تفريغ فيزيكال

اسم الموضوع: Solid state
Last part

إعداد الصيدلاني/ـة: ياسمين خليل

metastable

stable تعني مستقر ولكن أقل من

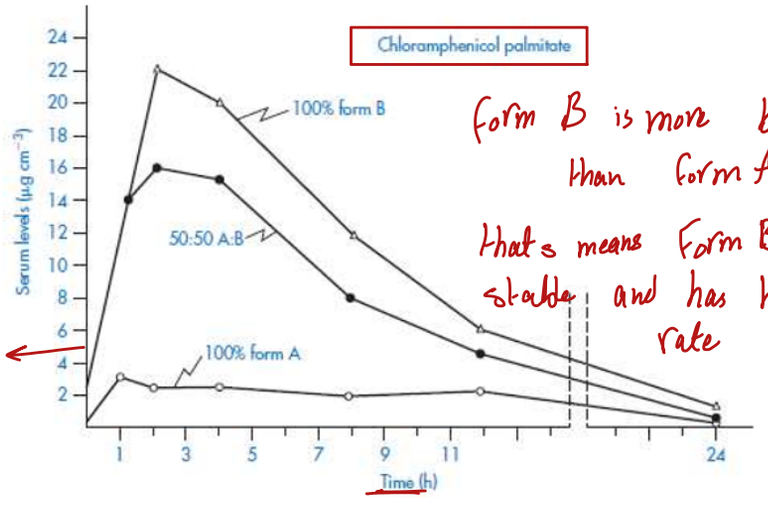
The ability of a drug or other substance to be absorbed and used by the body.

hydrophobic drugs = low bioavailability

less stable molecules are more bioavailable so higher dissolution rate

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).



Form B is more bio availability than form A

That's means Form B less stable and has higher dissolution rate

represent bio availability

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.

Conclusion: the most stable molecule has lower dissolution rate and lower bioavailability [hydrophobic drugs]

metastable

If the solvent is crystal lattic it calls = Solvate

but if the solvent is water = hydrate

Hydrates and solvates (pseudopolymorphs)

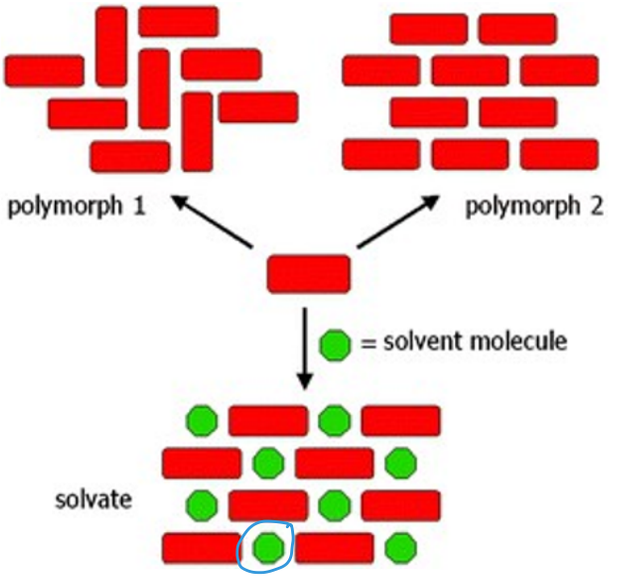
more than one component in the crystal

- 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.
- 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.

وجود جزيئات ماء بين جزيئات دواء [hydrate] يجعلها more stable

↓

low dissolution rate + low bio available



Hydrates and solvates (pseudopolymorphs)

وجود جزيئات ماء

- Hydrates often have very different properties from the anhydrous form in the same way as two different polymorphs have different properties from each other.

عدم وجود جزيئات ماء

- 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.

