نسأل الله أن يجعل هذا العمل متقبلًا
وان لا اكون قد قصرت في نقطة معينة
ولا يعني عدم وجود الخطأ

فسامحونا على اي خطأ ممكن يتواجد
ودعواتكم لنا✨

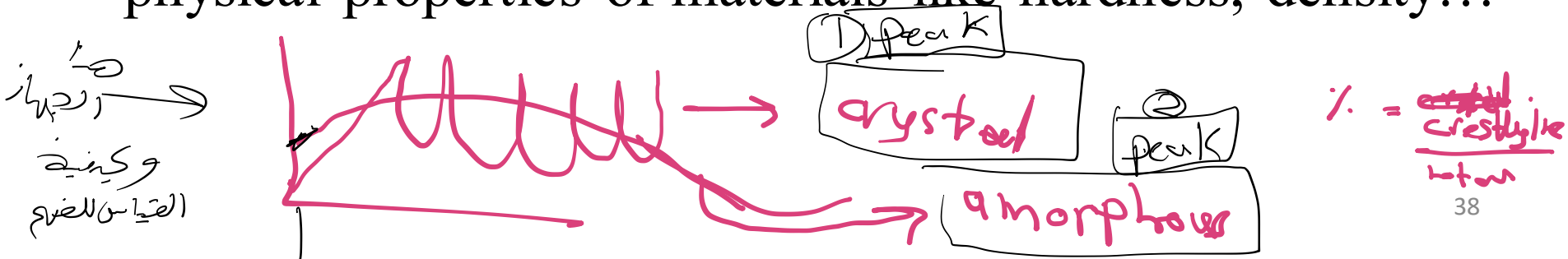
#Moayad Al Altamare

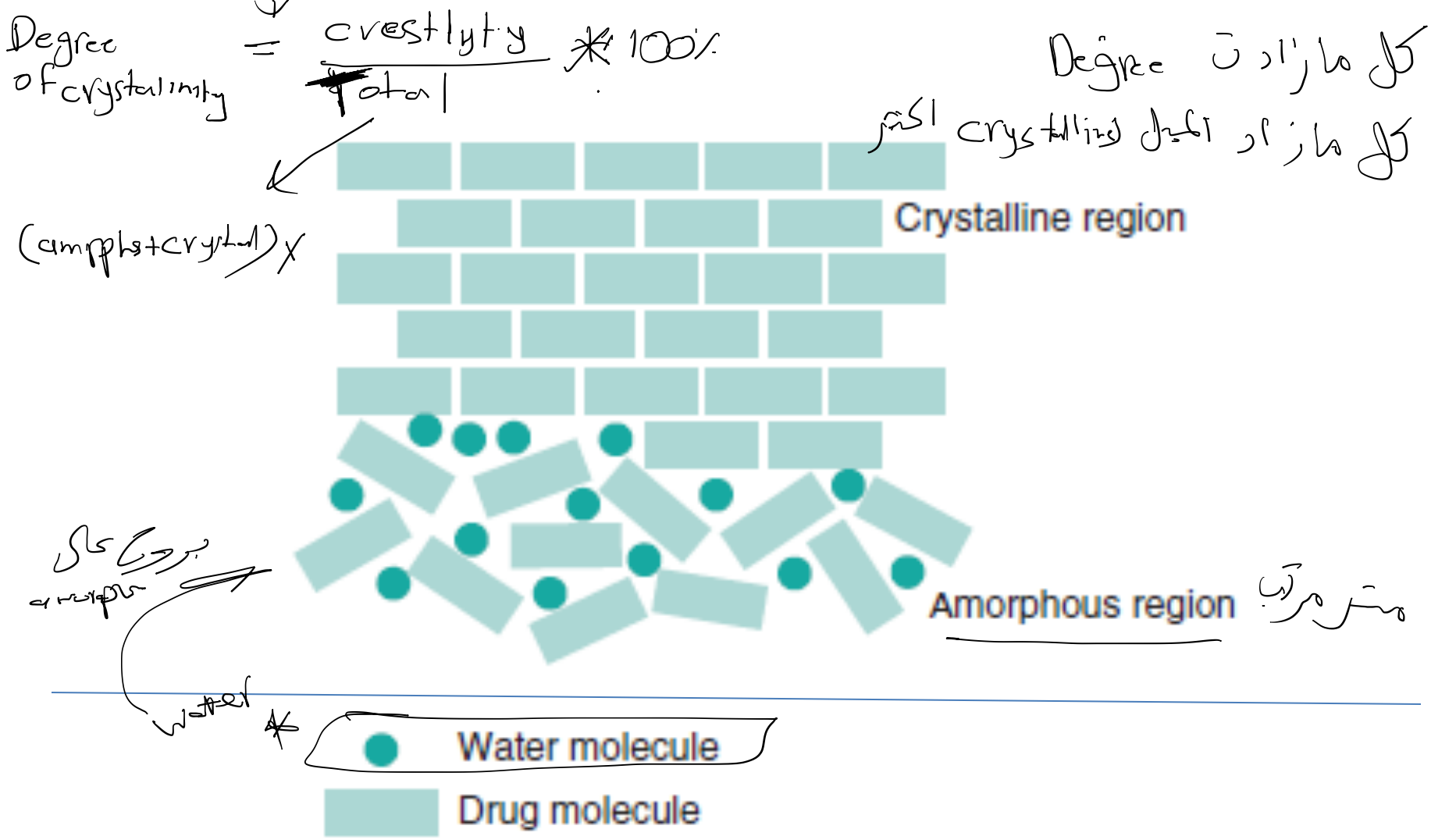
Degree of crystallinity

- The crystalline state characterized by perfectly ordered crystal lattice and amorphous state characterized by a disordered lattice represent two extremes and intermediate states are possible.

- The term ***degree of crystallinity*** is useful in attempts to quantify these intermediate states of lattice order

- The ***degree of crystallinity*** has a big influence on physical properties of materials like hardness, density…

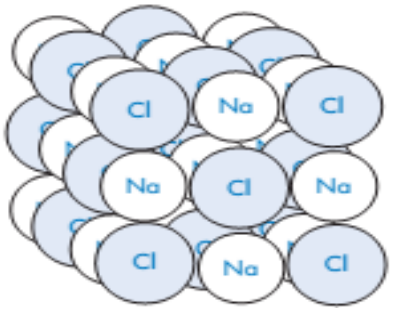


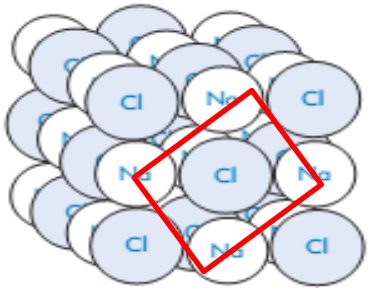


The disruption of a crystal giving the possibility for water vapor absorption in the amorphous region

Crystalline solids structure

- **Crystal structure**
- Crystals contain highly ordered arrays of molecules and atoms held together by noncovalent interactions.

