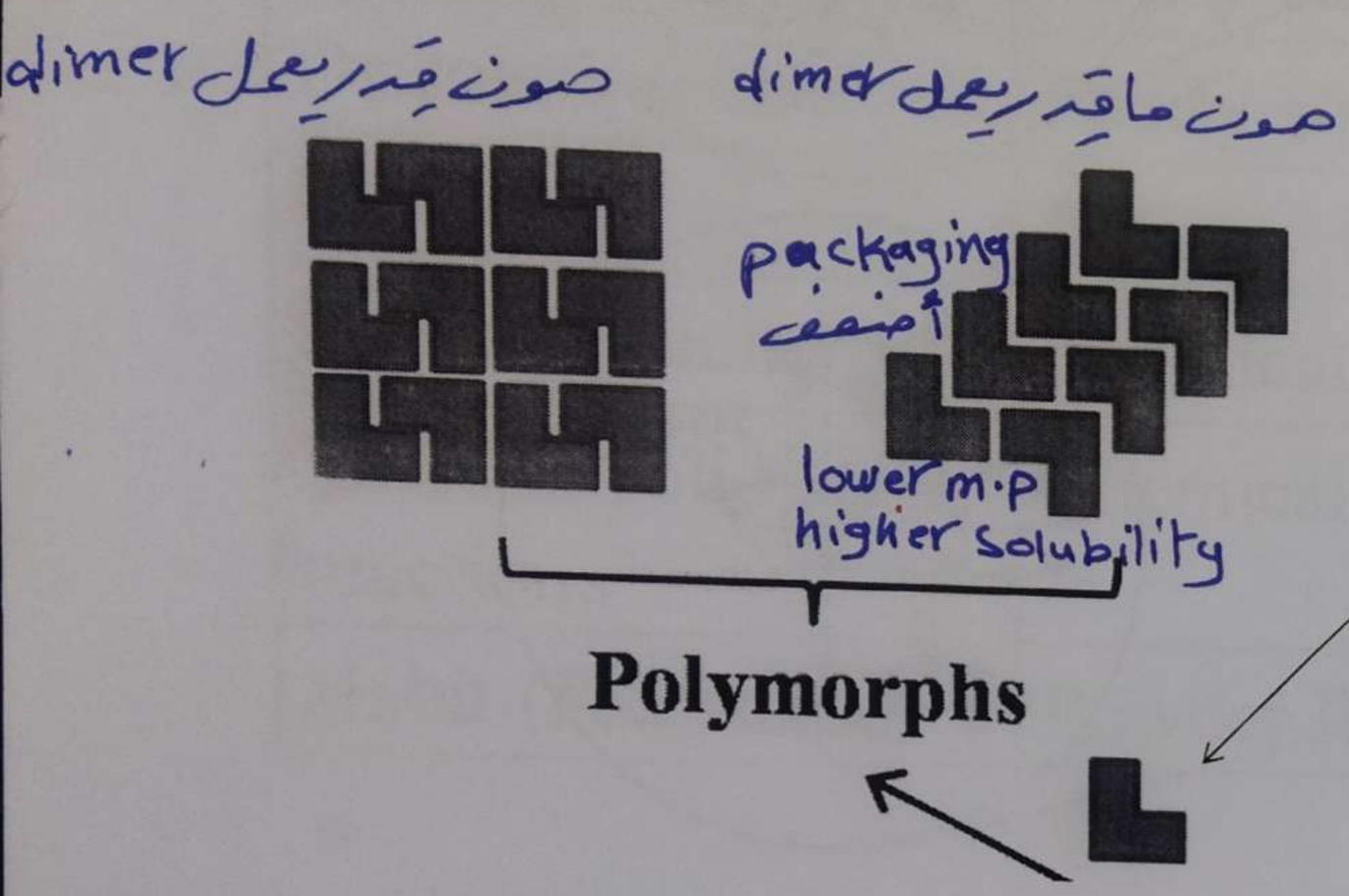
- Number of polymorphs ≥ 2

- If the crystallization conditions are changed, it is possible that the molecules may start to form crystals with a different packing pattern from that which occurred with the original conditions.

- The change in condition could be :
  - A different solvent → بعني زي لما كنا نعمل precipitation الـ antisolvent precipitation من الإيثانول عن الـ ... ما الأسيتون عن
  - Change in the stirring = mixing → rate الـ change وصار خلال العملية stirring لما أعمل internal structure الـ change عندي بيصير ممكن speed الـ
  - Different cooling conditions → cooling الـ technique, temperature, degree, rate الـ كل هذا بفرق
  - Different impurities in the crystallization liquid

* the same units but the order of pattern is different.





