INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION
国际创新药学院

Physical Behaviour of Drug Solids (I, II, III)

Course **BSc(Pharm) & BSc (ATT)**

Year **2024-2025 I**

Module **Medicines 1**

Lecturer **Dr. Congcong Xu**

LEARNING OUTCOMES

1. Outline the types of bonding that creates solid cohesion
2. Describe how melting point influences solubility
3. Explain how crystal behaviour influences physical behaviour of solids
4. Explain how amorphous behaviour influences physical behaviour of solids
5. Describe how particle size influences physical behaviour of solids

SOLID BEHAVIOUR

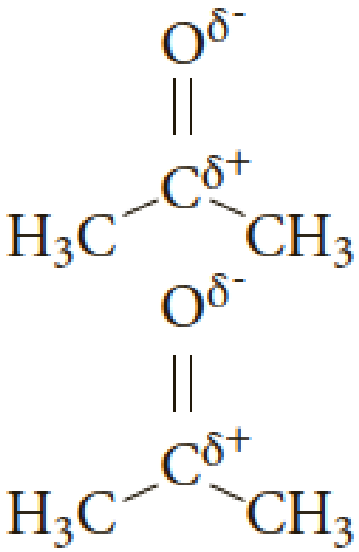
- A solid state of matter results when attractive forces exceed repulsive forces between molecules or ions

FORCES OF ATTRACTION BETWEEN MOLECULES

ATTRACTIVE FORCE	DESCRIPTION	EXAMPLE
Ion-Ion	Interaction between ion and ion	Na^+ and Cl^-
Ion-Dipole（偶极）	Interaction between an area of electron density and a cation or an area of electron deficiency and an anion	Na^+ and Oxygen in water
Dipole-Dipole (H-bonding)	Interaction between a molecule with a H atom and a strongly electronegative atom (F, O, N)	$H^{\delta+}$ and $O^{\delta-}$ of water (Δδ: Delta)
Dipole-Dipole	Interaction between an area of electron density created by unequal sharing of electrons in a covalent bond and an area of electron deficiency in an adjacent molecule	$C^{\delta+}$ of a carbonyl and $O^{\delta-}$ of the carbonyl on an adjacent molecule
Hydrophobic interaction	Interaction between two areas of hydrocarbon in a molecule	Folding of proteins to place amino acids with hydrophobic side chains on the inside of the polymer

DIPOLES IN ORGANIC COMPOUNDS

Acetone (丙酮)



Repulsive forces

There are also repulsive forces between ions and molecules encountered when the electron clouds of two atoms become close enough to enter the same space and repel each other. At a distance of 0.3–0.4 nm the attractive forces will equal the repulsive forces and the volume occupied by the two atoms is most stable.

INTERMOLECULAR ATTRACTIVE FORCES

SOLUBILITY

- Solubility: is the maximum concentration of a substance that will dissolve in a given solvent (usually water) at a given temperature

Solubility is an important parameter that often governs BIOAVAILABILITY

Table 2.3 Descriptive solubility: United States Pharmacopeia and European Pharmacopoeia terms for describing solubility

Descriptive term	Approximate volume of solvent (mL) necessary to dissolve 1 g of solute (at a temperature between 15 °C and 25 °C)	Solubility range (mg mL^{-1})
Very soluble	<1	≥1000
Freely soluble	From 1 to 10	100–1000
Soluble	From 10 to 30	33–100
Sparingly soluble 微溶性	From 30 to 100	10–33
Slightly soluble	From 100 to 1000	1–10
Very slightly soluble	From 1000 to 10 000	0.1–1
Practically insoluble[a]	>10 000	≤ 0.1

Some pharmacopoeias include the term 'partially soluble'. This refers to a mixture of components, of which only some dissolve.
[a]This term is absent from the *European Pharmacopoeia*.

SOLUBILITY OF CASE DRUGS

Drug	Solubility (g/L)
Aspirin	4.6 g/L (slightly soluble)
NaCl	359g/L (freely soluble)
Ferrous sulphate	447 g/L (freely soluble)
Glucose	909g/L (freely soluble)
Paracetamol	4.15g/L (slightly soluble)
Caffeine	11g/L (sparingly soluble)
Diazepam	0.01g/L (practically insoluble)
Castor oil	—

MELTING POINT AND SOLUBILITY

Melting point is a measure of the strength of interactions between molecules in a solid and of drug-drug attractive forces. **The lower the melting point the lower the attractive forces which confers greater aqueous solubility in any solvent.**

	Compound	Melting point (°C)	Solubility
磺胺嘧啶	Sulfadiazine	253	1 g in 13 dm^3 (0.077 g dm^{-3})
磺胺甲基嘧啶	Sulfamerazine	236	1 g in 5 dm^3 (0.20 g dm^{-3})
磺胺吡啶	Sulfapyridine	192	1 g in 3.5 dm^3 (0.29 g dm^{-3})
磺胺塞唑	Sulfathiazole	174	1 g in 1.7 dm^3 (0.59 g dm^{-3})

Melting point is a good predictor of molecular cohesion and solubility of solids

Boiling point is a good predictor of molecular cohesion and miscibility of liquids

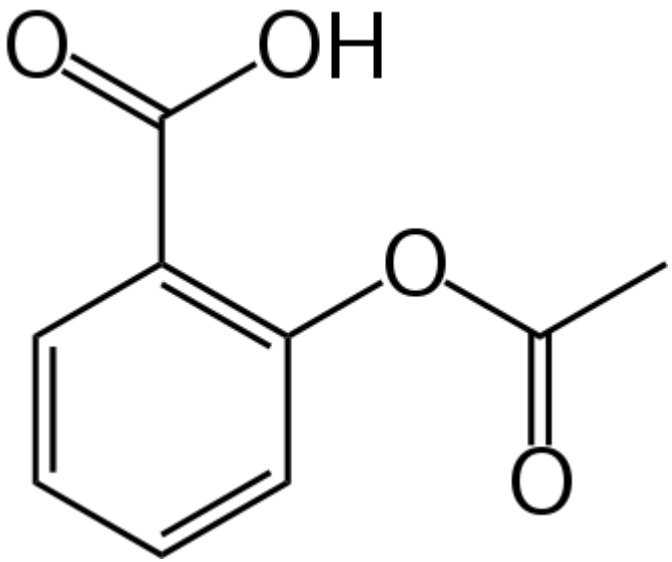
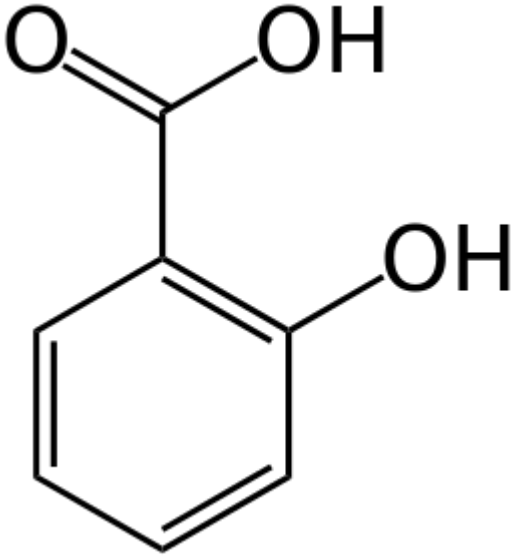
FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

- Temperature and heat input.
- Molecular structure of solute.
- Nature of solvent: cosolvents：‘like dissolves like’.
- Crystal characteristics: polymorphism（多态性）and solvation（溶解）.
- Particle size of the solid.
- pH.
- Common-ion effect (同离子效应）.

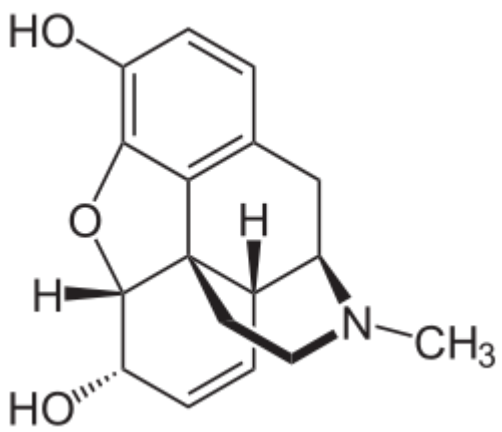
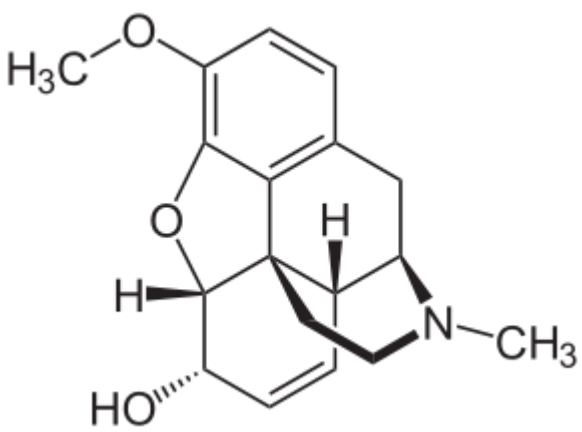
EFFECT OF MELTING POINT ON DRUG SOLUBILITY

MELTING POINT	IMPACT ON DRUG SOLUBILITY
>300°C	MAJOR FACTOR
>200°C	PROBABLE FACTOR
100-200°C	EQUIVOCAL FACTOR
<100°C	NOT A FACTOR

MELTING POINT: ASPIRIN AND SALICYLIC ACID

	
ACETYL SALICYLATE 乙酰水杨酸	**SALICYLIC ACID 水杨酸**
MP 135 C	MP 157-159 C
Solubility: 1g/300mL	Solubility: 1g/460mL