أكيد والسبب انه وجود جزيئات الماء يربط جزيئات الدواء مع بعض و بخلي الدواء يصير more stable

Hemi hydrates
1/2 water molecule
to 1 drug molecule

monohydrates
1 water molecule
to 1 drug molecule

Di hydrates
2 water molecule
to 1 drug molecule

tri hydrates
3 water molecule
to 1 drug molecule

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

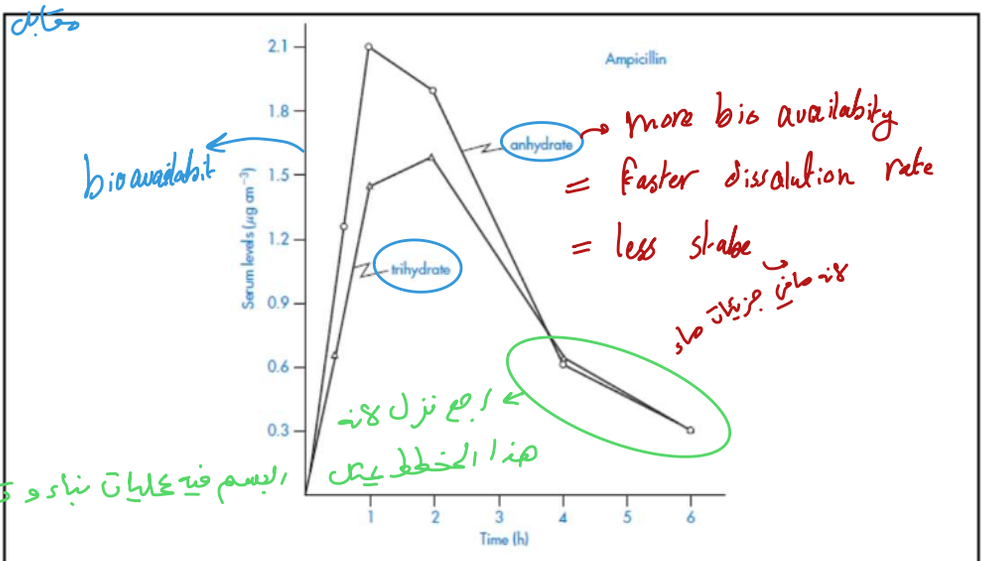
Sample	Intrinsic dissolution rate[b] ($\mu g\ min^{-1}\ cm^{-2}$)
Solvate C	21.05 ± 0.02
Solvate B	18.54 ± 0.47
Anhydrate	14.91 ± 0.47
Hemihydrate	17.01 ± 0.78
Monohydrate	9.13 ± 0.23

[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.

الشكل منطقي جداً، السبب إنه anhydrate (ما فيه ماء) عنده bioavailability أعلى من trihydrate (ثلاثة جزيئات ماء) يعني ما فيه قوى تجمع جزيئات الدواء مع بعض بالتالي إمتصاصه وذوبانه بالجسم أسهل من إنه تكون الروابط قوية مثل trihydrate

ثلاثة جزيئات ماء

مقابل جزيء واحد دواء



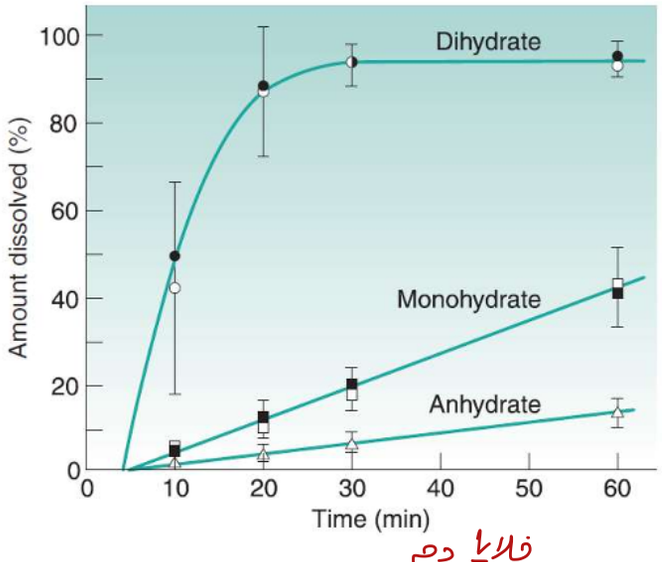
bioavailability

more bio availability
= faster dissolution rate
= less stable

لأنه ما فيه جزيئات ماء

راجع نزل لأنه هذا المخطط يمثل البسمة في عمليات تنقية و تحطيم

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



فلايا دم

The dissolution behaviour for erythromycin as the anhydrate, monohydrate and dihydrate, showing a progressively faster dissolution rate as the level of hydrate is increased. Adapted from Allen et al., 1978