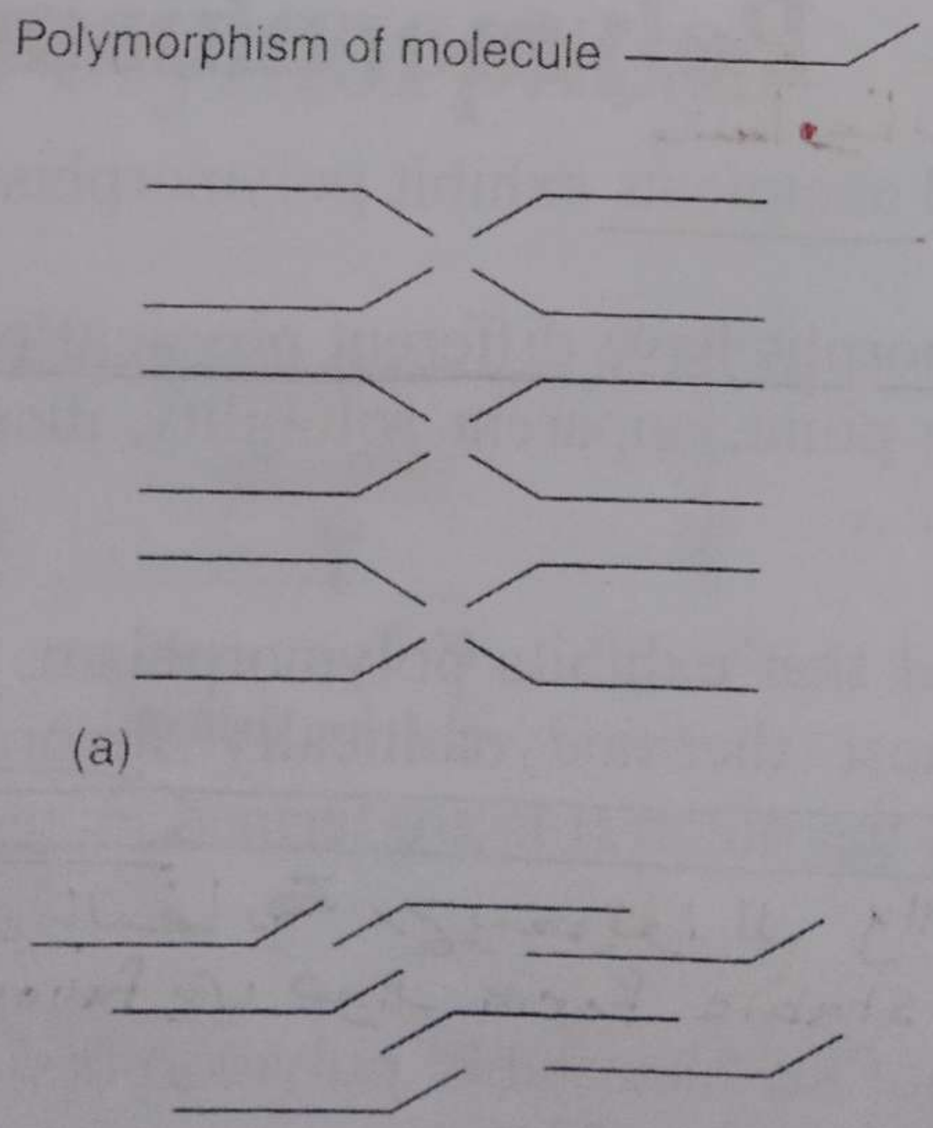
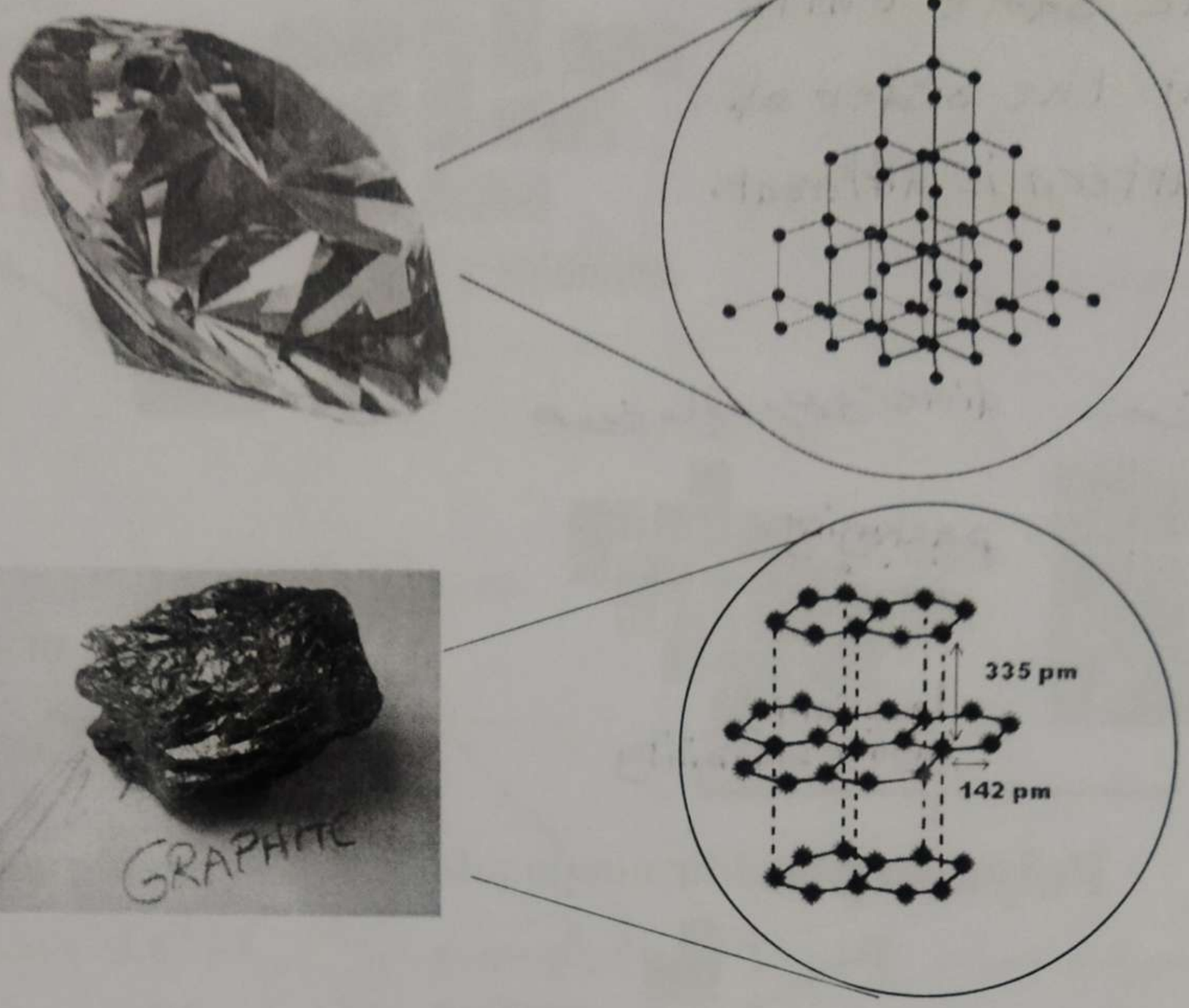