MELTING POINT: MORPHINE AND CODEINE

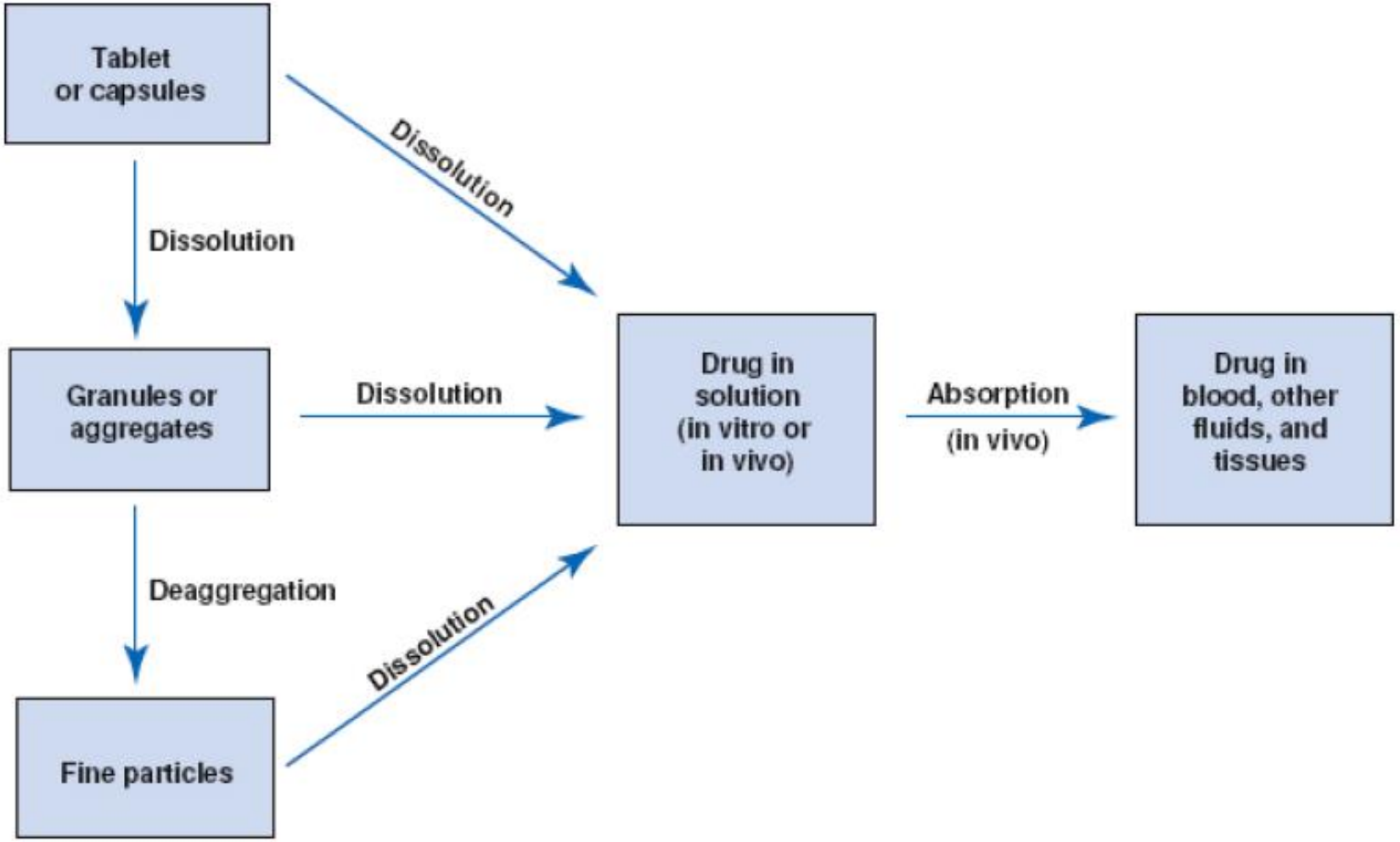
	
MORPHINE（吗啡）	**CODEINE（可待因）**
MP 250 C	MP 154-158 C
Solubility: 1g/5000mL	Solubility: 1g/120mL

DISSOLUTION（溶出）

Dissolution refers to the process by which a solid phase (e.g., a tablet or powder) goes into a solution phase such as water. In essence, when a drug "dissolves," solid particles separate and mix molecule by molecule with the liquid and appear to become part of that liquid. Therefore, drug dissolution is the process by which drug molecules are liberated from a solid phase and enter into a solution phase. In general, only drugs in solution can be absorbed, distributed, metabolized, excreted, or even exert pharmacologic action. Thus, dissolution is an important process in the pharmaceutical sciences.

- High soluble drug typically have high dissolution rate
- Dissolution data provides insight into the potential absorptio characteristics of drug *in vivo*

DISINTEGRATION, DEAGGREGATION, AND DISSOLUTION



DRUG PRODUCT & DRUG SUBSTANCE

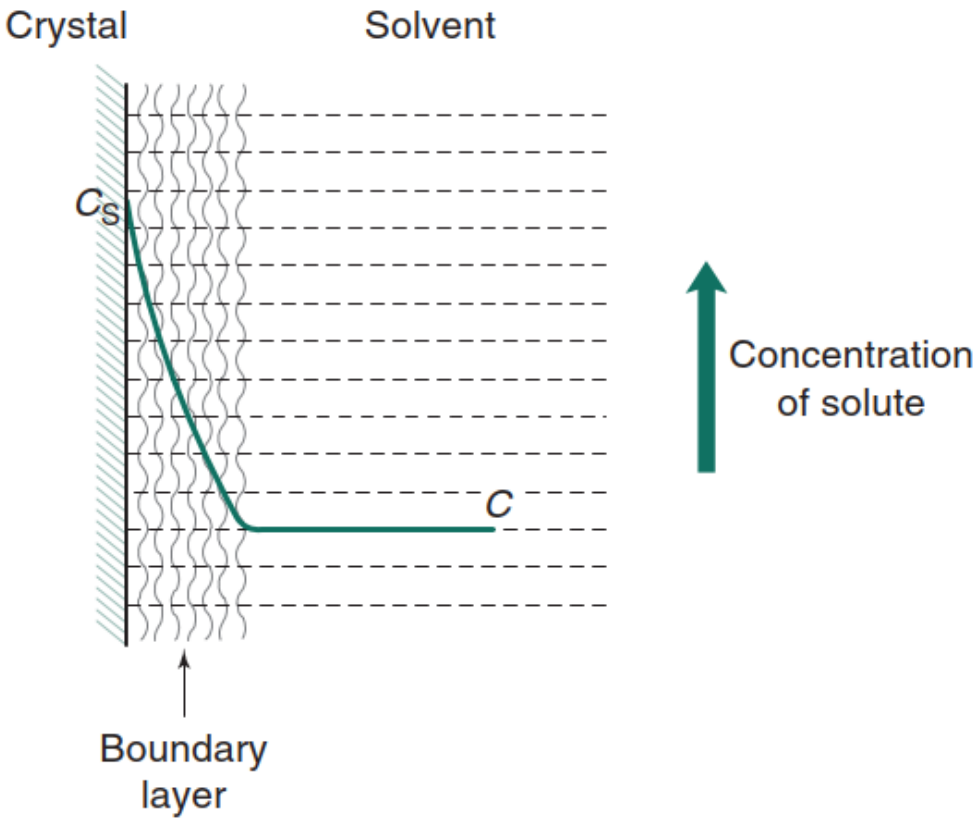
Drug Product (DP): A drug product is a finished dosage form (e.g., tablet and capsule) that contains a drug substance (DS), generally, but not necessarily in association with one or more other ingredients. A solid oral dosage form includes but is not limited to tablets, chewable tablets, enteric-coated（肠衣）tablets, capsules, caplets, encapsulated beads, and gelcaps（软胶囊）.

Drug Substance (DS): An active ingredient that is intended to furnish pharmacologic activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

PROCESS OF DISSOLUTION

The dissolution of a solid in a liquid may be regarded as being composed of two consecutive stages.

1. First is an interfacial reaction that results in the liberation of solute molecules from the solid phase to the liquid phase. This involves a phase change so that molecules of the solid become molecules of the solute（溶质）in the solvent in which the crystal is dissolving（溶解）.
2. After this, the solute molecules must migrate through the boundary layer surrounding the crystal to the bulk of solution.



INTERFACIAL REACTION OF DISSOLUTION

Leaving the surface. Dissolution involves the replacement of crystal molecules with solvent molecules. The process of the removal of drug molecules from a solid, and their replacement by solvent molecules, is determined by the relative affinity of the various molecules involved. The solvent-solute forces of attraction must overcome the cohesive forces of attraction between the molecules of the solid.

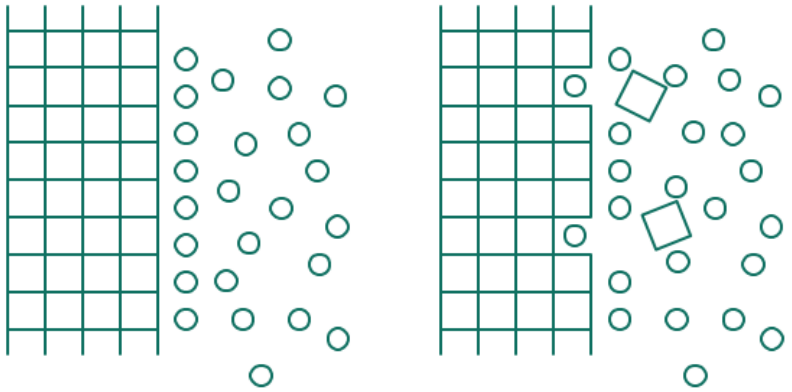


Fig. 2.2 Replacement of crystal molecules with solvent molecules during dissolution.