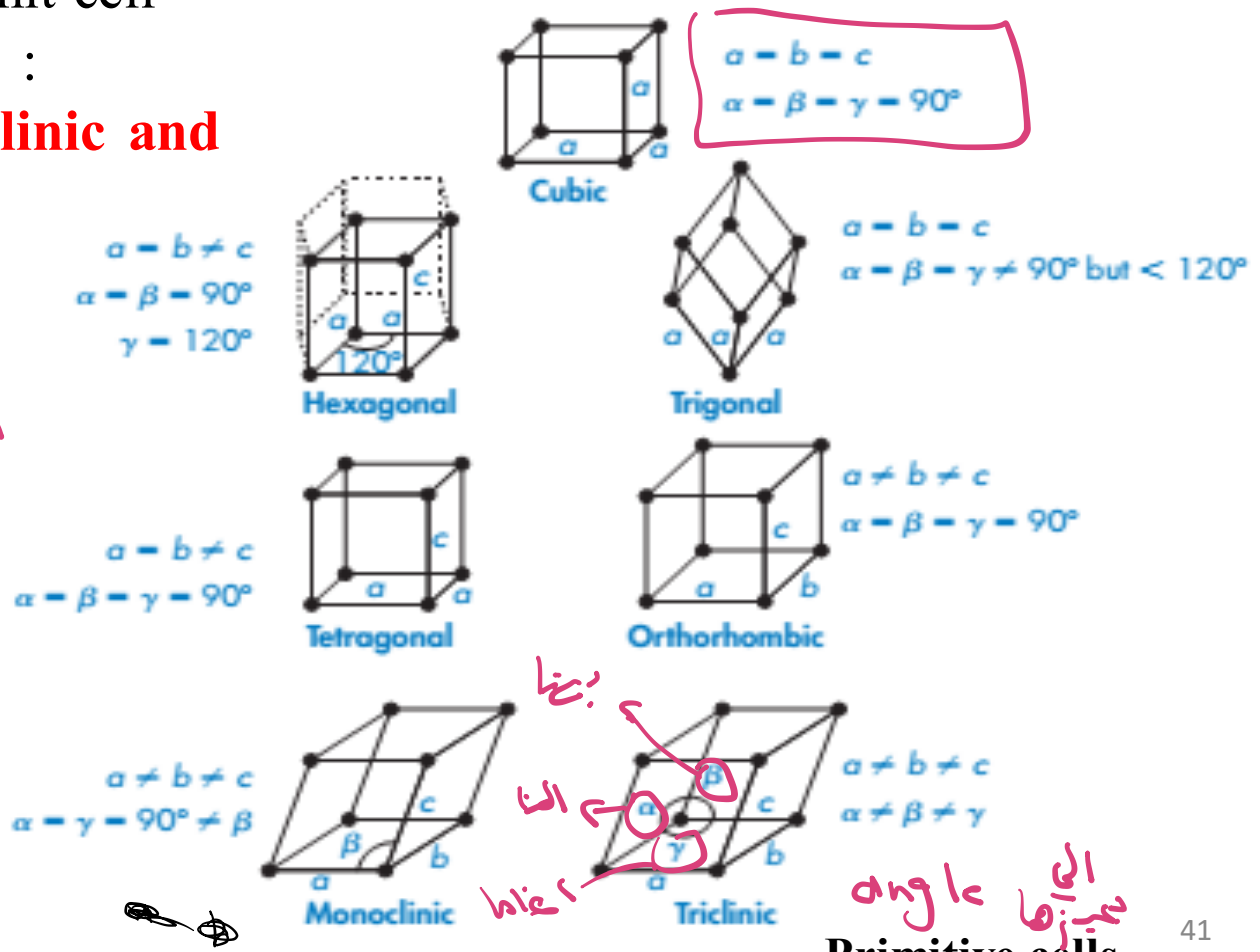




- You can draw a square on one side connecting the sodium ions. Similar squares could be drawn on all the sides to form a cubic repeating unit, which we call the **unit cell**.
- Within a specific crystal, each unit cell is the **same size** and contains the **same number** of molecules or ions **arranged** in the same way.
- It is usually most convenient to think of the atoms or molecules as points and the **crystal as a three-dimensional array** of these points, or a crystal lattice.

Crystal structure

- For all possible crystals there are **seven** basic or primitive unit cells, these depend on the lengths of the side and the angles as ***α*** (between sides *b* and *c*), ***β*** (between sides *a* and *c*), ***γ*** (between sides *a* and *b)*
  - Most common unit cell type in drugs are : **triclinic, monoclinic and orthorhombic.**

