States of Matter

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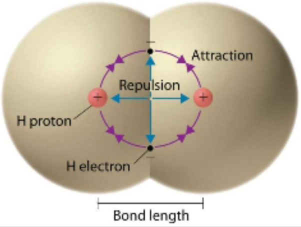
Binding forces between molecules

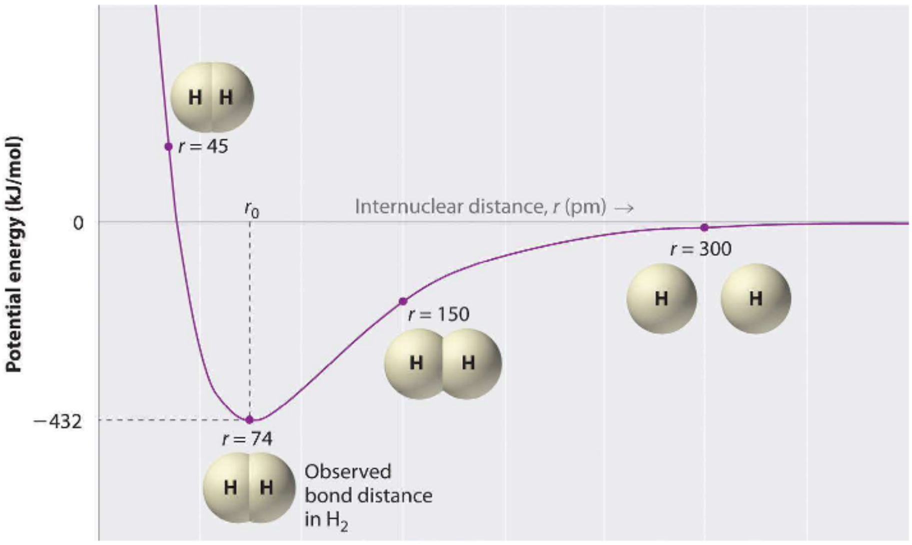
- For molecules to exist as aggregates in gases, liquids, and solids, *intermolecular forces* must exist.
- These *intermolecular forces* involve both attractive and repulsive forces.
- These forces must be balanced in an energetically favored arrangement for the molecules to interact.

Repulsive and Attractive Forces

- When two atoms or molecules are brought closer together, the opposite charges and binding forces in the two molecules are closer together than the similar charges and forces, causing the molecules to attract one another.
- When the molecules are brought so close that the similar charges touch, they repel each other like rigid elastic bodies.
- At a certain equilibrium distance, (about 3–4 Å), the repulsive and attractive forces are equal. At this position, the potential energy of the two molecules is a minimum and the system is most stable.



Repulsive and Attractive Forces



Intermolecular forces

Intermolecular forces can be divided into:

- **Van der Waals forces**
- **Ion–dipole interaction**
- **Ion–induced dipole interaction**
- **Ion-ion interaction**
- **Hydrogen bonds**

Van der Waals forces

- Van der Waal interactions are weak forces that involve the dispersion of charge across amolecule called a dipole.
- Van der Waal interactions can be classified into:
  - A.Dipole–dipole interaction, orientation effect, or **Keesom force**
  - B.Dipole-induced dipole interaction, induction effect, or **Debye force**
  - C.Induced dipole–induced dipole interaction, dispersion effect, or **London force**

Van der Waals forces

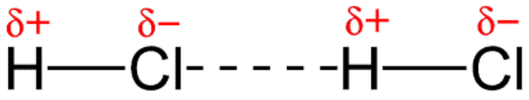
- **Keesom forces occur between polar molecules in which the permanent dipoles interact with one another (*dipole-dipole interactions) or (orientation effect).***
- Polar molecules have polar covalent bonds which are unevenly distributed in space due to the difference in the electronegativity of the atoms forming the bond e.g. HCl.
- The nucleus of the chlorine atom pulls the electron pair involved in the chlorine–hydrogen bond closer to itself and creates a permanent partial positive charge on the hydrogen and a permanent partial negative charge on the chlorine (**Permanent dipole),**

$$\overset{\delta^+}{H}-\overset{\delta^-}{Cl}$$

Dipole Moment has a Magnitude and a Direction

Van der Waals forces

- The Partial opposite charges (permanent dipoles) attract one another (**dipole-dipole interactions)**
- The dipole-dipole forces increases as the polarity of the molecule increases.
- **Keesom forces** are much weaker than ionic bonds because the charges involved in bonding are partial.