Moving into the liquid. On leaving the solid surface, the drug molecule must become incorporated in the liquid phase, i.e. within the solvent. Liquids are thought to contain a small amount of so-called free volume. This can be considered to be in the form of 'holes' that, at a given instant, are not occupied by the solvent molecules themselves. Individual solute molecules are thought to occupy these holes

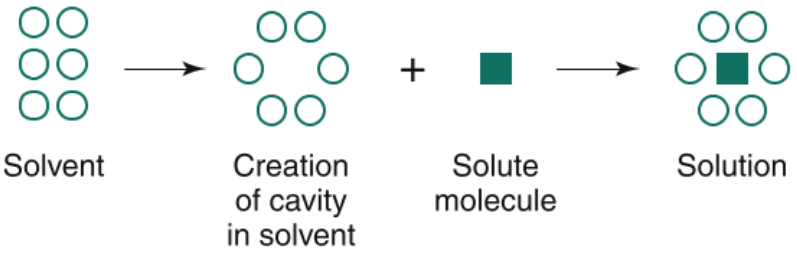
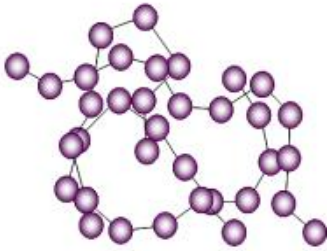


Fig. 2.3 The theory of cavity creation in the mechanism of dissolution.

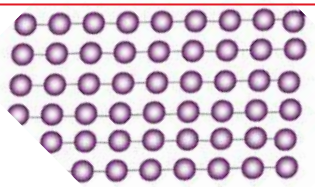
SOLID FORMS



SOLID

AMORPHOUS无定形的，非晶体

CRYSTAL晶体



POLYMORPHS同质多晶

SOLVATES & HYDRATES水合物

CO-CRYSTALS共晶体

Polymorphism is the phenomenon whereby molecules arrange themselves in more than one pattern within a crystal.

Solvates are orderly arrangements of drug molecules that include solvent molecules in the crystalline lattice. If the crystallization solvent is water, these forms are called hydrates.

Cocrystals are crystals composed of an active drug species and another organic molecule.

SOLID STATES: DEFINITIONS

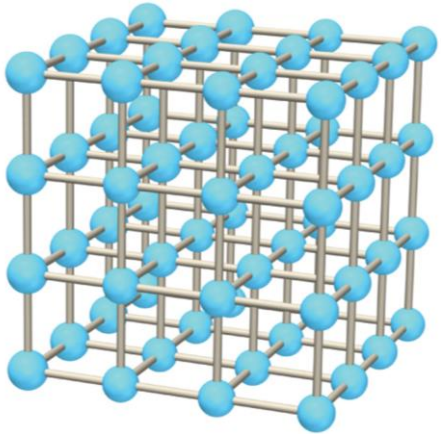
CRYSTALLINE SOLIDS: Possess a regular repetitive internal arrangement of atoms molecules, or ions in a structure called a crystal lattice

AMORPHOUS SOLIDS: Consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice

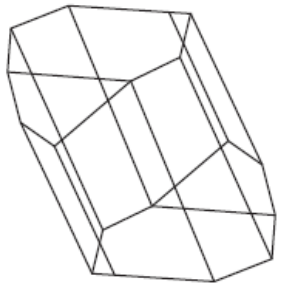
CRYSTALINE FORMS

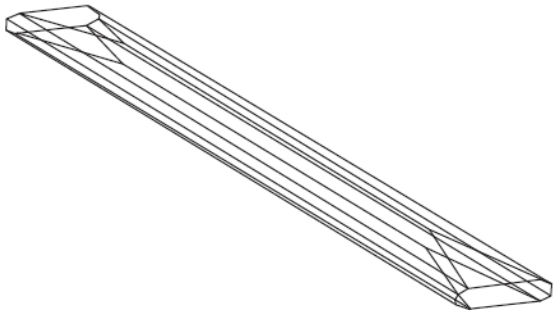
UNIT CELL（晶胞）: A unit cell is the simplest repeat unit in a crystal.

CRYSTAL LATTICE晶体点阵（晶格）: Is an orderly three dimensional arrangement of molecules (unit cells) that permits optimal attractive interactions between adjacent molecules within a solid

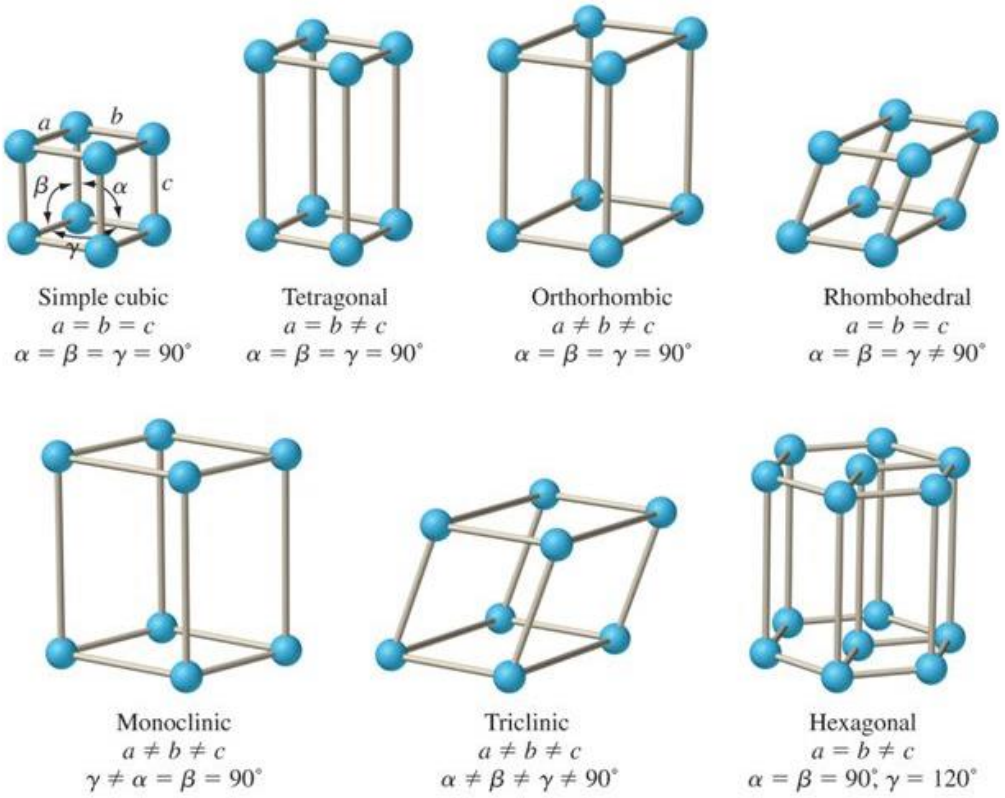


CRYSTAL HABIT（晶体惯态，晶习）: Is a term used to describe the shape of the drug crystal that can be appreciated by visual inspection



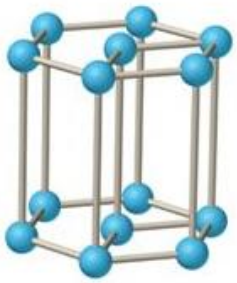


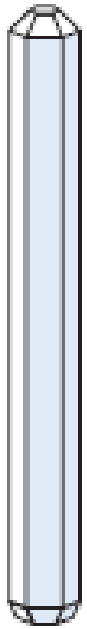
UNIT CELLS（晶胞）

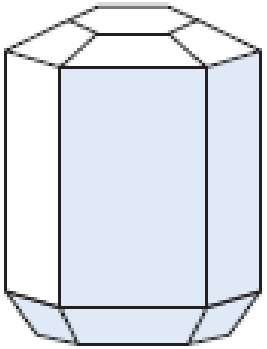


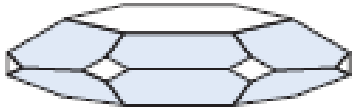
- Seven basic unit cells
- Most common for drugs are triclinic（三斜晶系）, monoclinic（单斜晶）and orthorhombic（正交晶）

CRYSTAL HABITS OF A HEXAGONAL UNIT









Acicular
针状

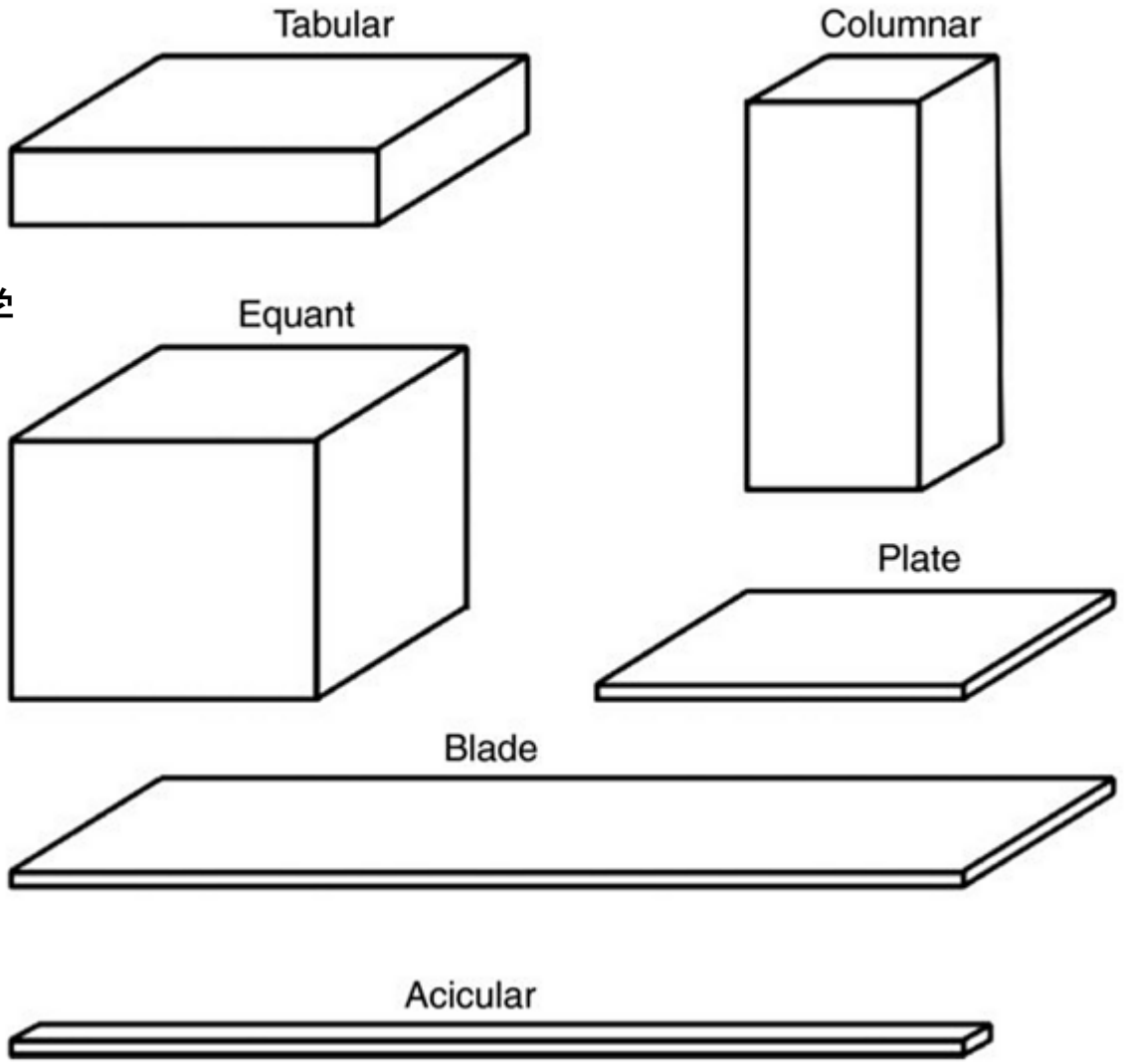
Prismatic
棱柱状

Tabular
扁平状

Habit can influence use.