Fig. 9.1 Representation of two polymorphic forms of a crystal consisting of a molecule represented by a 'hockey-stick' shape.

Covalent bonds



Polymorphism

متساوعات

- Many drugs and excipients exhibit polymorphism.

- Different polymorphs have different physical properties such as: true density, melting point, apparent solubility, dissolution rate, hardness, hygroscopicity ....

- For a compound that exhibits polymorphism, only one of the forms will be the most thermodynamically favorable (stable) at room temperature and the other(s) is/are termed metastable.

لهيك بالنهاية رح يتحولوا لل thermodynamically favorable يعني stable form هوا

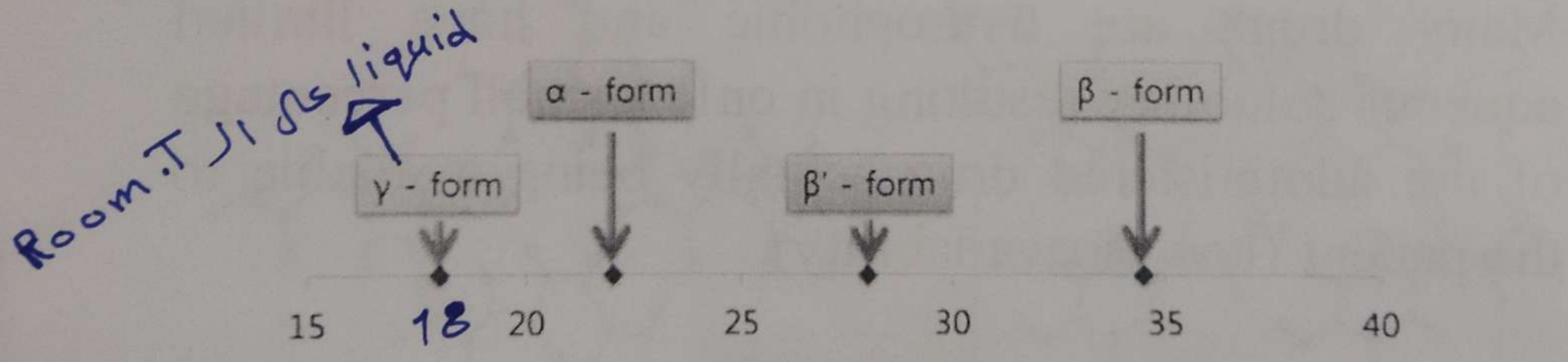
- Transformation of the metastable polymorph(s) to the stable one may occur and may be catalyzed by:
  - Energy (heating, milling)
  - Presence of solvent