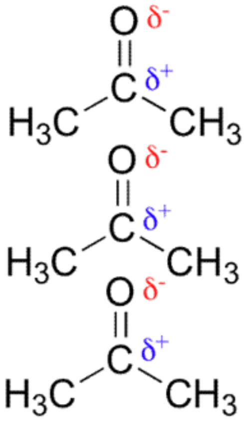


$$\overset{\delta+}{H}-\overset{\delta-}{Cl}\text{- - - - -}\overset{\delta+}{H}-\overset{\delta-}{Cl}$$

Van der Waals forces

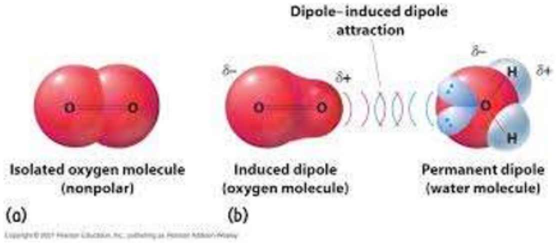
- Example of Keesom forces

- Acetone



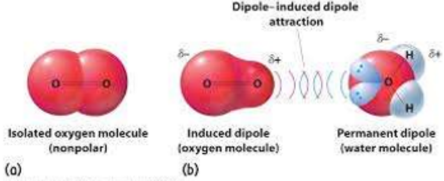
Van der Waals forces

- **Debye** forces occur between a polar and a nonpolar molecule in which the permanent dipole in the polar molecule induce an electric dipole in the non polar one (dipole-induced dipole interactions) or (induction effect) e.g. water and oxygen.



Van der Waals forces

- The oxygen molecule is nonpolar. However, when it comes close to the oxygen atom in a water molecule, the partial negative charge on the oxygen atom repels the electrons in the oxygen molecule. This causes (induces) a temporary partial positive charge in the end closest to the water molecule and a buildup of a partial negative charge in the end furthest away. This induced dipole is temporary and forms only when the two molecules are extremely close to one another.



Van der Waals forces

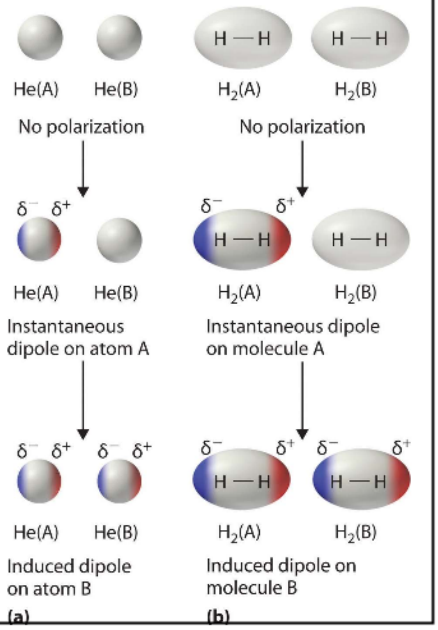
- The strength of Debye forces increases with the ease of distortion of the electron cloud of the nonpolar molecule (i.e. polarizability of the molecule).

- Debye forces is weaker than Keesom forces because the dipole in the nonpolar molecule is temporary (induced) and forms only when the two molecules are extremely close to each other.