CRYSTAL HABIT（晶体惯态）

HABIT INFLUENCES
FLOW
DISPERSIBILITY分散性
AERODYNAMICS空气动力学
DISSOLUTION
SOLUBILITY
BIOAVAILABILITY
COMPRESSIBILITY



CRYSTAL FORMATION

- Crystal growth is the reverse of dissolution
- The rate of crystallisation influences habit
- The process by which a crystal forms is called nucleation（成核）and growth

- Super-saturation
  - Cooling
  - Evaporation
  - Seed crystals（晶种）
  - Precipitant (water, pH)

POLYMORPHISM（同质多晶）

POLYMORPHISM: Is the phenomenon whereby molecules arrange themselves in more than one pattern within a crystal

- Regulators typically approve *one crystal form* *(other forms metastable亚稳态)*
- The most stable crystal form will have the highest melting point
- Polymorphism is difficult to predict
- Approximately 36% of marketed drugs exhibit polymorphism
- Polymorphisms typically have different crystal habits（晶体惯态）

- *Polymorphic behaviour Is a major concern of the pharmaceutical industry because it has considerable formulation, therapeutic, legal, and commercial implications*

POLYMORPHISM

- Polymorphism can influence the melting point, solubility, dissolution rate and bioavailability of a drug, and processing properties such as powder flow and compressibility.

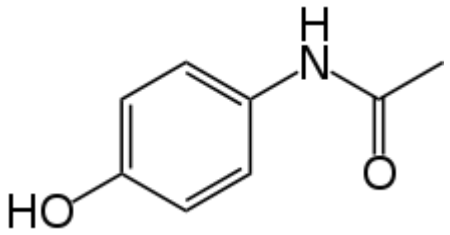
- There will be one polymorph in which the intermolecular attractive forces are best aligned and it will be the most thermodynamically stable. This form of the drug is the highest melting and the least soluble in any solvent.

- Less stable polymorphs can spontaneously convert to the more stable form over time.

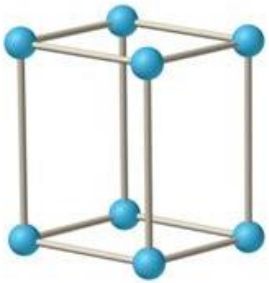
- Because polymorphs have different physical properties they offer the opportunity to select a lower melting point and therefore a more soluble form of a drug for use in a solid dosage form.

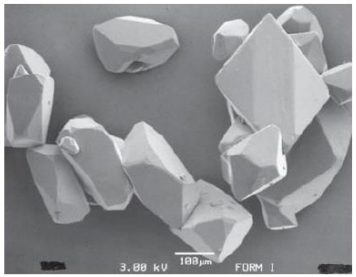
- Polymorphism can complicate the preparation of suspensions because as the drug moves in and out of solution it will ultimately re-form in the most thermodynamically stable and least soluble form.

POLYMORPHISM: PARACETAMOL



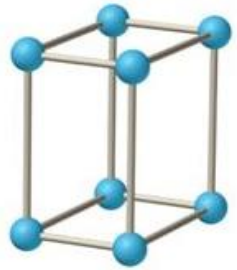
FORM 1

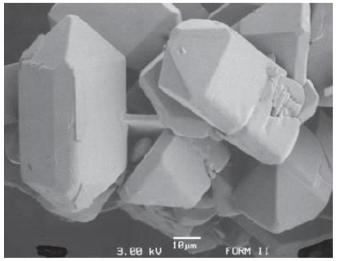




单斜晶

FORM 2





正交晶

More stable form at room temperature

Commercially used form

Not suitable for direct compression into tablets

Binders粘合剂 required in tabletting压片

Costly processing

Easily crystallised from solvents

Less stable form at room temperature

Not used commercially

Form suitable for direct compression into tablets

No binders necessary in tabletting

Processing advantage

Nucleation from FORM II Seed

EFFECT OF POLYMORPHISM ON BIOAVAILABILITY

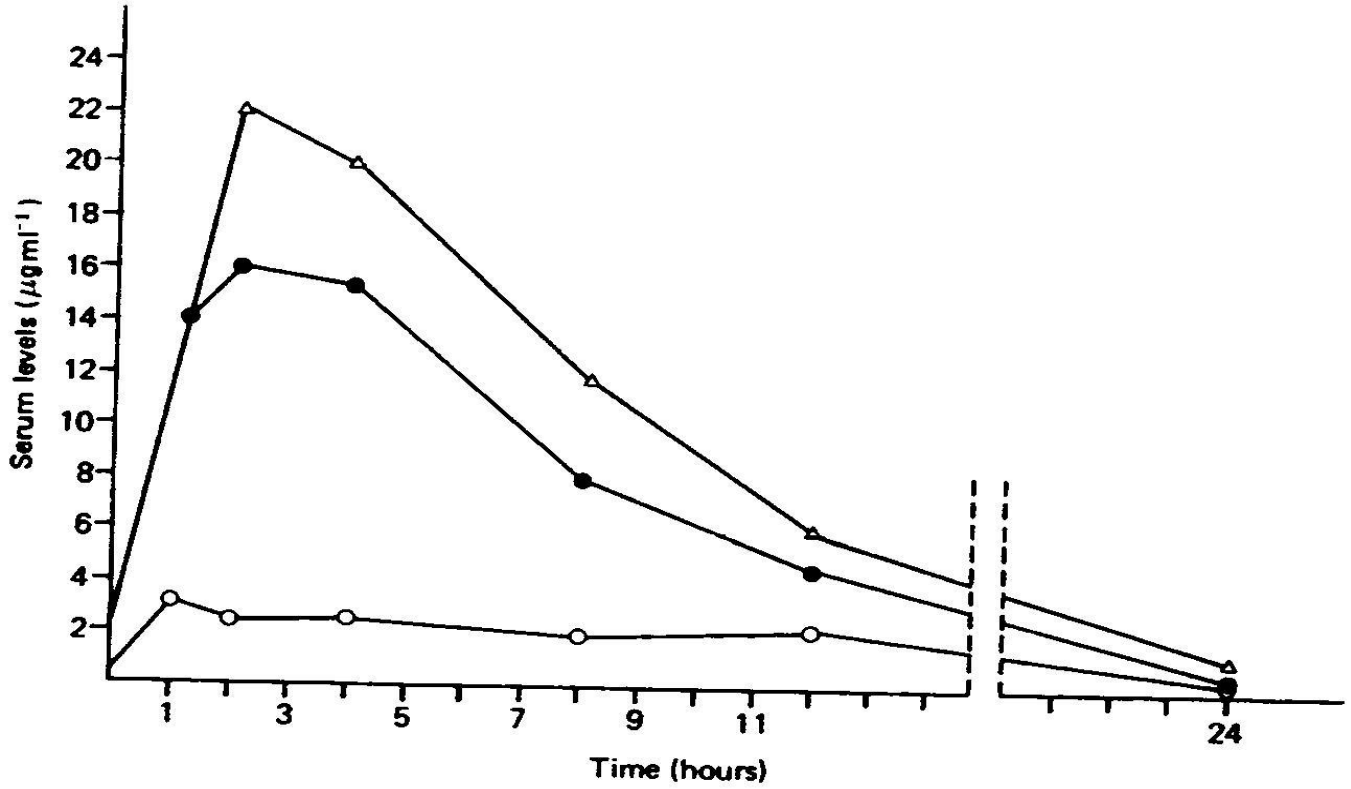


Figure 1.10 Comparison of serum levels obtained with suspensions of chloramphenicol palmitate after oral administration of a dose equivalent to 1.5 g of chloramphenicol: Δ, 100% form B; ● 50% form A and 50% form B; ○, 100% form A

CASE STUDY: RITONAVIR利托那韦

- In 1998 Abbott Laboratories withdrew Norvir (ritonavir), essential at that time in the treatment of HIV/AIDS, because the capsules unexpectedly failed dissolution tests（溶出试验）.

- The public were without an essential drug while researchers investigated. They finally identified that the drug crystals had changed into a more stable, less soluble polymorph which contaminated laboratories and effectively halted production processes.

- They had to completely reformulate the drug and develop a new capsule product. The case cost Abbott hundreds of millions of dollars and over 600 scientists working for nearly a year to resolve the issue. The estimated loss in sales in 1998 alone is $250m.