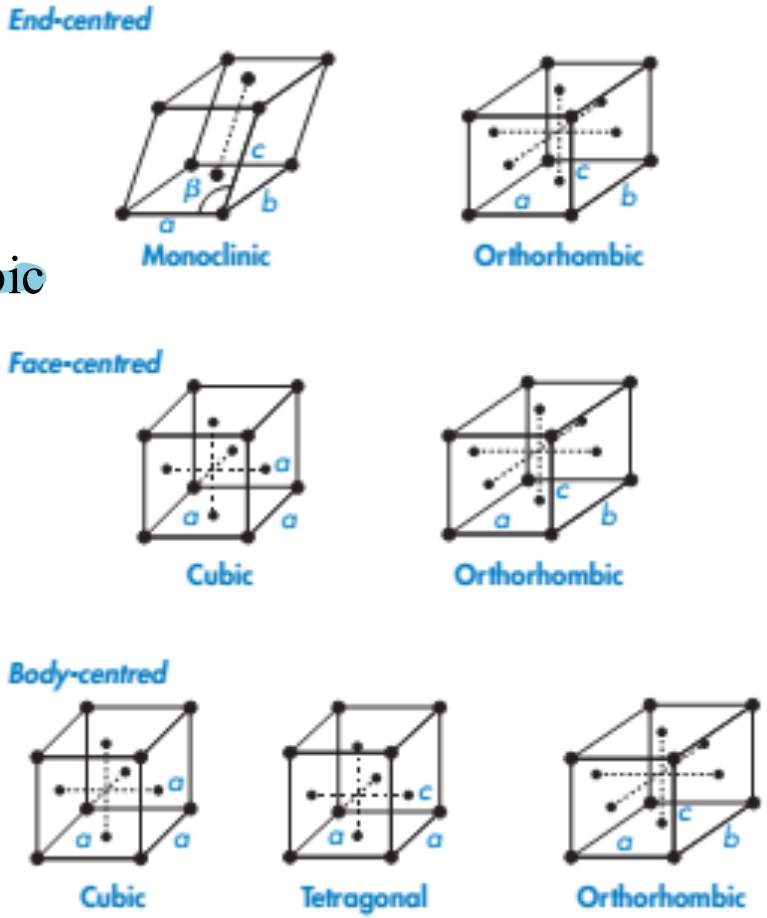


Primitive cells

Crystal structure

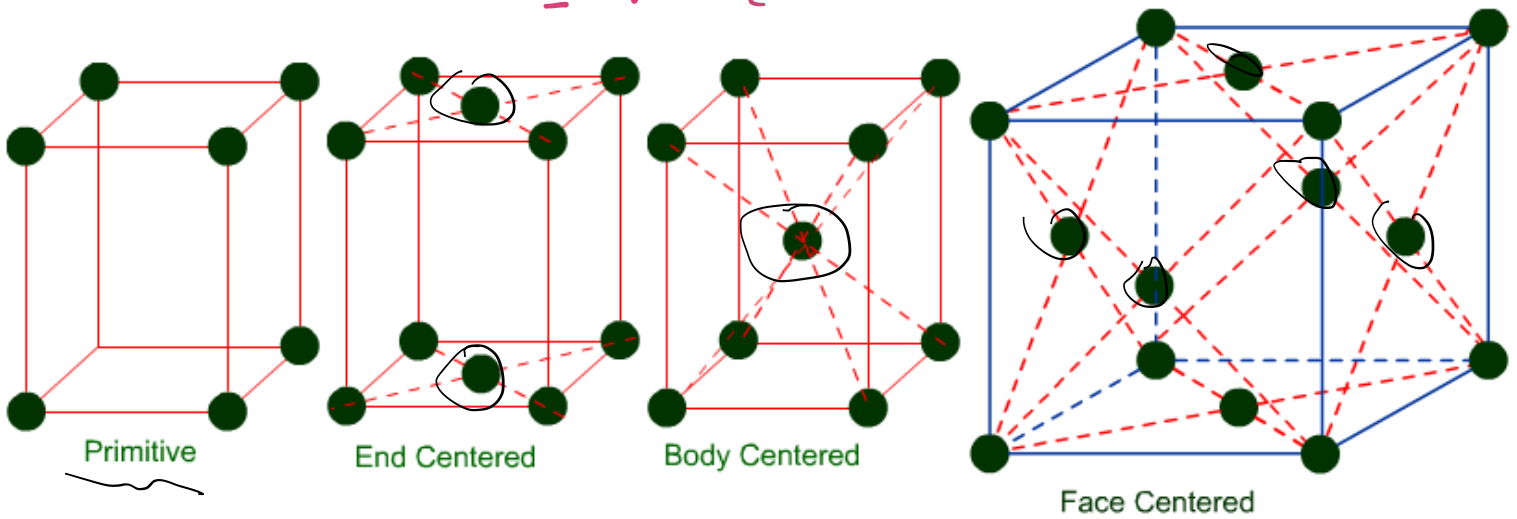
- Unit cells have atoms molecules only at each corner of the unit cell.
- It is possible to find unit cells with atoms molecules also at the centre of the top bottom faces (*end-centred*), at the centre very face (*face-centred*) or with a single atom in the centre of the cell (*body-centred*

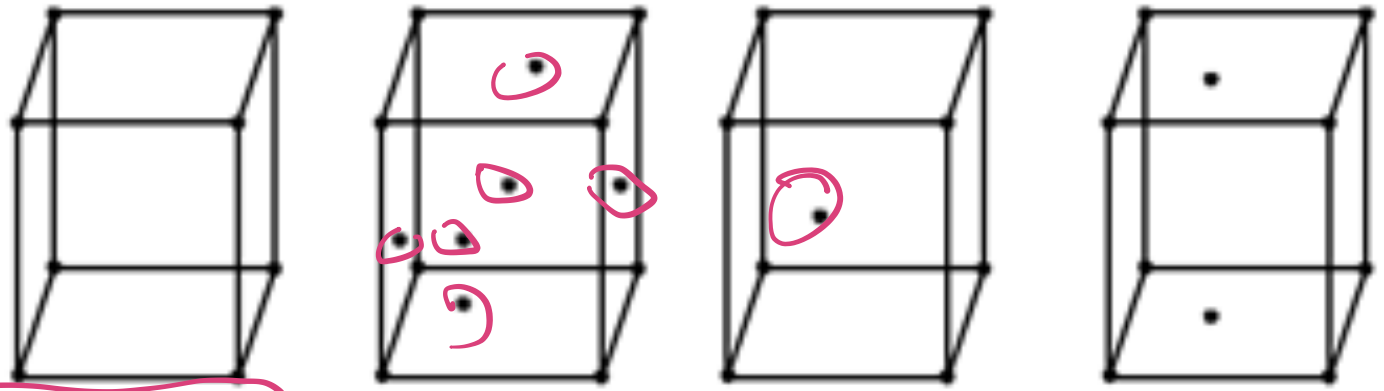
- These variations do not occur with very type of unit cell:
  - End-centred: monoclinic and orthorhombic
  - Face-centred: cubic and orthorhombic
  - Body-centred: cubic tetragonal and orthorhombic
- All together there are 14 types of unit cell
- These are called **Bravias lattices**