صنوف كتير مصنعة بالعمليات التصنيعية

Physical properties of pharmaceutical significance that may be affected by polymorphism

Physical property	Examples on pharmaceutical importance
Melting point	Suppository base (Theobroma oil)
Apparent solubility	Poorly soluble drugs
Dissolution rate	Poorly soluble drugs
Hardness	Milling, Tableting (paracetamol)
Hygroscopicity	Chemical stability
Rates of solid state reactions	Chemical stability
Habit (i.e., shape)	Powder flow, mixing

Polymorphism



- **Theobroma oil**
- Polymorphous natural fat
- γ-form→18°C (unstable)
- α-form→22°C (unstable)
- β'-form→28°C (unstable)
- β-form→34.5°C (Stable)→ used for stable suppositories

Polymorphism

- In general there will be the following correlation between the melting point of different polymorphs and their dissolution rate:

High melting point = strong lattice = hard to remove molecules = low dissolution rate (and vice versa)

- The stable form has the highest melting point → slowest dissolution.

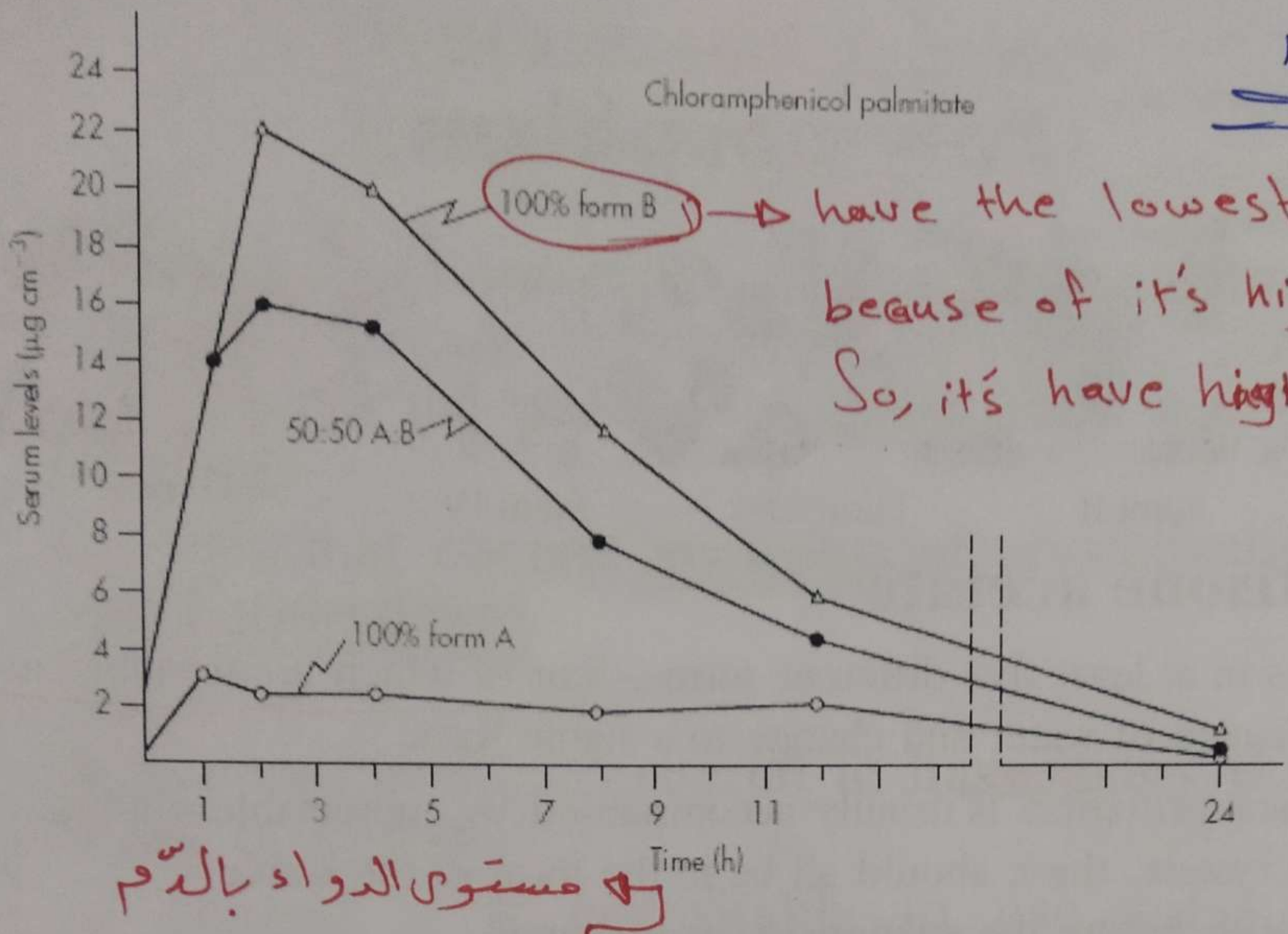
- When a metastable polymorphic form is dissolved it can give a greater amount of material in solution than the saturated solution. These supersaturated solutions will eventually return to the equilibrium solubility due to the precipitation of stable crystal form.