Ritonavir: An Extraordinary Example of Conformational Polymorphism

John Bauer,[1,2] Stephen Spanton,[1] Rodger Henry,[1] John Quick,[1] Walter Dziki,[1] William Porter,[1] and John Morris[1]

ANHYDRATES AND SOLVATES

ANHYDROUS无水的: Solid devoid of water in its solid structure

SOLVATES溶剂化物: Solids with a solvent incorporated into their crystal structures

- Aqueous hydrates often less soluble in water
- Non-aqueous hydrates are often more soluble in water

HYDRATES水合物: When the solvent that is incorporated into the crystal lattice is specifically water, the solvate is called a hydrate

- Approximately 30% of drugs form hydrates
- 50% of hydrates are monohydrates 一水合物(Drug:Water 1:1)
- 20% of hydrates are dihydrates二水合物 (Drug:Water 1:2)
- Hydrates can lose water of hydration, becoming sticky (efflorescence风化)

CO-CRYSTALS共晶: Crystals composed of active drugs species and another organic molecule

- Co-former: The other molecule H-bonds with drug providing a lower melting point and a more soluble solid than the pure crystalline form
- Generally GRAS一般认为安全（Generally Recognized as Safe）
- Examples: caffeine, vitamins, adenine腺嘌呤, cytosine胞嘧啶
- Co-crystals can be more stable than polymorphs, reduce stability concerns

SOLIDS IN SOLID BEHAVIOUR

3 OUTCOMES WHEN MIXING SOLIDS

2 PHASE COARSE PHYSICAL SUSPENSION

↓

AD MIXING

2 PHASE SOLID IN SOLID EUTECTIC 共溶的 MIXTURE

↓

Cooled molten熔化的 mixture
Solvent evaporation

1 PHASE SOLID IN SOLID SOLUTION

↓

Cooled molten mixture
Solvent evaporation

EFFECT OF HYDRATION ON DISSOLUTION OF OXYPHENBUTAZONE

羟布宗

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

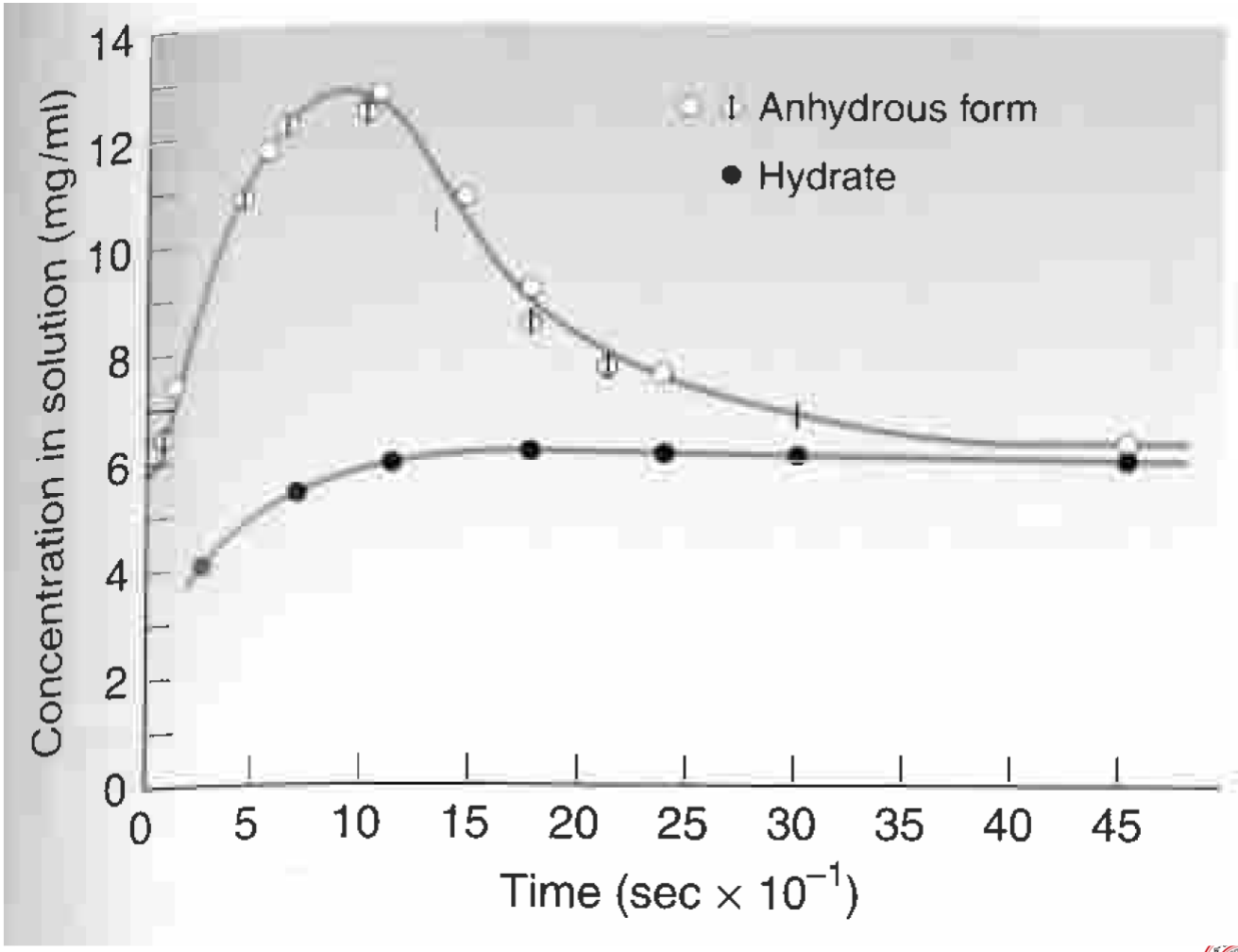
Sample	Intrinsic dissolution rate[b] ($\mu g\ min^{-1}\ cm^{-2}$)
Solvate C	21.05 ± 0.02
Solvate B	18.54 ± 0.47
Anhydrate	14.91 ± 0.47
Hemihydrate 半水化合物	17.01 ± 0.78
Monohydrate	9.13 ± 0.23

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

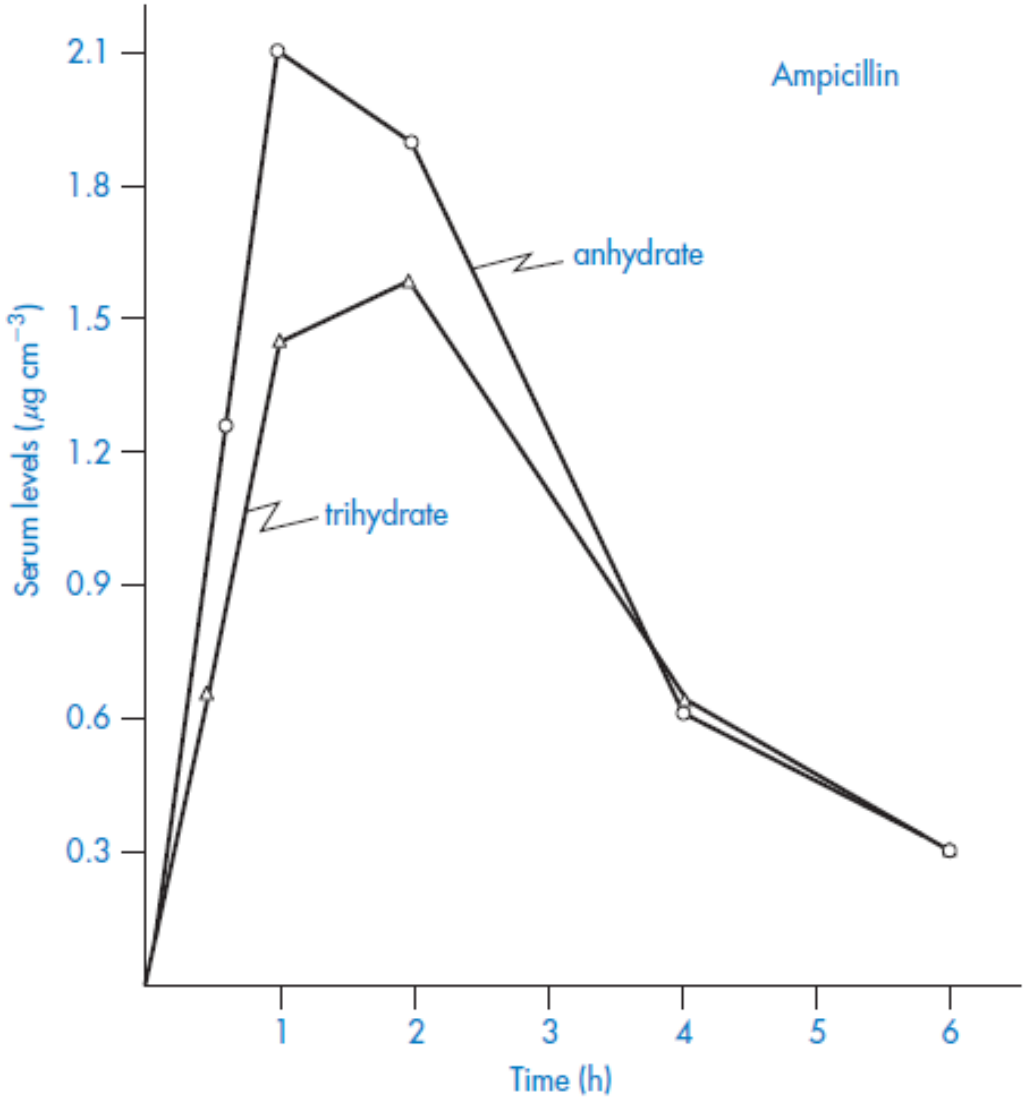
[b] Mean ± range of uncertainty of two determinations.

Hydrates are often more stable than the anhydrous form leading to reduced aqueous solubility and lower bioavailability.