في مثال فلايا الدم الحمراء كل ما زادت جزيئات الماء كل ما زادت معدل الذوبان و إمتصاصها بالجسم وصار أقل استقرار

= less stable — bioavailability — dissolution rate

Dehydration/Desolvation

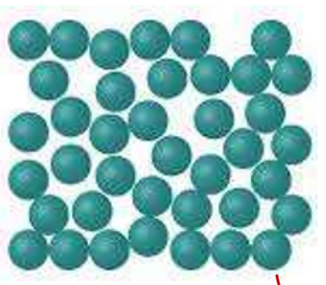
- Hydrates and solvates are less stable at higher temperatures.

- Indeed, heating has been routinely applied to remove crystallization solvents that are incorporated into the lattice, i.e., desolvation.

The amorphous state

- When a material is in the solid state but the molecules are not packed in a repeating long-range ordered fashion, it is said to be *amorphous*.
- Amorphous state may exhibit some degree of molecular arrangement, but no long-range ordered molecules.

Crystalline



Amorphous

The amorphous state

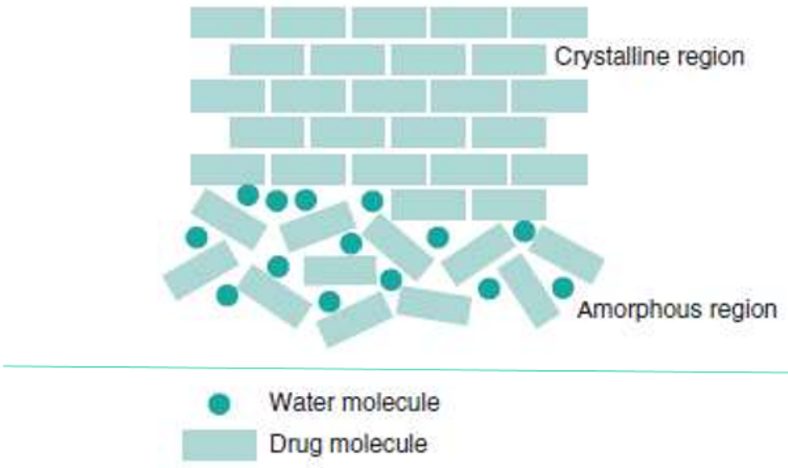
- Polymeric materials have molecules that are so large and flexible that it is not possible for them to align perfectly to form crystals.

- For these materials it will be usual to have ordered regions within the structure surrounded by disorder, so they are described as semicrystalline.

- Amorphous form in low molecular weight material may be produced by:
  - Rapid solidification of the melt
  - Spray or Freeze drying
  - Milling of crystalline material

The amorphous state

- Amorphous solids have different properties from the crystalline form of the same material:
  - They tend to flow when subjected to sufficient pressure over a period of time
  - They do not have definite melting point.
  - They have a characteristic temperature called glass transition temperature (Tg). If the sample is stored below the Tg the amorphous form will be brittle and is described as the glassy state. If the sample is above its Tg it becomes rubbery.
  - They have higher solubility and bioavailability.
  - They have the ability to absorb water in much larger quantities than crystalline materials.
  - They have low chemical and physical stability (overtime, amorphous solid may transform to the more stable crystalline state).



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

لوصف مدى ترتيب الجزيئات

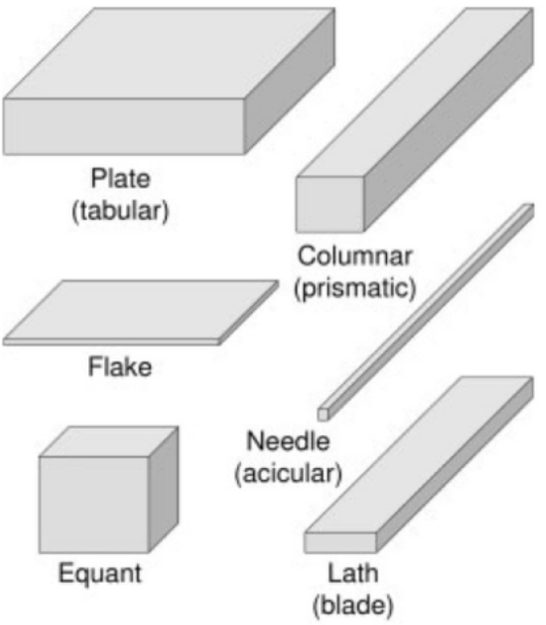
Degree of crystallinity

- 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…

Crystal habit = External phase of crystal

- 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.