Polymorphism and bioavailability

- Many drugs are hydrophobic and have limited aqueous solubility resulting in only a small percentage of the administered drug actually being available to the patient (low bioavailability).

- Importance of polymorphism in bioavailability is related to different solubility and dissolution rate for different polymorphs, which might be significant (e.g. chloramphenicol palmitate).

- We must choose the polymorph that is chemicaly stable, physicaly stable and the same time have highest solubility and dissolution which can increase the bioavailability.



صعب جدًا

100% form B → have the lowest melting point because of it's high bioavailability So, it's have high solubility.

مستوى الدواء بالدّم

Comparison of serum levels (μ g cm-3) obtained with suspensions of chloramphenicol palmitate after oral administration of a dose equivalent to 1.5 g of chloramphenicol.

paracetamol ← ال

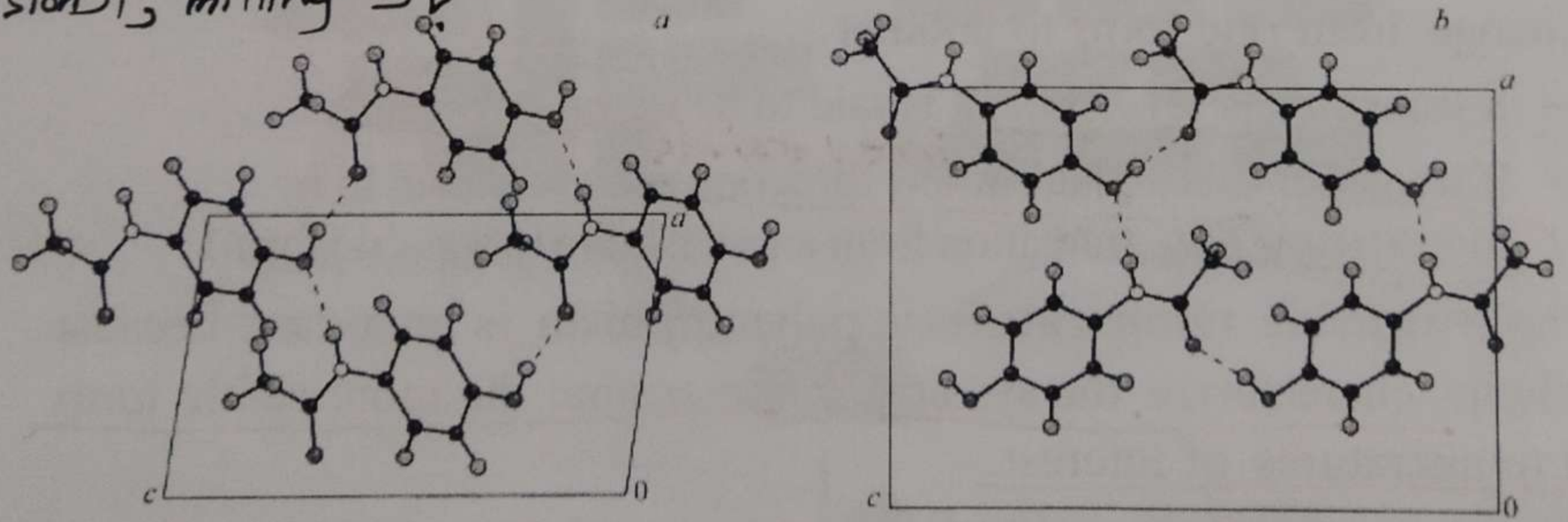
Polymorphism يأثر على

hardness وإذا أثر على ال

hardness ال ممكن يعمل مشاكل

compression وال milling بال

Polymorphism



Form I: Monoclinic

Form II: Orthorhombic

Paracetamol polymorphic forms

Form I is the most stable polymorph, but it is not appropriate for **direct compression into tablets** due to its weak compression properties.

Form II can readily undergo plastic deformation upon compaction. breakage ممكن ينكسر ويصير عنده

Polymorphism

Form I Form II Form III Form IV Form V

- **Cortisone acetate**
- It exists in at least five different forms, four of which are unstable in the presence of water and change to a stable form.
- This transformation is usually accompanied by appreciable **caking** of the crystals, these should all be in the form of the stable polymorph before the **suspension** is prepared.
- Heating, grinding under water, and suspension in water are all factors that affect the interconversion of the different cortisone acetate forms.
- Polymorphism is an important factor in **suspension technology**.