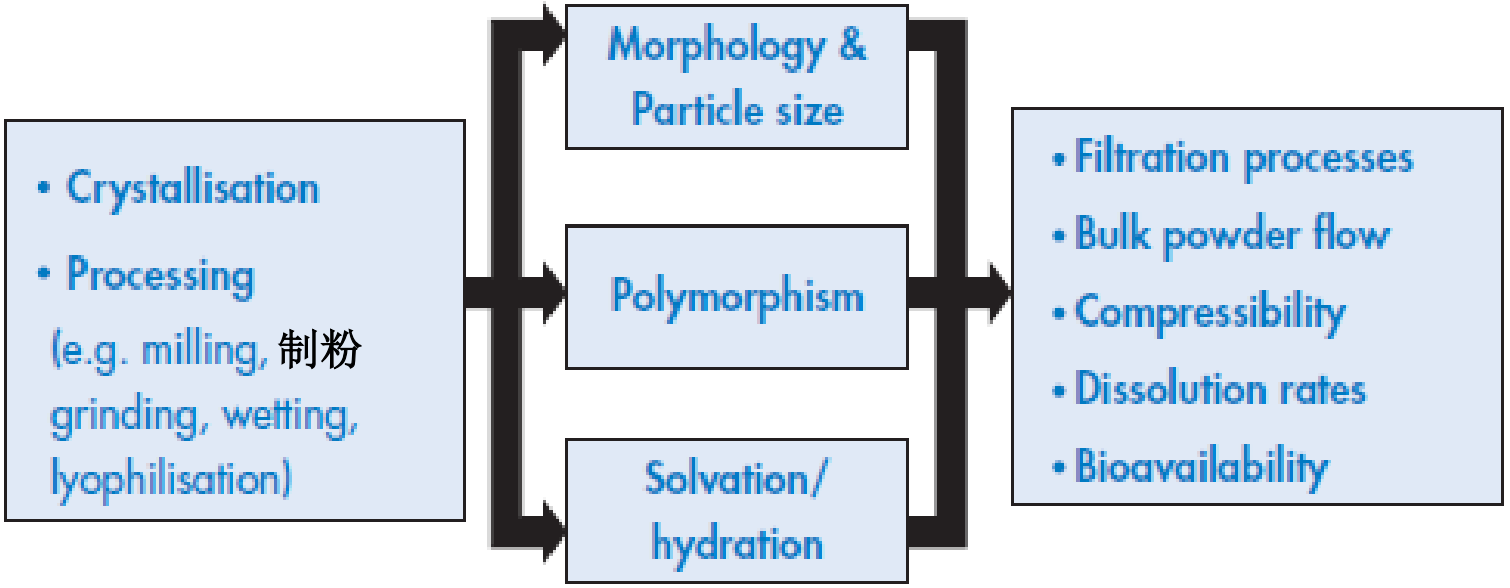
EFFECT OF HYDRATION ON DISSOLUTION OF THEOPHYLINE (茶碱) MONOHYDRATE



EFFECT OF HYDRATION ON BIOAVAILABILITY OF AMPICILLIN



CAUSE AND EFFECT OF CRYSTAL CHANGE



- Each lattice type has different energy, rigidity, hardness, shape, size & ultimately melting point, therapeutic application (needles), dissolution and bioavailability
- Preparing meta-stable (亚稳态）forms can increase solubility
- Each lattice will convert to the lowest energy form over time
- Interfacial tension will define crystal growth

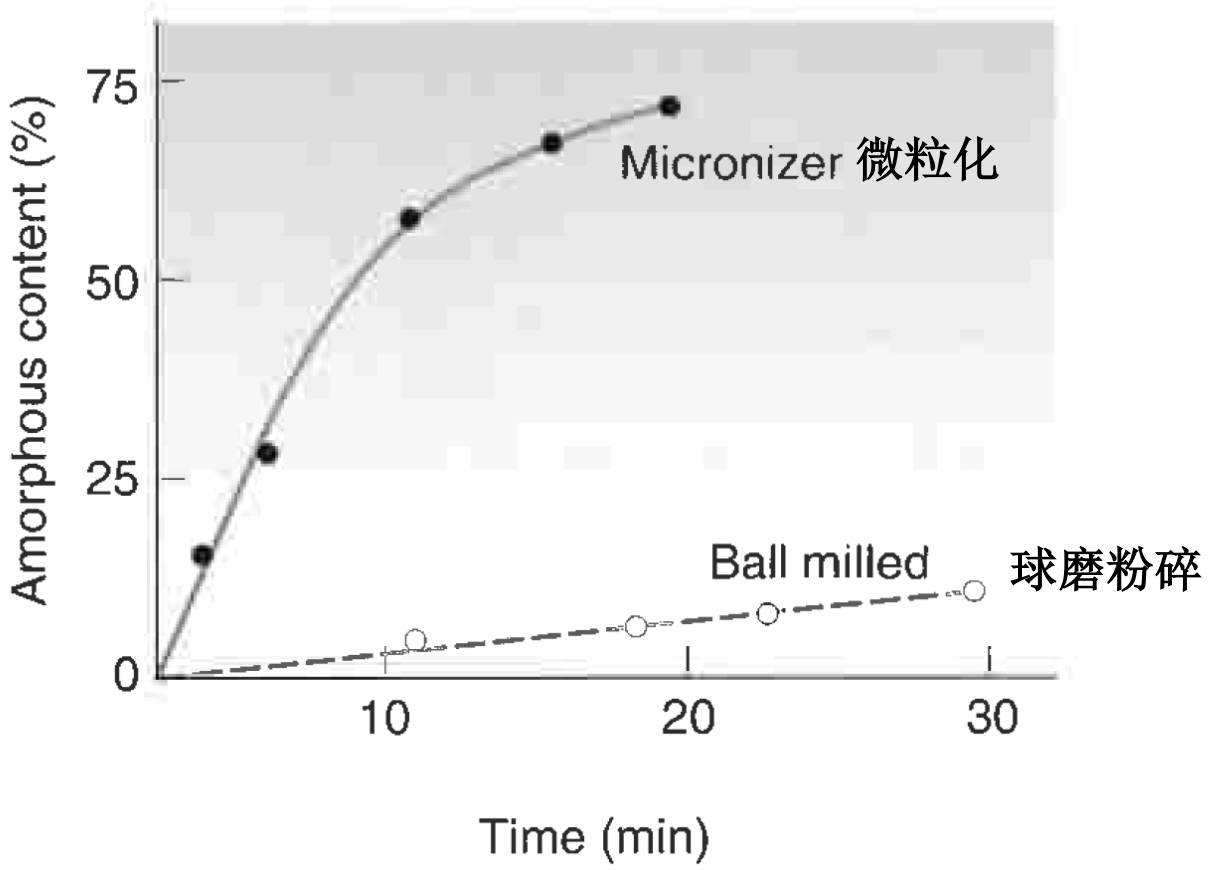
AMORPHOUS SOLIDS（非晶体）

PUT SIMPLY, AMORPHOUS MATERIALS ARE SIMPLY A PILE OF MOLECULES

- Many polymers are amorphous materials
- Many excipients are amorphous materials
- Crystalline solids can be processed into amorphous form which lowers the melting point and improves solubility
  - Processes: micronisation微粒化, milling碾磨, freeze drying, spray drying喷雾干燥
  - E.g. when a drug solution is cooled so rapidly that they lose conformational mobility prior to forming their lattice (freeze drying)

- Porous low density materials susceptible to sorption of vapour
- Many drugs used in orally disintegrating tablets are amorphous forms of the drug to improve solubility, but require individual packaging to avoid adsorption of moisture

HIGH ENERGY MECHANICAL PROCESSING OF CRYSTALLINE MATERIAL CAN SIGNIFICANTLY INCREASE THE AMORPHOUS CONTENT



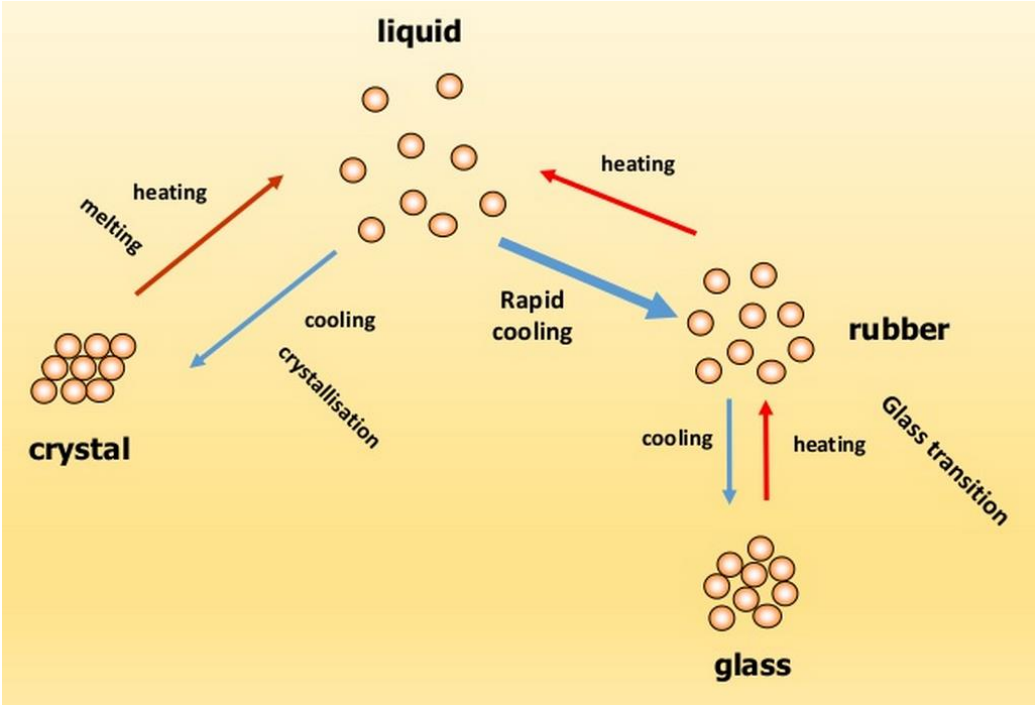
GLASS TRANSITION TEMPERATURE (T_G)

玻璃化转变温度

- Amorphous materials do not have sharp melting points

T_g: Is the temperature below which the material is said to be in a glassy state and is brittle（易碎的）; above the Tg the molecules become more mobile and molecules are more rubbery（有弹力的）

Tg can be lowered by the addition of plasticisers（增塑剂）, which fit between the material and make it more mobile



GLASS TRANSITION TEMPERATURE (T_G)

AMORPHOUS

- Melt over a large temperature range
- Characterised by glass transition temperature
- No long range order
- Process stresses can destroy crystal lattice structures leading to amorphous form
- Drugs in amorphous form have greater solubility than their equivalent crystal form
- Poor flowability
- Better compression properties
- Absorb large quantities of water

CRYSTAL

- Melt over a narrow temperature range
- Characterised by melting point
- Crystal lattice: Set defined geometry
- Polymorphisms
- Only 1 crystal is stable at a given temp/pressure
- Good flowability
- Poor compression properties

PARTICLE SIZE

Crystalline or amorphous solids are processed into solid masses referred to as particles.