Centred cells

Illustration of the Bravias lattice





Primitive unit cell

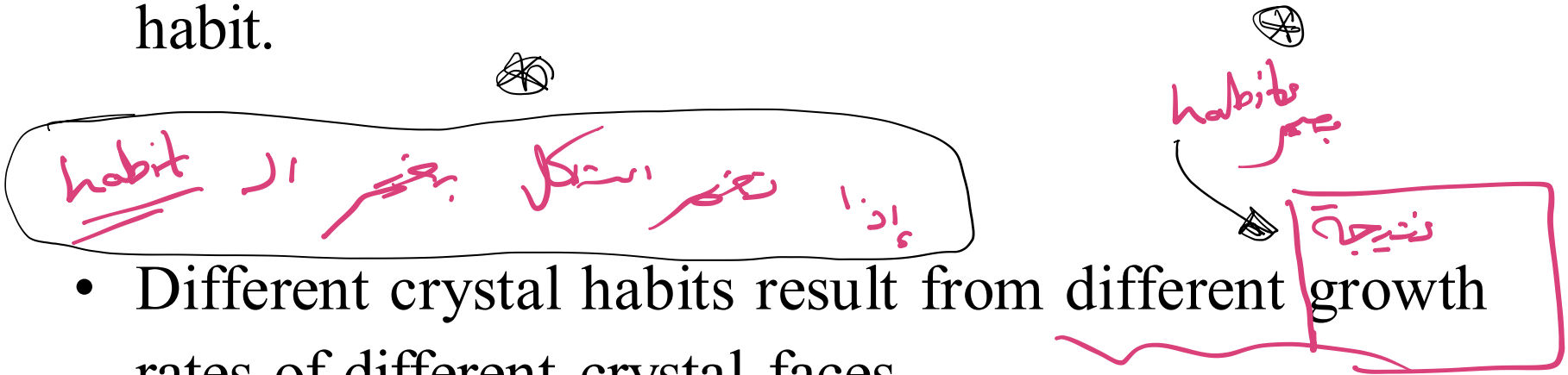
Face centred unit cell

Body centred unit cell

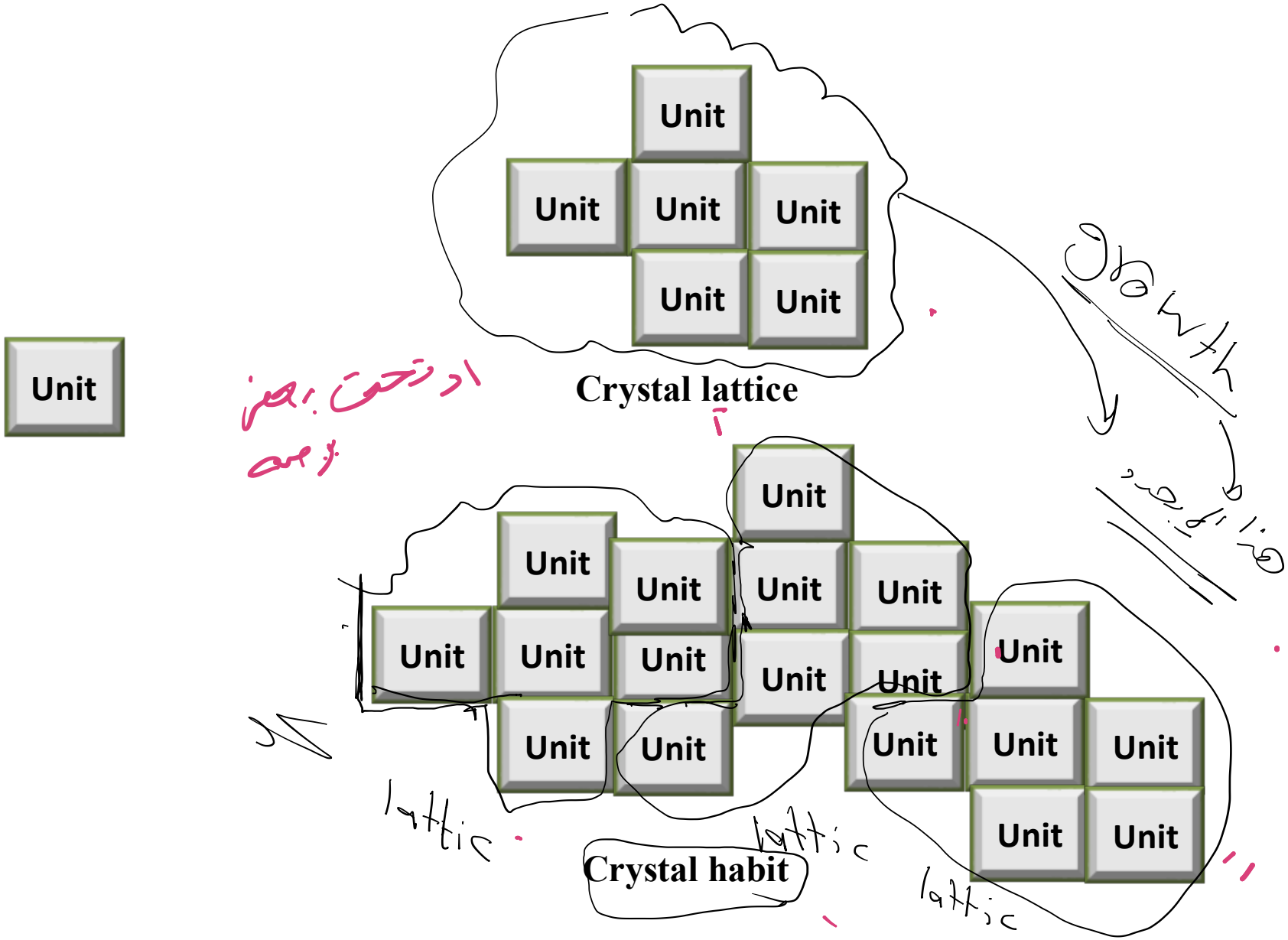
End centred unit cell

Crystal habit

- The **external shape** of crystal is termed crystal habit.



- Different crystal habits result from different growth rates of different crystal faces.
- The largest face is always the slowest growing.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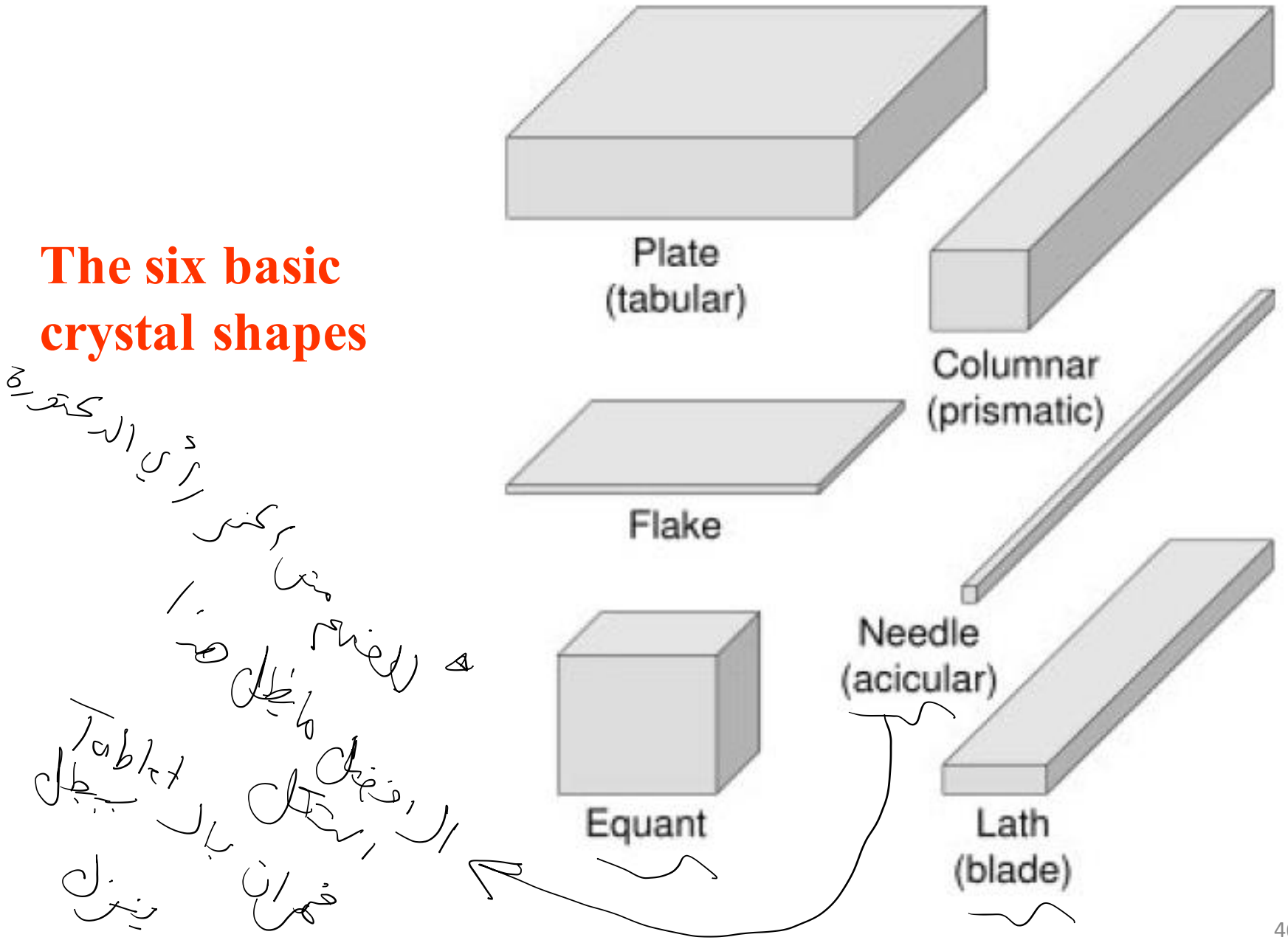
Crystal habit