Transformation between polymorphic forms

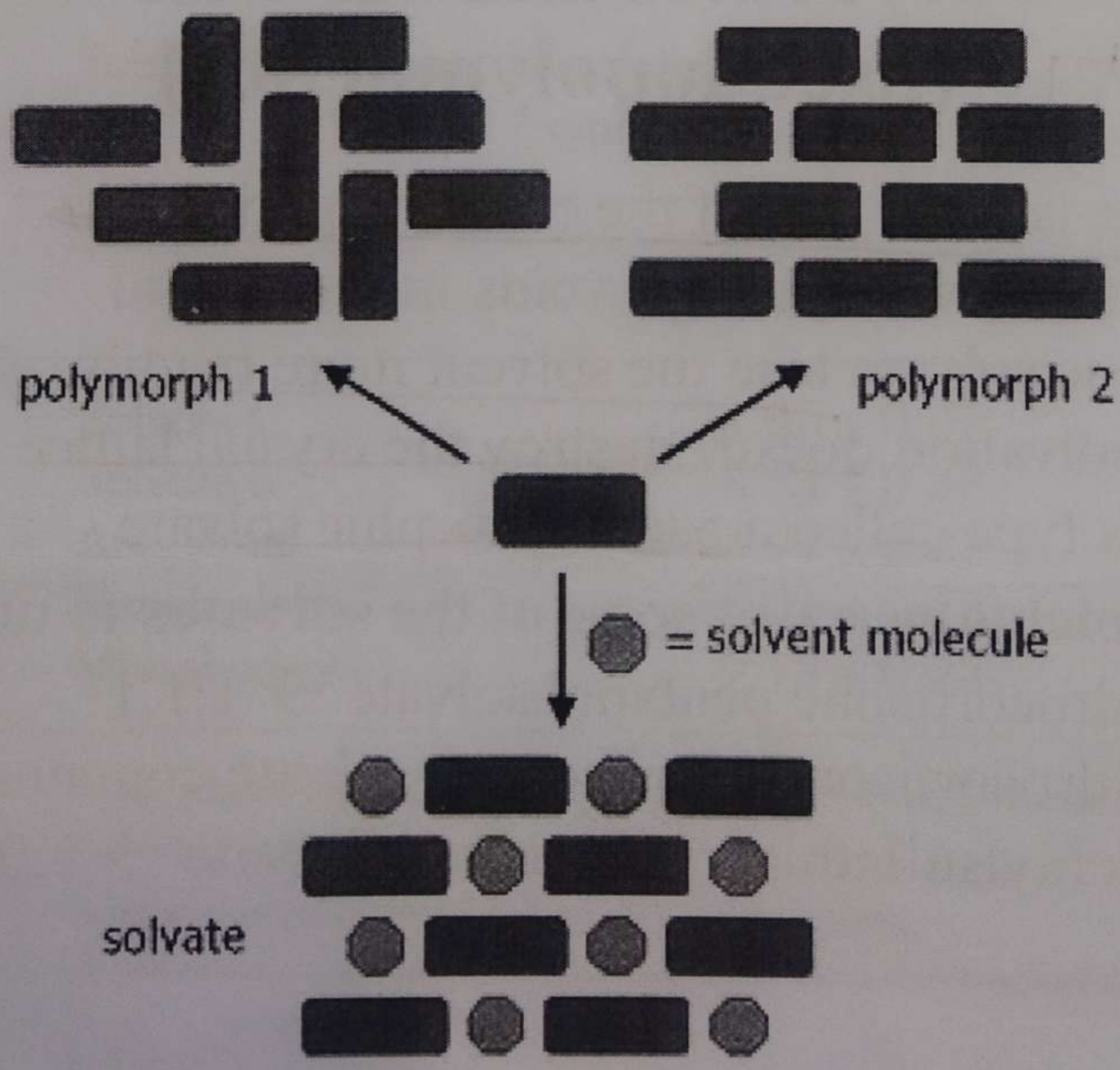
- Change from one form to another
  - If transition is reversible, it is said to be **enantiotropic.**
  - If transition takes place in one direction only, it is said to be **monotropic** (e.g. transition from a metastable to a stable form)
- The **transition temperature** in polymorphism is important because it helps characterize the system and determine the more stable form at temperatures of interest.
- Transformation leads to analytical issues and formulation problems
  - Caking of suspensions
  - Crystal growth as a result of transformation could cause grittness of creams
  - Producing unacceptable melting point characteristics (theobroma oil)
  - Differences in bioavailability (for poorly-water soluble drugs where bioavailability is based on the dissolution rate, the most stable polymorph usually has the lowest dissolution rate).

    If the free energy differences between the polymorphs are small there will be no significant differences in the extent of absorption

Hydrates and solvates (pseudopolymorphs)

- Entrapment of molecules of the solvent within the crystal lattice in a stoichiometric ratio leads to solvates. If the solvent is water they are termed hydrates.
- Cyrstals that contain no water of crystalization are called **anhydrate**.