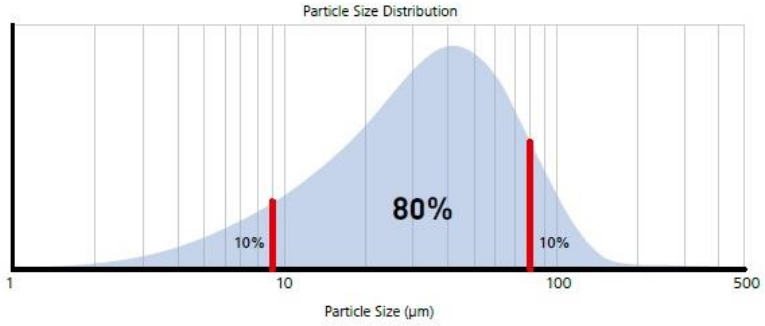
Particle size range in dosage forms can vary from 0.1µm to 1000µm in tablet granulation.

Drug solids have a range of particle sizes which are presented on a frequency distribution plot.

Particle size reduction is achieved by milling bashing grinding.

Conventional grinding in a mortar and pestle (研钵和研杵) is referred to as **TRITURATION（研磨）**

Median diameter of particles triturated in a mortar is **53.52 µm**



PARTICLE SIZES IN COMMERCIALLY MANUFACTURED DOSAGE FORMS

DOSEAGE FORM	DRUG PARTICLE SIZE RANGE (µm)
Ophthalmic （眼睛的）suspensions	< 10
Oral suspensions	10-50
Parenteral suspensions (non-IV)	0.5-25
Parenteral (IV) (NP, liposomes, emulsions)	0.1-0.5
Aerosols for the lung	1-5
Tablets and capsules (IR, immediate release)	<50
Topical aerosols	50-100
Topical emulsions	<50
Topical suspensions	10-50

INFLUENCE OF DECREASING PARTICLE SIZE

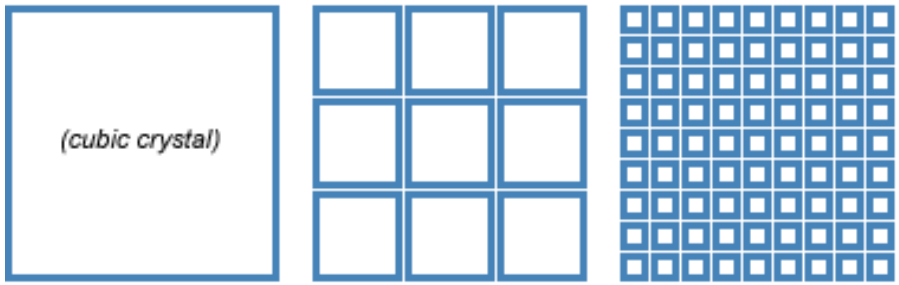
- Increases dissolution rate
- Can increase solubility (very small particles, high interfacial energy)
- Influences pharmacokinetics
- Improves mixing of solids of comparable size
- Improves dose uniformity
- Increases degradation due to air, moisture, light
- Decreases flowability (a result of cohesivity)
- Influences application by a specific route (e.g. pulmonary)
- Decreased wettability（润湿性）

EFFECT OF PARTICLE SIZE ON DRUG ACTION

- A drug must be in solution (molecular dispersion) before it can be absorbed across the intestinal epithelium
- If solubility of a drug is <0.3% then dissolution can be the rate controlling step in absorption (e.g. griseofulvin灰黄霉素)
- Particle size play a critical role in controlled release from parenteral preparations where suspensions can promote more sustained release
- Particle manipulation can prevent peak plasma concentrations from reaching toxic thresholds (or side effects e.g. nitrofurantoin)
- Capsules can avoid compression of solids into larger grains and particles and hence facilitate controlled release

PARTICLE SIZE REDUCTION & DISSOLUTION

- Particle size reduction increases the surface area of solid in contact with solvent, which in turn increases the rate of solution.
  - As particle becomes smaller, the surface area to volume ratio increases
  - Larger surface area allows a greater interaction with the solvent
  - There is a lower limit to the beneficial effects of particle size.



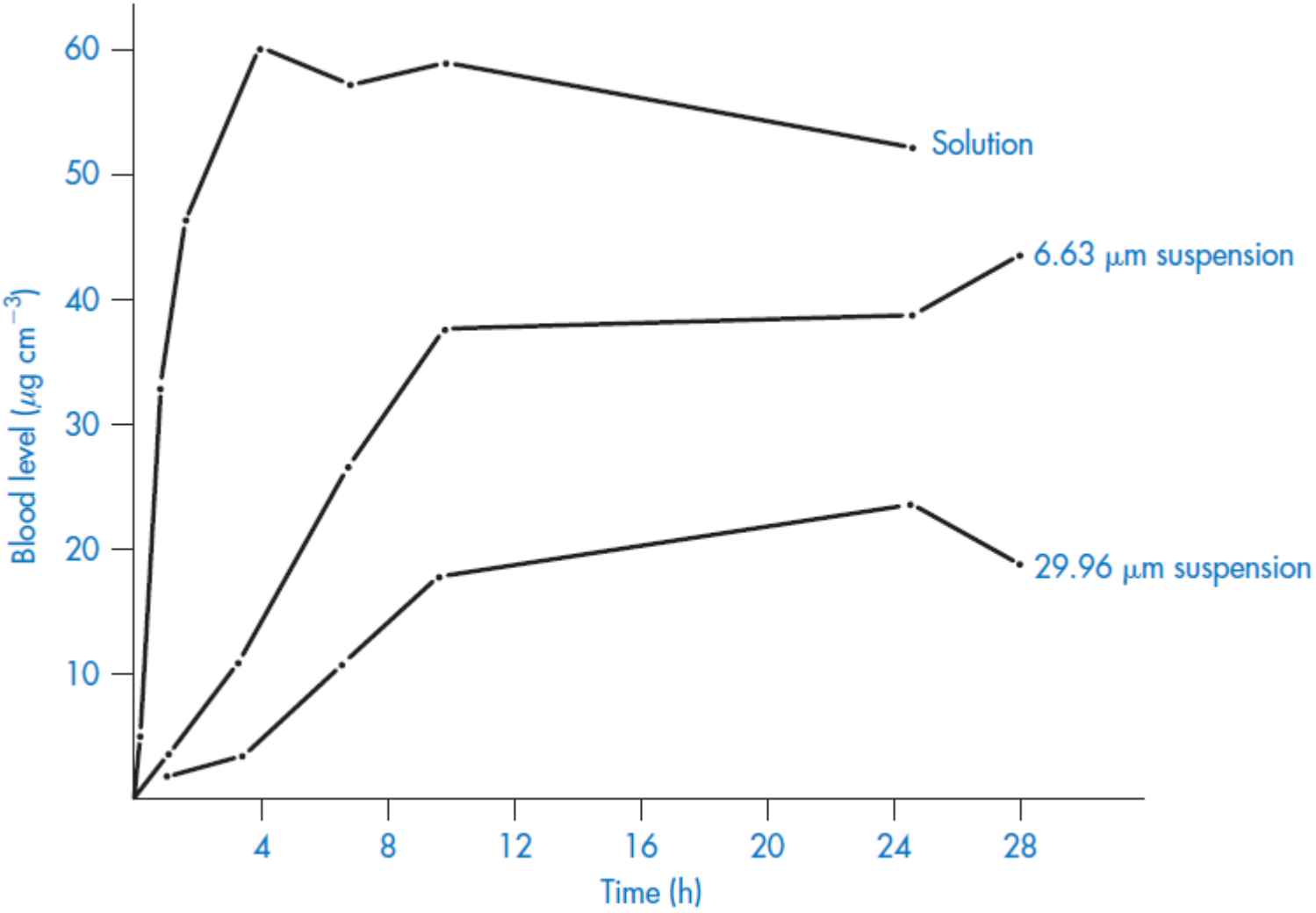
PARTICLE SIZE REDUCTION & SOLUBILITY

- Solubility of a substance can be increased below a threshold particle size, where high interfacial energy in the system can increase tendency for the substance to go into solution

LOW INTERFACIAL TENSION（界面张力）

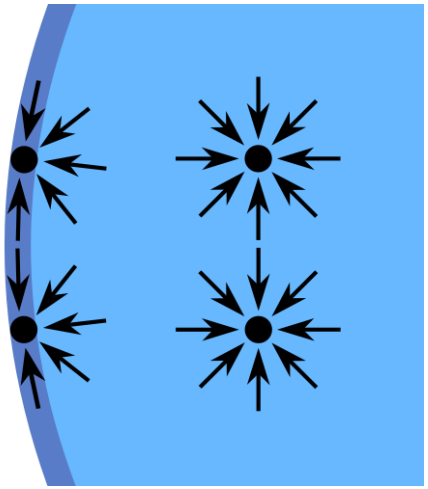
HIGH INTERFACIAL TENSION

EFFECT OF PARTICLE SIZE ON RELEASE KINETICS OF PHENOBARBITAL（苯巴比妥）FROM AN IM INJECTION



PARTICLE SIZE AND FLOWABILITY

Surface free energy: Molecules at the surface of a particle have an imbalance in chemical interaction compared to those in the bulk of the phase, which manifests as a net inward force of attraction (manifested as surface tension and surface energy). The greater the surface area (smaller the particle size the greater the energy in the system.