The six basic crystal shapes



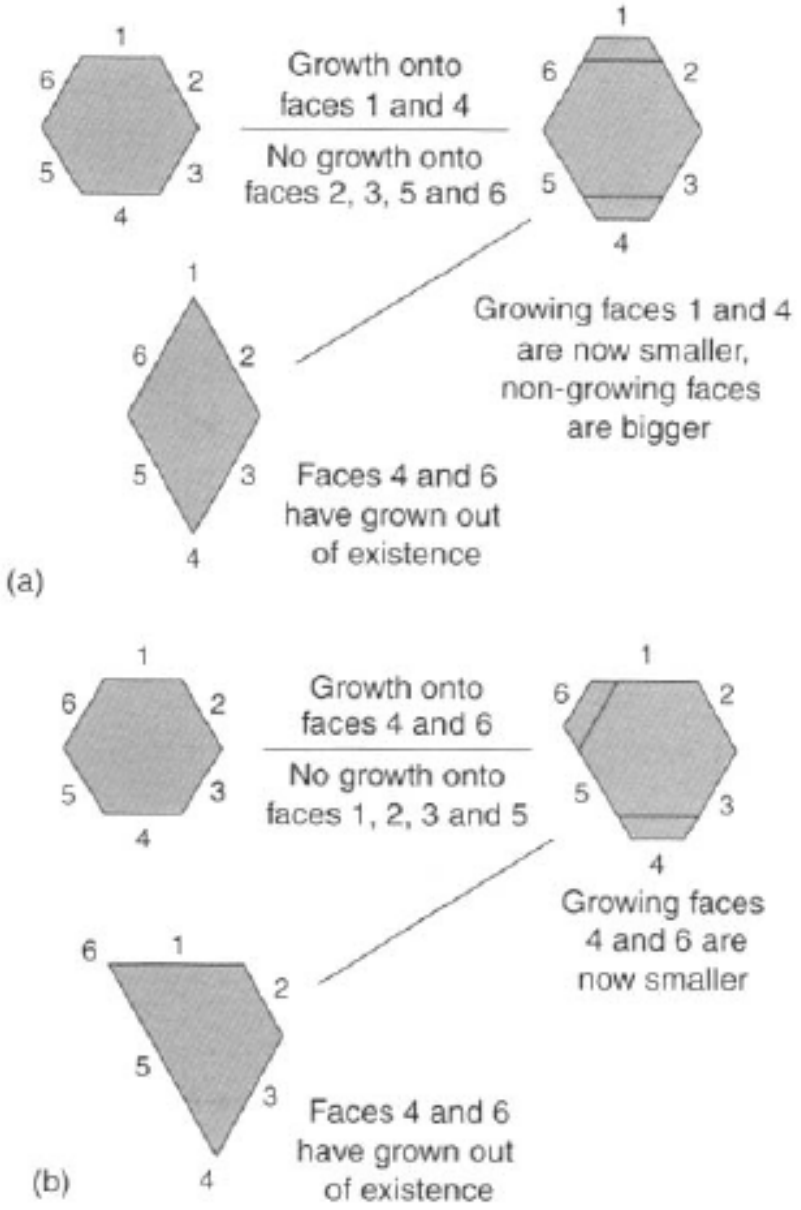


Fig. 9.10 (a) Demonstration of how growth on to faces 1 and 4 of a hexagonal crystal form result in the formation of a diamond. (b) Demonstration of how growth on to faces 4 and 6 of a hexagonal crystal result in the formation of a trapezium.

Crystal habit

- Changes in internal structure usually give different habits.

- However, it is also possible to change the external shape for the same crystal packing by changing the crystallization conditions.

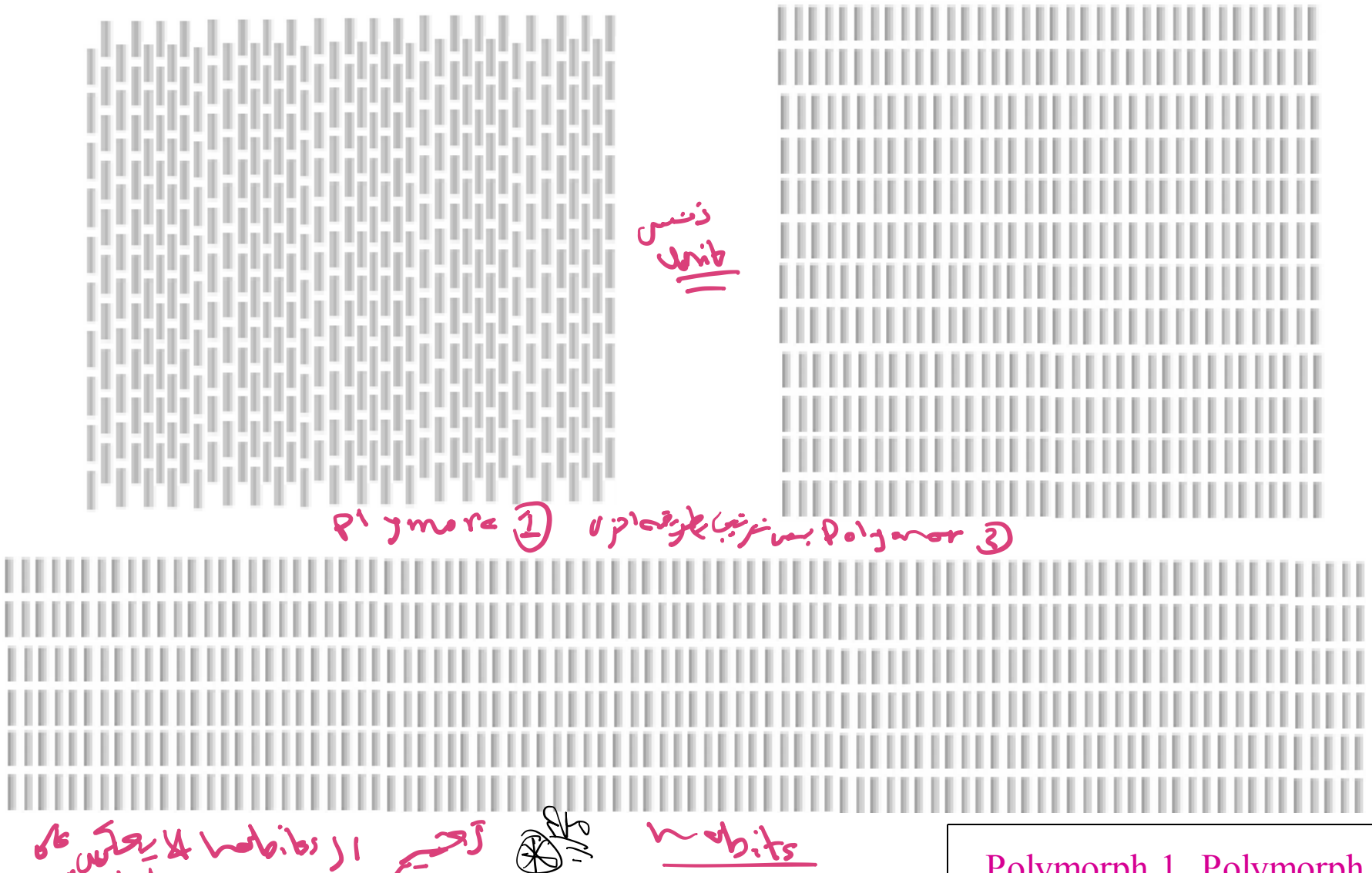
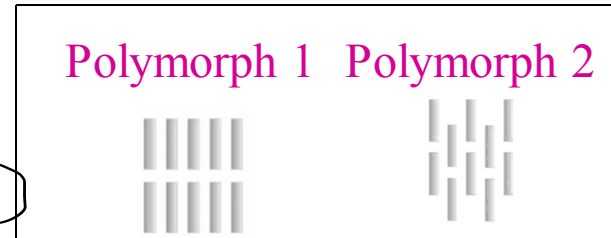
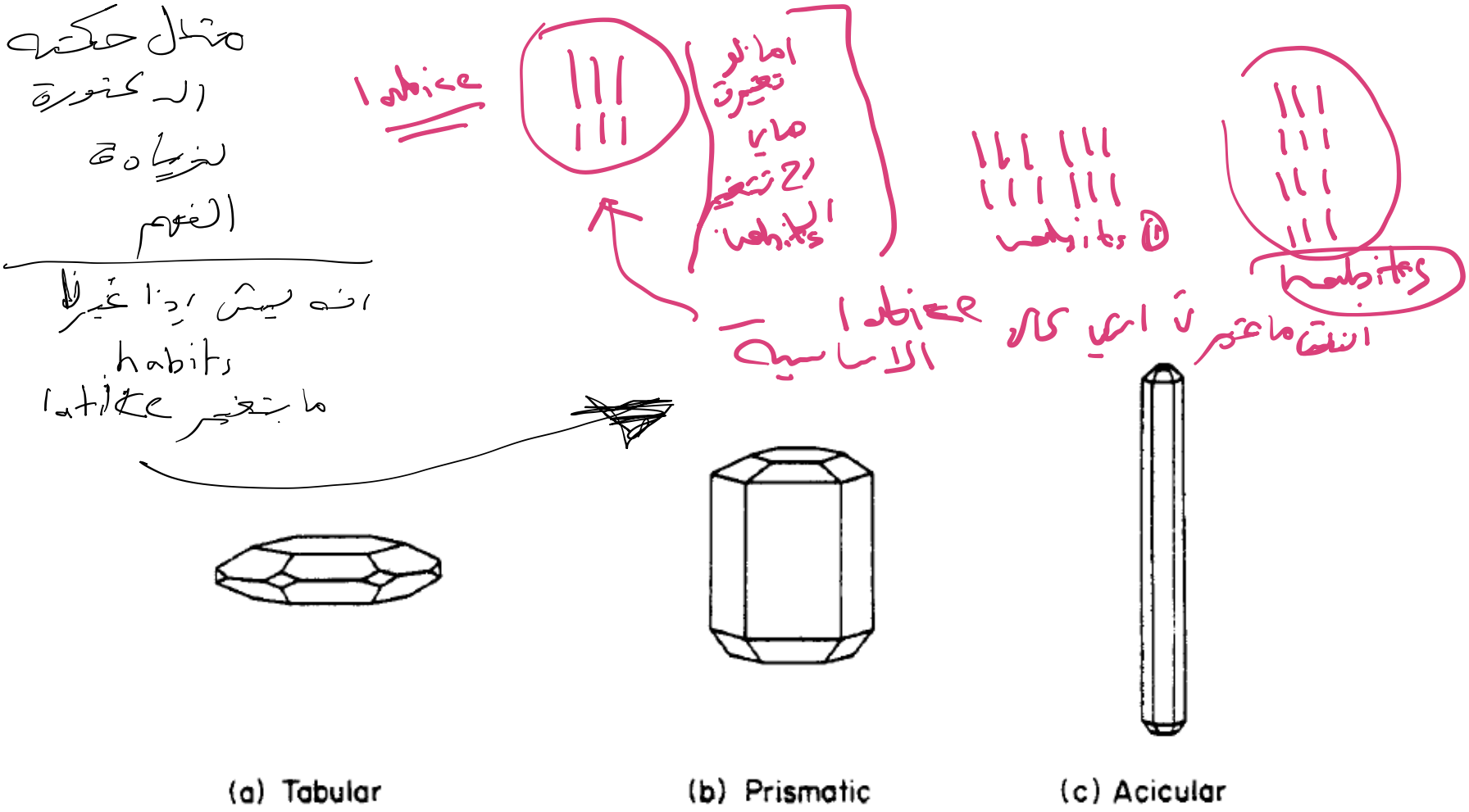