- It is possible for a material to have many different levels of hydrate.
- In general it is undesirable to use solvates for pharmaceuticals because the presence of retained organic solvents would be regarded as unnecessary impurity in the product.



Hydrates and solvates (pseudopolymorphs)

- Crystal solvates exhibit a wide range of behavior between the interaction between the solvent and the crystal structure.
- Solvent may play a role in holding the crystals together
- It could be a part of a hydrogen bonded network within the crystal structure
  - These solvates are stable
  - It is difficult to remove the solvent
  - When the crystals lose the solvent they collapse and recrystallize in a new crystal form
  - They reassemble polymorphic solvate

Hydrates and solvates (pseudopolymorphs)

- Solvent is not a part of the crystal bonding
  - It merely occupies the voids in the crystal
  - These solvate lose the solvent more readily
  - Desolvation doesn't destroy the crystal lattice
  - This type called a pseudomorphic solvate

Hydrates and solvates (pseudopolymorphs)

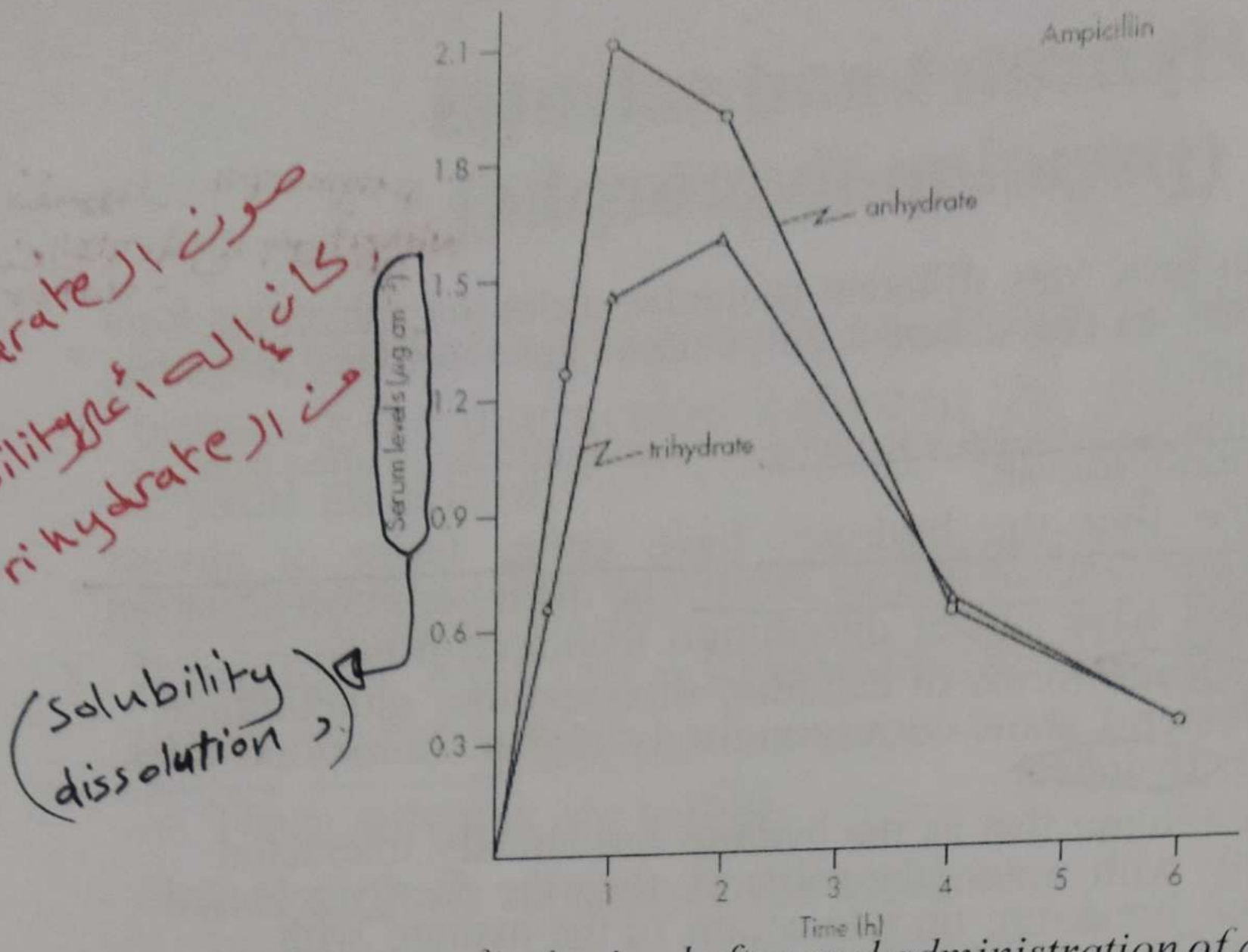
- Hydrates often have very different properties from the anhydrous form in the same way as two different polymorphs have different properties from each other.
  - Different melting points and solubilities sufficiently different to affect their pharmaceutical behaviour.
- It is possible that the hydrates have either faster or slower dissolution rate than anhydrous form. The most common situation is that hydrates have slower dissolution than anhydrous.
  - The anhydrous forms of caffeine, theophylline, glutethimide and cholesterol show correspondingly higher dissolution rates than their hydrates.
  - One can assume that as the hydrate has already interacted intimately with water (the solvent), then the energy released for crystal break-up, on interaction of the hydrate with solvent, is less than for the anhydrous material.
  - The nonaqueous solvates tend to be more soluble in water than the nonsolvates. The *n*-amyl alcohol solvate of fludrocortisone acetate is at least five times as soluble as the parent compound, while the ethyl acetate solvate is twice as soluble.