Particles reduce their surface free energy by aggregation

Particles > 250 µm are free flowing
Particles < 100 µm have flow issues
Particles < 10 µm have a high resistance to flow

HOWEVER SHAPE GREATLY INFLUENCES FLOW

HYGROSCOPICITY AND DELIQUESCENCE

吸水性　　潮解

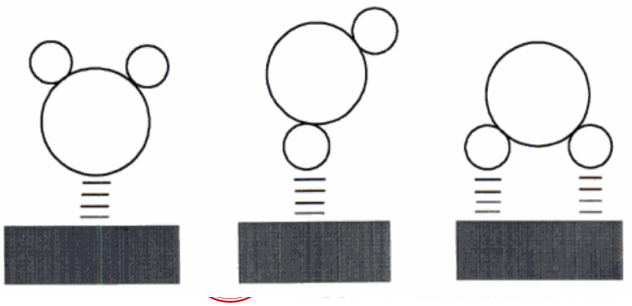
- Hygroscopic powder: Take up water from the atmosphere.

- Deliquescent powder: Sorption of water vapour from the environment and gradually form a solution that impacts the chemical stability of the drug or excipient

- Drugs and excipients with polar surface groups will adsorb a layer of water on their surface , particularly if their surface is large

- Metal salts are prone to hygroscopicity (Na^+, K^+, Ca^{2+}, Mg^{2+})

- Desiccants（干燥剂）can be added.



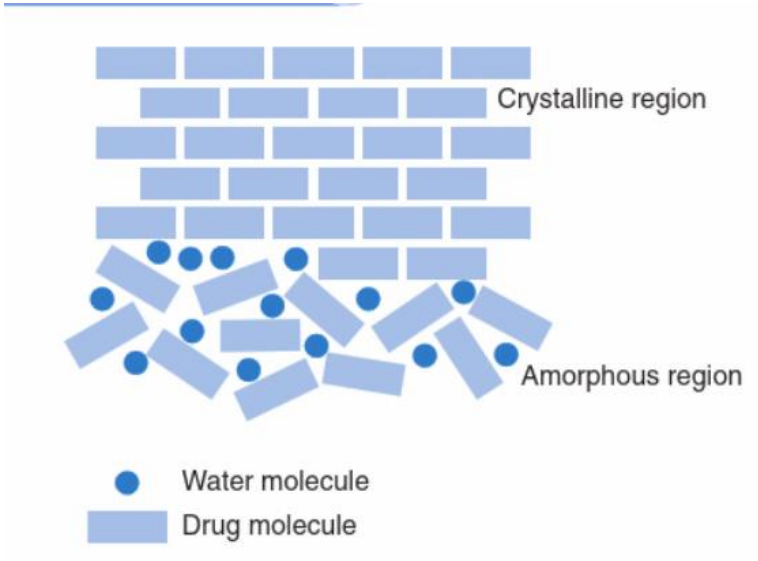
HYGROSCOPICITY AND DELIQUESCENCE

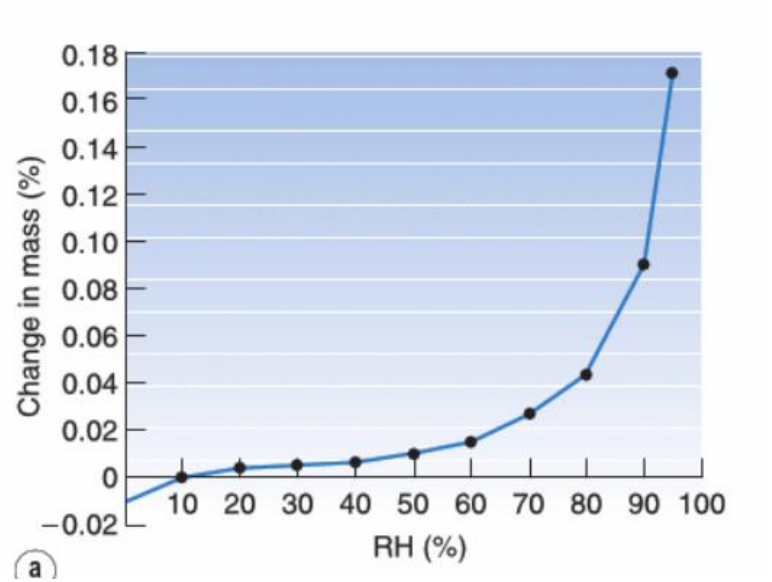
Hygroscopy and Deliquescence

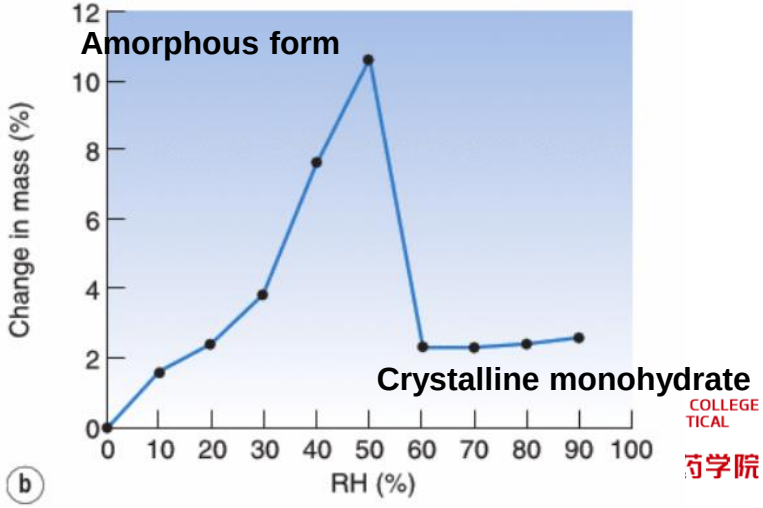
EXAMPLE DRUGS AND EXCIPIENTS THAT EXHIBIT HYGROSCOPICITY AND DELIQUESCENCE

Substance	TYPE	PROPERTY
Bacitracin（杆菌肽）	Drug	Hygroscopic
Diphenhydramine（苯海拉明）	Drug	Deliquescent
Sodium valproate（丙戊酸钠）	Drug	Deliquescent
Bentonite（皂土）	Excipient	Hygroscopic

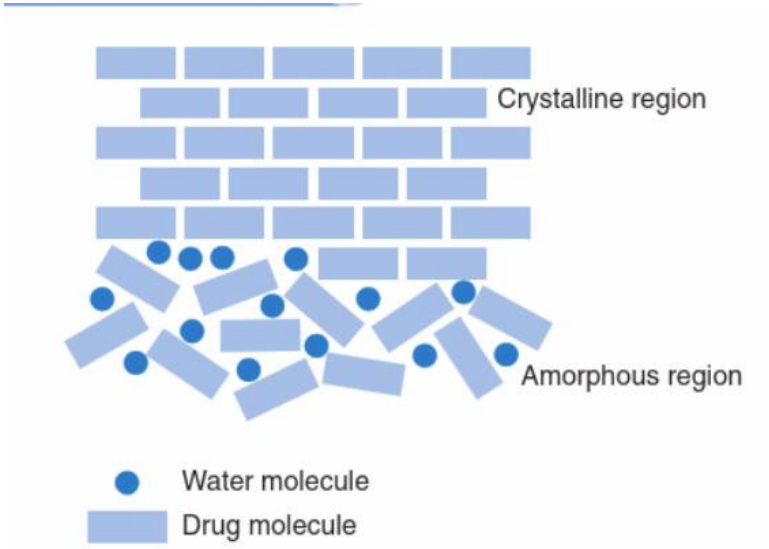
EXAMPLE OF WATER SORPTION FOR LACTOSE MONOHYDRATE

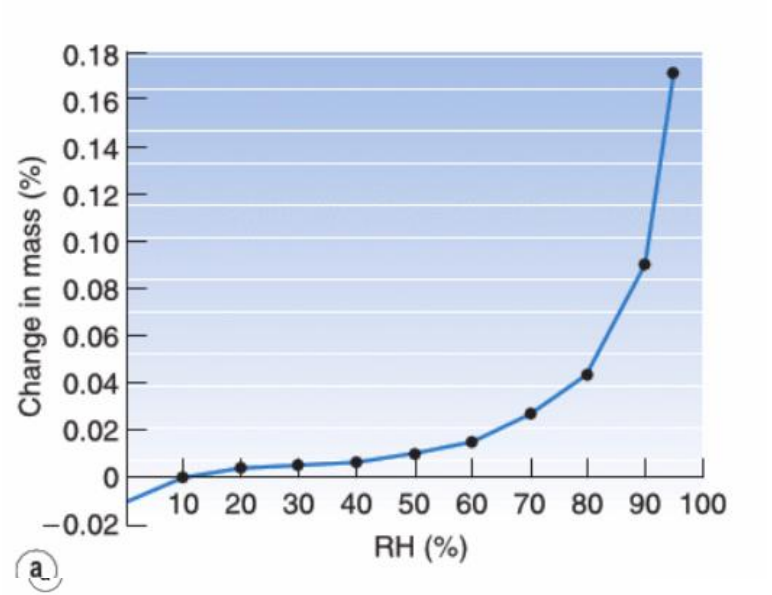


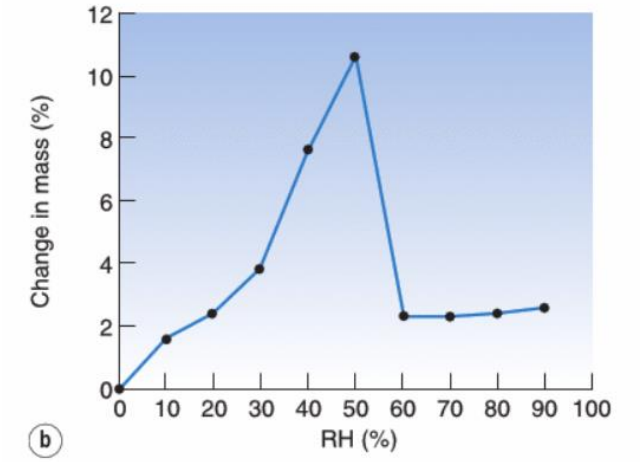




EXAMPLE OF WATER SORPTION FOR LACTOSE MONOHYDRATE（一水合乳糖）







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