Van der Waals forces

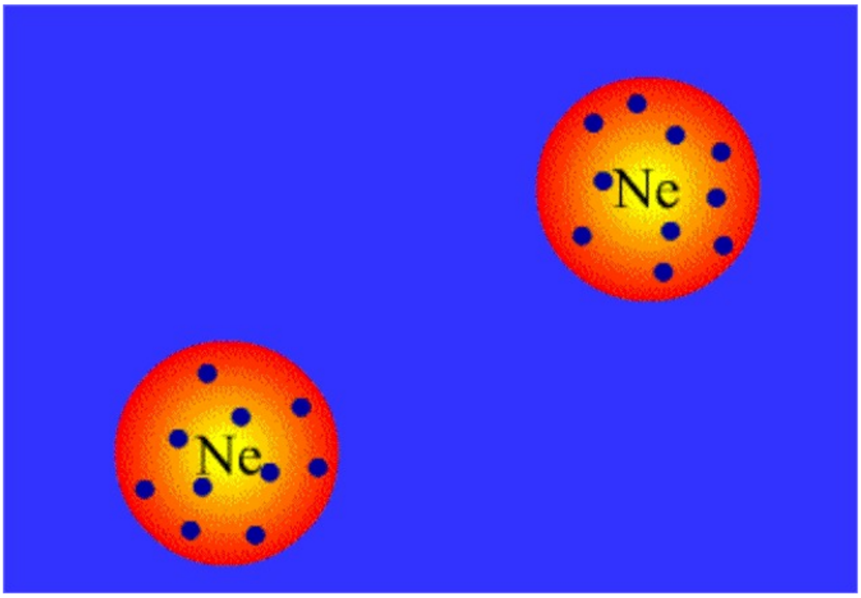
- **London forces** occur between two nonpolar (neutral) molecules in which molecules can induce polarity on each other (*induced dipole-induced dipole interactions) or (dispersion effect).e.g.Helium , Neon, hydrocarbons…*

Van der Waals forces



- This attraction is produced by temporary asymmetry in the distribution of the electrons around the nucleus.

Van der Waals forces

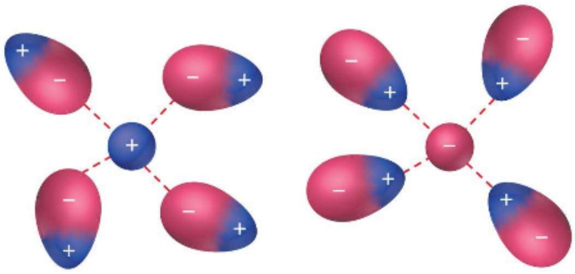


Van der Waals forces

- **London forces** occur between all atoms and molecules (between polar/polar and polar/nonpolar molecules as well)
- The larger the atom or molecule, the greater its polarizability (easier to induce a momentary dipole) and the stronger the dispersion forces become.
- This is because:
  1. The electrons are farther from the positive nucleus and so are held less strongly
  2. The number of electrons is greater
- London Force is the weakest of all the intermolecular forces.

Ion-dipole forces

- Ion-dipole forces occur between a charged ion and a polar molecule (i.e. a molecule with a dipole) Cations are attracted to the negative end of a dipole, while anions are attracted to the positive end of a dipole

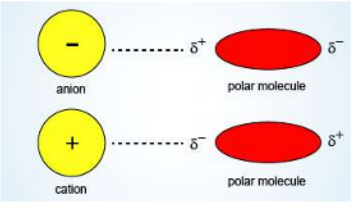


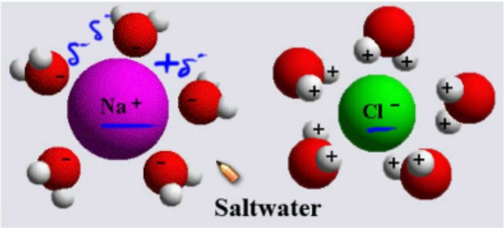
Cation–dipole attractions

Anion–dipole attractions

Ion-dipole forces

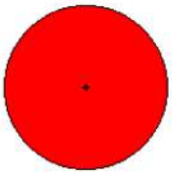
- These types of interactions account in part for the solubility of ionic crystalline substances in water; the cation, for example, attracts the relatively negative oxygen atom of water and the anion attracts the hydrogen atoms of the dipolar water molecules.



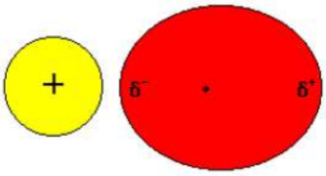


Ion-Induced dipole

- **Ion-Induced dipole forces occur between a charged ion and a nonpolar molecule.**
- These forces result when the approach of an ion induces a dipole in an atom or in a nonpolar molecule by disturbing the arrangement of electrons
- Ion-induced dipole forces are presumably involved in the formation of the iodide complex
- $I_2 + K + I^- = K + I_3^-$



Spherical atom with no dipole. The dot indicates the location of the nucleus.