Table 1.4 Intrinsic dissolution rates of the crystal forms of oxyphenbutazone[a]

Sample	Intrinsic dissolution rate[b] ($\mu g\ min^{-1}\ cm^{-2}$)
Solvate C	21.05 ± 0.02
Solvate B	18.54 ± 0.47
Anhydrate	14.91 ± 0.47
Hemihydrate	17.01 ± 0.78
Monohydrate	9.13 ± 0.23

[a] Reproduced from A. P. Lotter and J. G. van der Walt, *J. Pharm. Sci.*, 77, 1047 (1988).

[b] Mean ± range of uncertainty of two determinations.



Serum levels ($\mu g\ cm^{-3}$) *obtained after oral administration of a suspension containing 250 mg ampicillin as* the anhydrate and as the trihydrate.

Differences in solubility and dissolution rate between solvates can lead to measurable differences in their bioavailabilities.

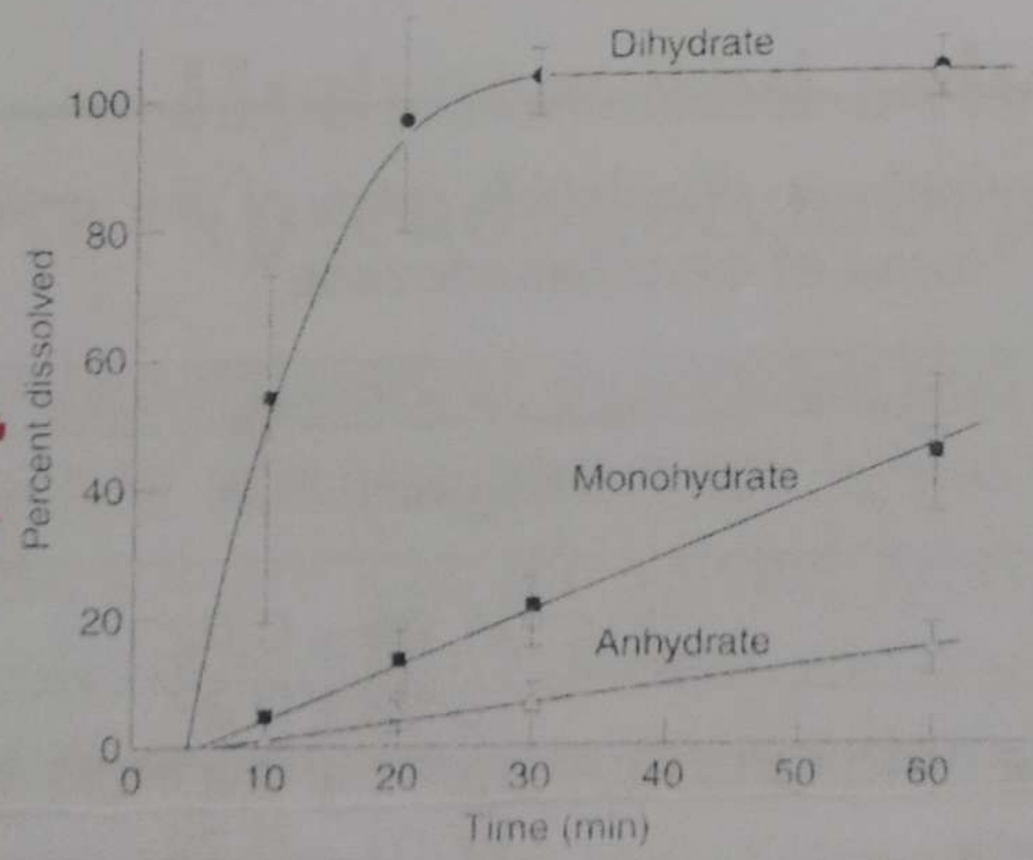


Fig. 9.5 The dissolution behaviour for erythromycin as anhydrate, monohydrate and dihydrate, showing a progressively faster dissolution rate as the level of hydrate is increased. (Reproduced from Allen et al 1978, with permission.)