Diagram showing molecule packing effect on crystal external shape. Different external shape does not necessarily indicate different internal structure





Crystal habit illustrated on a hexagonal crystal

Crystal habit

- Crystal habit can alter the properties of drug and excipients such as:
  - Powder flow
  - Compression behavior
  - Specific surface area
  - Dissolution rate
  - Sedimentation and caking of suspension

- **Crystal engineering**: Crystal habits may be changed by manipulating the growth of different faces to obtain crystals with suitable properties.

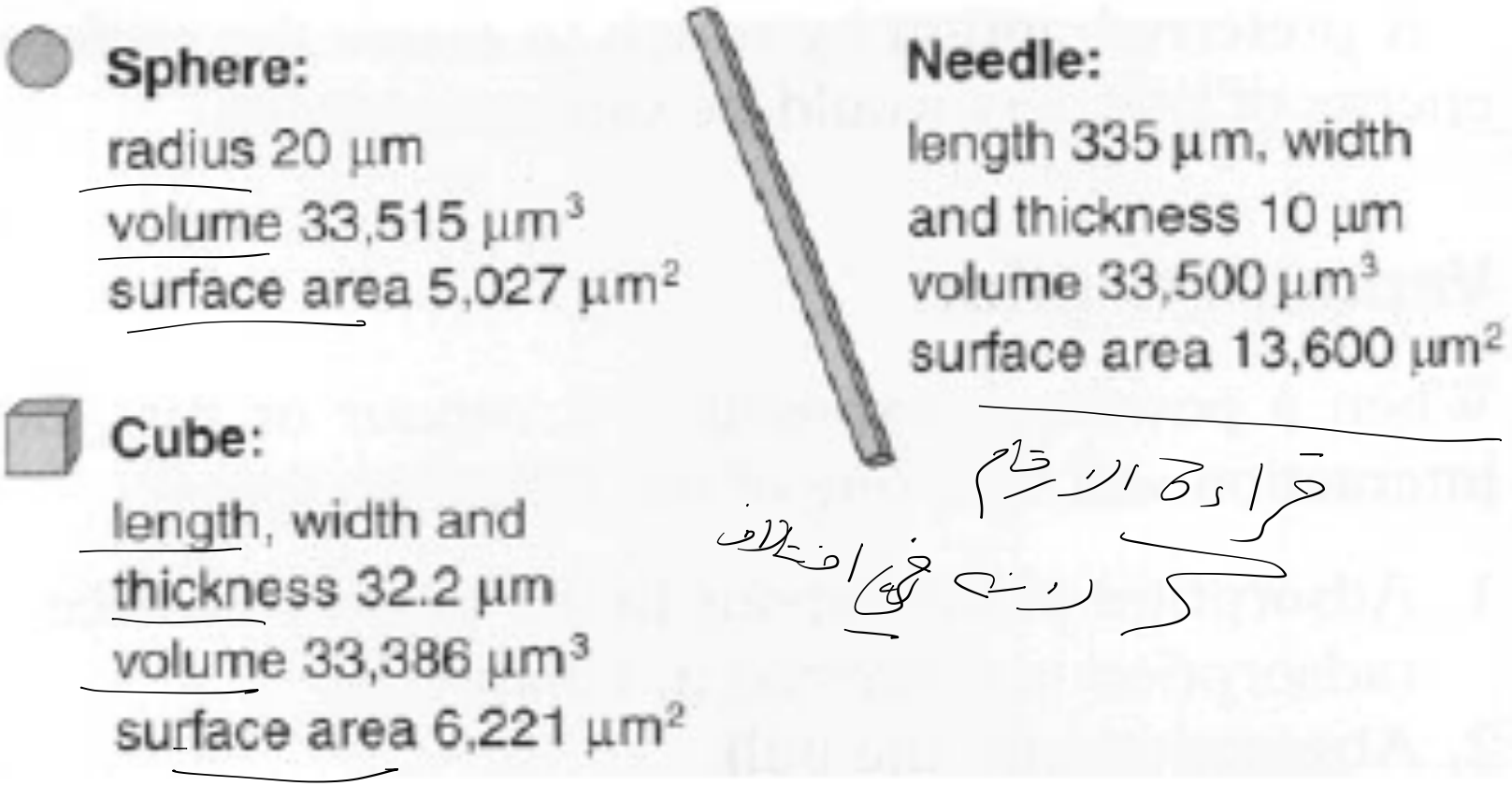


Fig. 9.11 The relative surface areas of a sphere, a cube and a needle that each have similar volumes of material.