The six basic crystal shapes



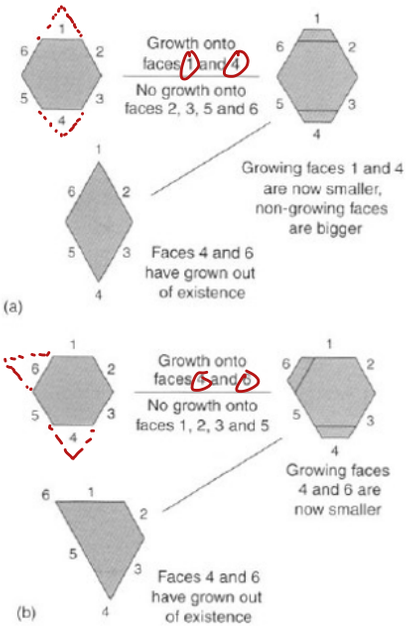


Fig. 9.10 (a) Demonstration of how growth on to faces 1 and 4 of a hexagonal crystal form result in the formation of a diamond. (b) Demonstration of how growth on to faces 4 and 6 of a hexagonal crystal result in the formation of a trapezium.

Crystal habit

- Changes in internal structure usually give different habits.

by change crystallization conditions

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

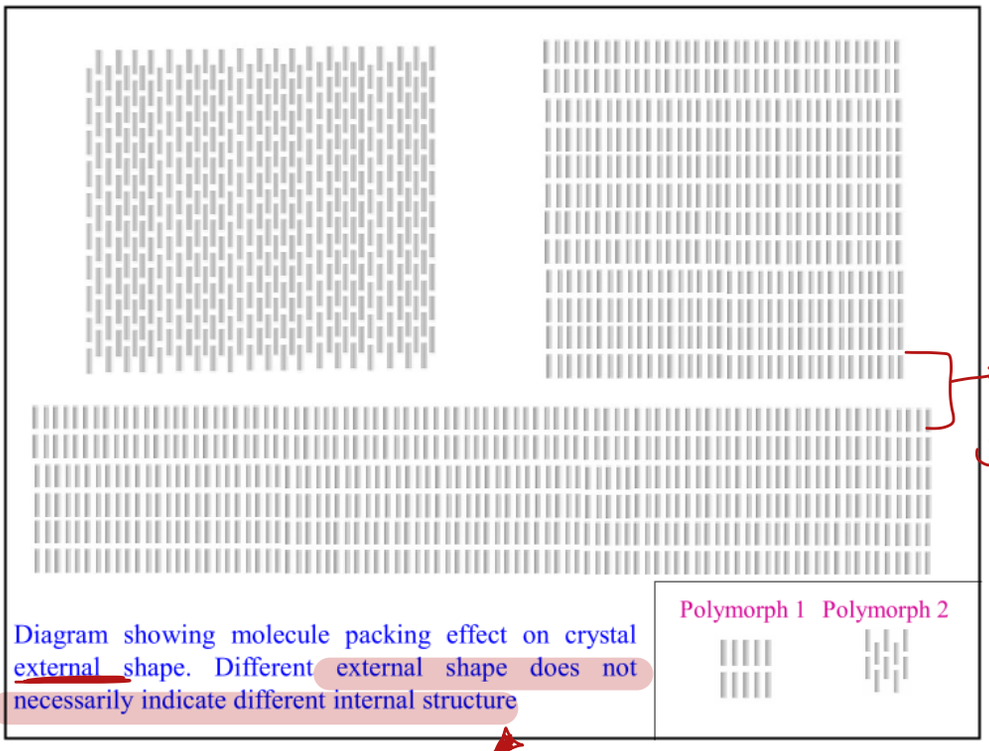
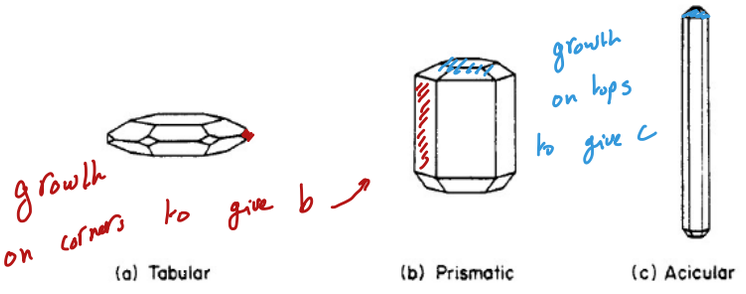