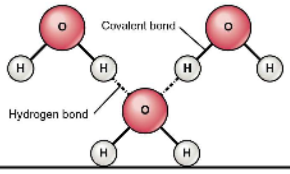
Upon approach of a charged ion, electrons in the atom respond and the atom develops a dipole.

Ion-ion interactions

- A cation on one compound will interact with an anion of another compond.
- Ion-ion interactions may be intermolecular (e.g. a hydrochloride salt of a drug) or intramolecular (e.g., a salt bridge interaction between counter ions in proteins).

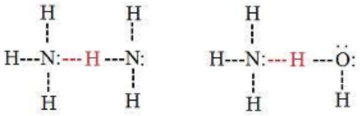
Hydrogen bond

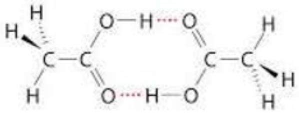
- Hydrogen bond is a strong type of dipole-dipole interaction that occurs between a molecule containing a hydrogen atom and a strongly electronegative atom such as fluorine, oxygen, or nitrogen
- In order to create the bond, the hydrogen atom must be covalently attached to another electronegative atom.
- A perfect example of hydrogen bond is water.
- Hydrogen bonds can also exist between alcohol molecules, carboxylic acids, aldehydes, and DNA and polypeptides.



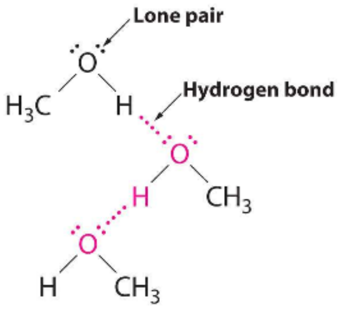
Hydrogen bond

Examples

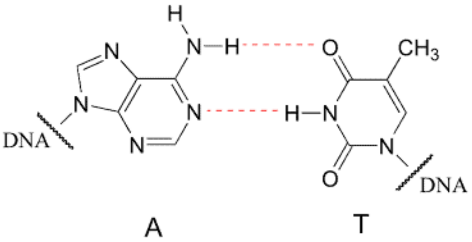




Hydrogen bonding in acetic acid



Hydrogen bonding in methanol



Hydrogen bond

- Hydrogen bonds are responsible for many unusual physical properties of water including its abnormally low vapor pressure , high boiling point, and the greater volume of ice water.
- Hydrogen bonding is stronger than all Van der Waals intermolecular forces (they are given their own classification), but are still weaker than ionic and covalent bonds.

Bond energies

- Bond energy is a measure of the strength of bond.

Intramolecular forces:

Ionic>covalent>metallic

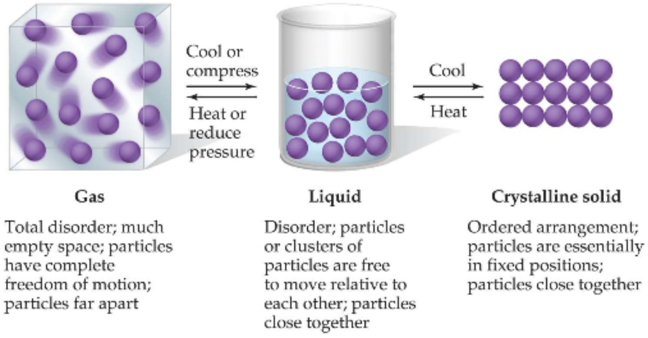
Intemolecular forces:

- Ion-dipole>ion-induced dipole>hydrogen bond>keesom>Debye>London

States of Matter

- Three primary state of matter

1) Gaseous state 2) Liquid state 3) Solid state



- Other mesophases:

Liquid crystals, Supercritical fluids

The gaseous state

- Gases are described as molecules that have high kinetic energy → rapid motion of molecules.
- Gas molecules exert relatively small forces on each other (molecules try to act independently of one another).