Crystal habit

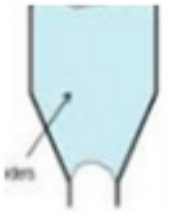
- What is the importance of the crystal habit of a drug?
  - In general, there may not be significant differences in the bioavailability of drugs with different crystal habits.
  - However, the crystal habit is of importance from a technological point of view.

- Plate-like crystals are easier to inject through a fine needle than needle-like crystals.

Crystal habit

- The crystal habit can also influence the ease of compression of a tablet and the flow properties of the drug in the solid state.

The plate-like crystals of tolbutamide cause powder bridging in the hopper of the tablet machine and also capping problems during tableting. Neither of these problems occurs with tolbutamide in other crystal habits.



Crystal habit

- Why we get different crystal habits for the same material?
  - The habits acquired depend on the conditions of crystallization, such as,
    - Solvent used
    - Temperature
    - The concentration and presence of impurities.
  - For example: Ibuprofen
    - If crystallized from hexane ⇒ elongated needle-like crystals ⇒ poor flow properties.
    - If crystallized from methanol ⇒ equidimensional crystals ⇒ better flow properties and compaction characteristics, making them more suitable for tableting.

Importance of particle size

Particle size influence

- Drug dissolution
  - Important for poorly-soluble drugs (ex. griseofulvin, tolbutamide, spironolactone, indomethacin and nifidipine)

Dissolution of solid drugs

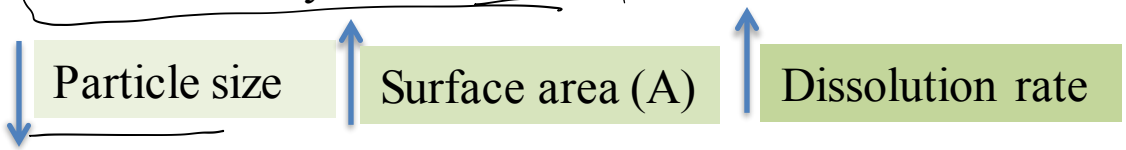
- Noyes-Whitney equation (1897)

$$\frac{dW}{dt} = \frac{DA}{\delta}(C_s - C)$$

- dw/dt: the rate of increase amount of the material in solution dissolving from the solid.
- Cs: the saturation solubility of the drug in solution in the diffusion layer.
- C: the concentration of the drug in the bulk solution.
- A: the surface area of the solid particles exposed to the solvent.
- δ: the thickness of the diffusion layer.
- D: the diffusion coefficient of the dissolved solute.

Dissolution of solid drugs

- The relevance of polymorphism and solid-state properties to this equation lies in the fact that *A* is determined by particle size.
  - Particle size reduction, if it leads to a change in polymorph, results in a change in *C*s, and if dissolution is the rate limiting step in absorption then bioavailability is affected.



- If dissolution is the rate-limiting step in absorption then bioavailability is affected.

Importance of particle size

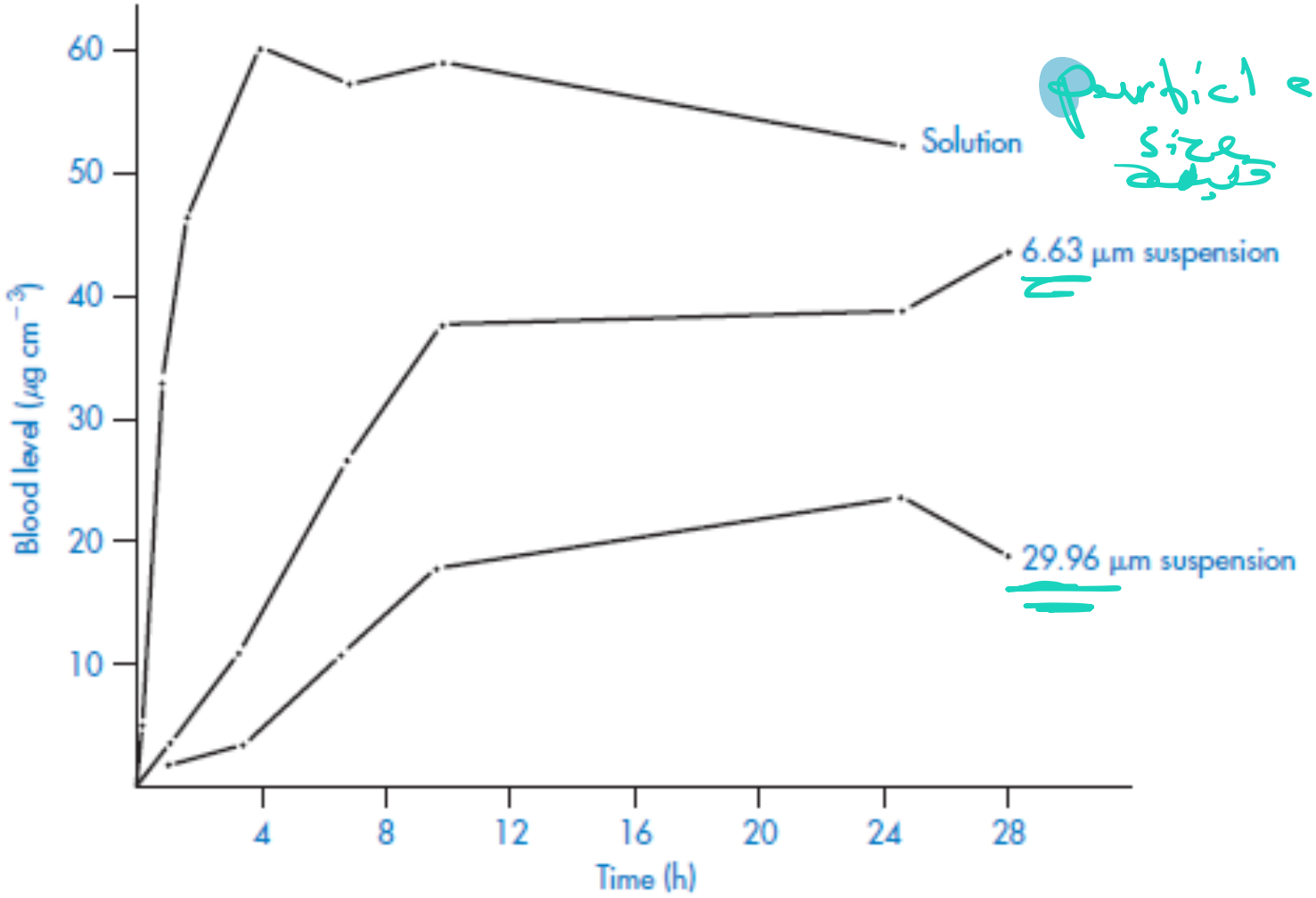
Particle size influence

- Mixing of powders
  - Content uniformity for potent drugs
  - segregation
- Hygroscopicity