Diagram showing molecule packing effect on crystal external shape. Different external shape does not necessarily indicate different internal structure

نفس الشكل الداخلي ويختلفوا بالشكل الخارجي

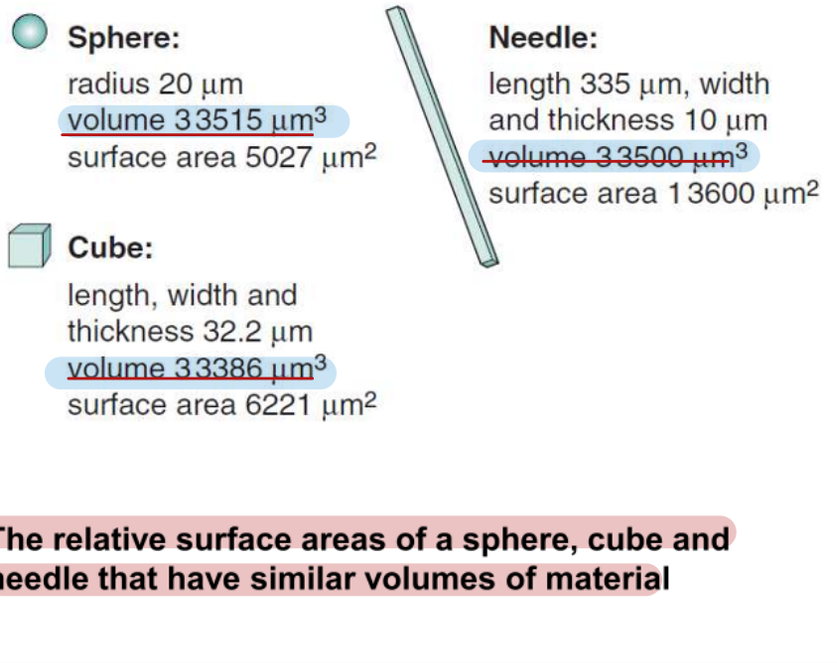


Crystal habit illustrated on a hexagonal crystal

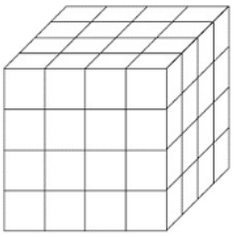
Crystal habit

- Crystal habit can alter the properties of drug and excipients such as:
  - Powder flow
  - Compression behavior
  - Specific surface area (total surface area of a material per unit of mass or volume)
  - Dissolution rate
  - Sedimentation and caking of suspension

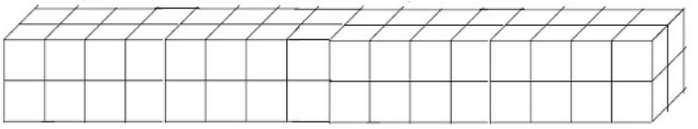
- Crystal engineering: Crystal habits may be changed by manipulating the growth of different faces to obtain crystals with suitable properties.



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



Volume = 4 ×4 × 4 = 64 μm^3
Area = 4 ×4 × 6 = 96 μm^2
Specific surface area = 1.5 μm^{-1}