General properties

- A gas mixes rapidly and completely with any other gas.
- A gas uniformly fills any container and assumes its shape (volume).
- Gas is the only state that is compressible.
- The vigorous motion produces a pressure called vapor pressure.

Pressure units

- The SI unit is the Pascal (Pa) where:

  $$1 \text{ Pa} = 1 \text{ N m}^{-2}$$

- The relationship of other commonly used pressure units to the Pascal is as follows:
  - ☐1 bar = 10^5 Pa
  - ☐1 mmHg = 1 torr = 133.32 Pa
  - ☐1 atm = 1.013×10^5 Pa
  - ☐1 psi = 6894.76 Pa
- Standard atmospheric pressure is 760 mmHg = 760 torr = 1.013 bar = 1.013×10^5 Pa

Ideal gas

- Ideal gas is a gas where no intermolecular interactions exist and collisions are perfectly elastic, and thus no energy is exchanged during collision.
- The properties of the ideal gas can be described by the general ideal gas law, which is derived from Boyle, Charles and Gay-Lussac laws

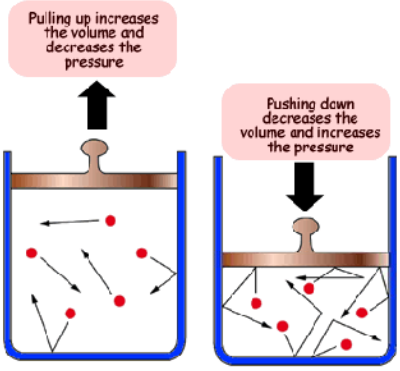
Ideal gas

- **Boyle's law** states that the volume and pressure of a given mass of gas is inversely proportional (i.e. when the pressure of a gas increases, its volume decreases).

$$P \propto \frac{1}{V} \quad or \quad PV = k$$

$$P_1V_1 = P_2V_2$$

P: pressure, **K**: constant,
V: volume

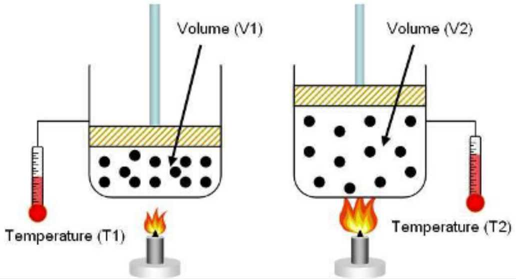


In the smaller space the particles suffer more collisions with the walls of the container - it is this that we measure as 'pressure exerted by the gas'.

Ideal gas

- The **Charles** law states that the volume and absolute temperature of a given mass at constant pressure are directly proportional:

$$V \propto T \quad \text{or} \quad V = kT$$



Ideal gas

- **Gay-Lussac's law** states that the pressure of a given mass of gas varies directly with the absolute temperature of the gas, when the volume is kept constant:

$$P/T = k$$

Ideal gas

- Boyle, Gay-Lussac and Charles law can be combined to obtain the familiar relationship:

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2}$$

Ideal gas

Example

- In the assay of ethylnitrite spirit, the nitric oxide that is librated from a definite quantity of spirit and collected in a gas burette occupies a volume of 30.0 ml, at a temperature of 20 °C and a pressure of 740 mm Hg. Assuming the gas is ideal, what is the volume at 0 °C and 760 mm Hg?

$$\frac{740 \times 30.0}{273+20} = \frac{760 \times V_2}{273}$$

$V_2 = 27.2$ mL

General ideal gas law

- General ideal gas law (also called equation of state) relates the **pressure**, **volume**, and **temperature** of a given mass of gas.

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2} \quad \Rightarrow \quad \frac{P V}{T} = R$$

- **R:** the molar gas constant value for the PV/T ratio of an ideal gas.