Importance of particle size

Particle size influence

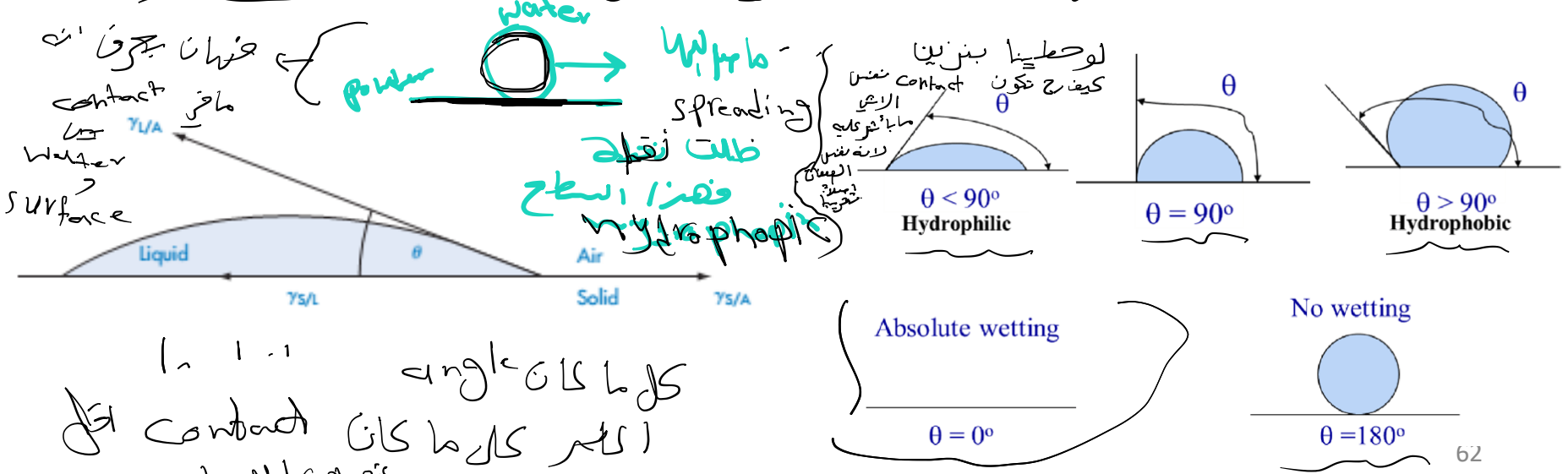
- The properties and behavior of various dosage forms:
  - suspensions: sedimentation rate, texture, taste, rheology
  - parenteral suspensions: syringeability, injectability and sustained release.
  - ophthalmic suspensions: irritation of the eye surface (small particle size is used)
  - Dry powder inhalers: The position and retention of particles in the bronchopulmonary tract
  - topical formulation: grittiness (powder must be impalpable)



Blood levels ($\mu g\ cm^{-3}$) of phenobarbital versus time after intramuscular injection of three dosage forms.

Wetting of powders

- Penetration of water into tablets or into granules precedes dissolution.
- The wettability of the powders determines the contact of solvent (water) with the particulate mass.
- The wettability is measured by the contact angle (θ) of the substance with water.
- The lower the contact angle, the better wettability.



Wetting of powders

- The measurement of the contact angle gives an indication of the nature of the surface.
- Hydrophobic drugs have dual problems: they are **not readily wetted**, and even when wetted they **have low solubility**. But **absorption** across lipid membranes is facilitated.
- **Powders**:
- Slightly hydrophobic
  - Indomethacin and stearic acid
- Strongly hydrophobic
  - magnesium stearate, phenylbutazone and chloramphenicol palmitate
  - Formulation of these drugs as suspensions presents wetting problems

Wetting of powders

- θ can be affected by the crystallographic structure (e.g. chloramphenicol palmitate).

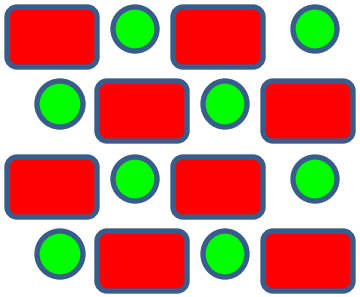
Material	contact angle (θ)
Chloramphenicol	59
Chloramphenicol palmitate (α form)	122
Chloramphenicol palmitate (β form)	108

- Surface modification or changes in crystal structure are clearly **not** routine methods of lowering the contact angle.
- The normal method of improving wettability is by the inclusion of **surfactants** in the formulation.
  - The surfactant will adsorb onto the surface of the powder, thus **reducing** the **surface tension**, thus **reducing the contact angle** and **improve the dispersibility** of the powder.

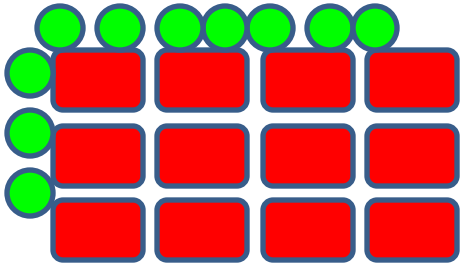
Vapor sorption by solids

- When a powder is exposed to a vapor or gas, the interaction will take one of the following forms:
  - Adsorption of vapor to the powder surface
  - Absorption into the bulk
  - Hydrate / solvate formation
  - Deliquescence

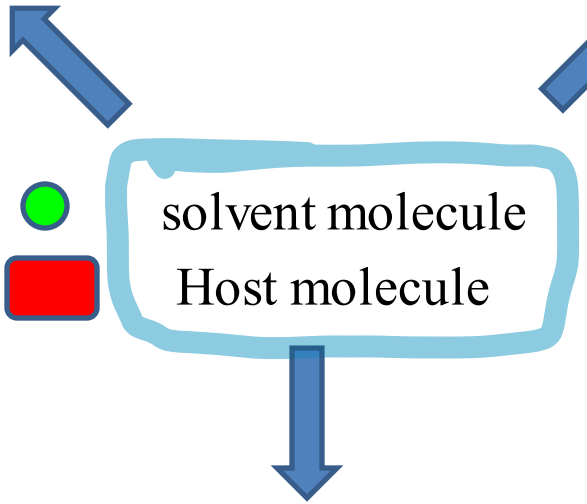
- Absorption into the bulk can occur if the sample is amorphous, whereas the interaction will be limited to adsorption if the powder is crystalline.
- Less sensitive a solid material or formulation is to changes in the relative humidity, the more **stable** will be the pharmaceutical shelf life and product performance.

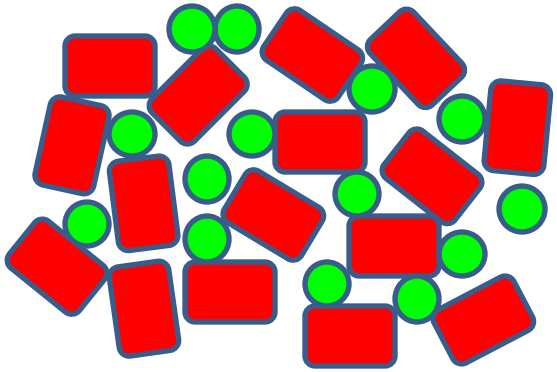


Solvate formation



Adsorption on surface





Absorption in disordered region