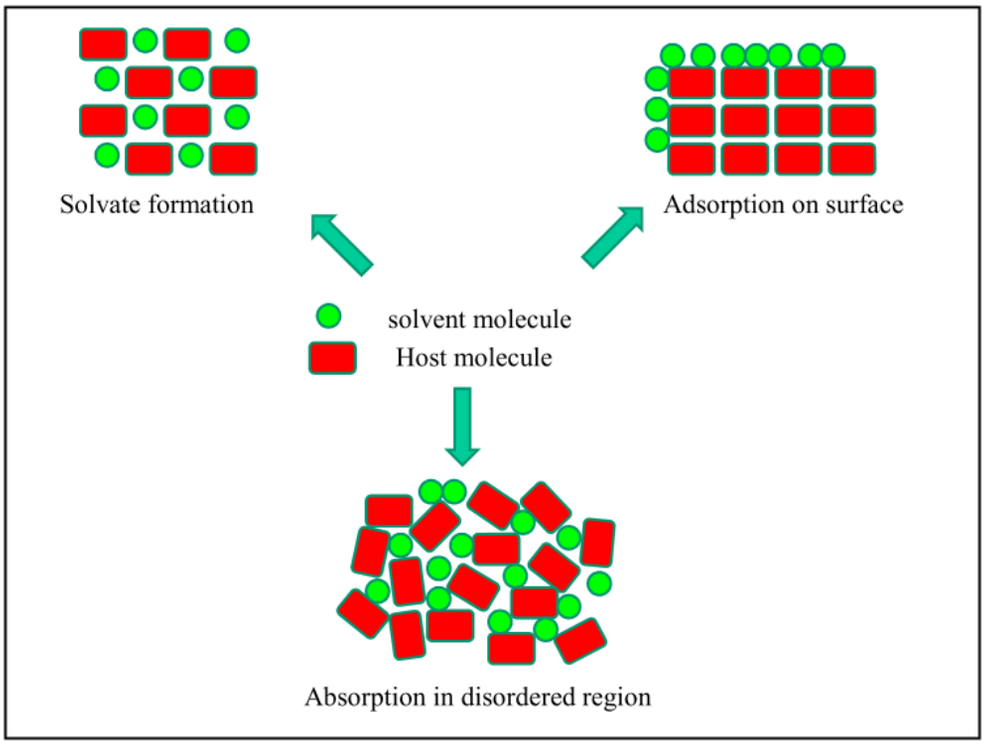


Volume = 2 ×2 × 16 = 64 μm^3
Area = (2 ×16 × 4) + (2 × 2 × 2) = 136 μm^2
Specific surface area = 2.125 μm^{-1}

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.



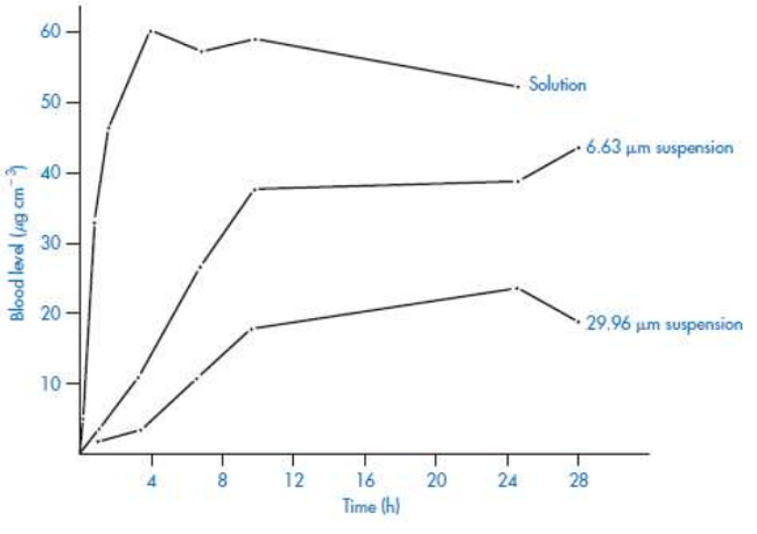
Importance of particle size

Particle size influence

- Drug dissolution
  - Important for poorly-soluble drugs (e.g. griseofulvin, tolbutamide, spironolactone, indomethacin and nifidipine)
- Mixing of powders (content uniformity for potent drugs, segregation)
- Hygroscopicity

أسعار الادوية مش هتفض

كل ما قل الحجم زادت مساحة السطح



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

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)

لا تنسوا الدعاء لاخواننا المسلمين المستضعفين في غزة والسودان وسوريا وكل مكان

اللهم انصر واعز الاسلام والمسلمين

ادعوا لوالدي بدخول الجنة يغير حساب ولا سابقه عذاب ♡