- For n moles the equation becomes:

PV = nRT

General ideal gas law

- The volume of 1 mole of an ideal gas under standard conditions of temperature and pressure (i.e., at 0° C and 1 atm) has been found by experiment to be 22.414 liters.
- Substituting this value in general ideal gas law:

$$\mathbf{R = \frac{P\,V}{T} = \frac{1 \times 22.414}{273.16} = 0.08205\ atm\ L/mole\ K}$$

- The molar gas constant can also be expressed by energy units:
- **R = 8.314 Joules/mole K or**
- **R = 1.987 cal/mole deg**

1 atm $= 1.0133 \times 10^6$ dynes/cm^2
1 Joule = 1 N.m = 1 Pa.m^3
1 cal = 4.184 Joule

General ideal gas law

Example: Calculation of volume using the ideal gas law

- **What is the volume of 2 moles of an ideal gas at 25°C and 780 mm Hg?**

- 780 mm Hg/760 mm Hg = 1.0263atm
- 25°C + 273 = 298 K

- **PV=nRT** → $V = \frac{\mathbf{nRT}}{\mathbf{P}} = \frac{2 \times 0.08205 \times 298}{1.026} = 47.65\ \mathrm{L}$

Aerosols and ideal gas law

- An Aerosol product consists of the following component parts:
  1) product concentrate
     - active ingredient &
     - Additives (such as, antioxidants, surface- active agents, and solvents)
  2) Propellant
     - liquefied gas or a mixture of liquefied gases or
     - compressed gases (carbon dioxide, nitrogen, and nitrous oxide)
- When the propellant is a liquefied gas or a mixture of liquefied gases, it frequently serves the dual role of propellant and solvent or vehicle for the product concentrate.
  3) Container
  4) Valve and actuator

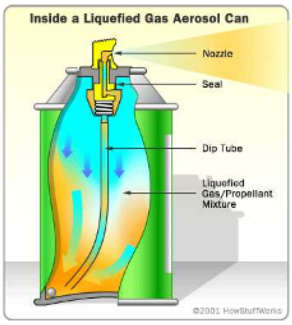
Aerosols and ideal gas law

- By depressing a valve on the container, some of the drug–propellant mixture is expelled owing to the excess pressure inside the container.
- Outside the container, the liquid propellant reverts to gas and vaporizes off, while the drug forms a fine spray.

Aerosols and ideal gas law

In pharmaceutical aerosols a drug might be:

- Dissolved or suspended in a liquefied propellant (a material that is liquid under the high pressure inside the container but forms a gas under normal atmospheric conditions).
  - ➢ Part of the propellant exists as a gas and exerts the pressure necessary to expel the drug, whereas the remainder exists as liquid and provides a solution or suspension vehicle for the drug.



- Dissolved or suspended in a liquid and expelled by a compressed gas (propellant)

Aerosols and ideal gas law

- The propellant is responsible for developing the proper pressure within the container, and it expels the product when the valve is opened and its ,in the atomization or form production of the product.

Types of propellants:

1) Liquefied gases

a. Fluorinated hydrocarbons

b. Hydrocarbons (propane, butane, and isobutane)

2) Compressed gases

Carbon dioxide, nitrogen and nitrous oxide.

➢ The pressure in the case of compressed gas propellants can be determined by ideal gas law assuming ideal gas behavior.

General ideal gas law

Example: Calculation of pressure using the ideal gas law

Calculate the pressure at 25°C within an aerosol container of internal volume 250 cm^3 containing 160 cm^3 of concentrate above which has been introduced 0.04 mol of nitrogen gas. Assume ideal behavior.

Answer

$$PV = nRT$$

$$P = \frac{0.04 \times 8.314 \times 298}{(250 - 160) \times 10^{-6}}$$

$$P = 1.01 \times 10^{6}\ \mathrm{N\ m^{-2}}\ \text{(or Pa)}$$

General ideal gas law: Molecular weight of gas

The approximate molecular weight of a gas can be determined by use of the ideal gas law:

$$\mathbf{PV = nRT}$$

since **n=g/M** then:

$$\mathbf{PV = \frac{g}{M} RT}$$

$$\mathbf{M = \frac{gRT}{PV}}$$

General ideal gas law: Molecular weight of gas

Example: Molecular weight determination using the ideal gas law

If 0.30 g of ethyl alcohol in the vapor state occupies 200 mL at a pressure of 1 atm and a temperature of 100 °C, what is the molecular weight of ethyl alcohol?

100 °C + 273 = 373 K

200 mL ÷ 1000 mL =0.2 L

$$\mathbf{M} = \frac{\mathbf{gRT}}{\mathbf{PV}} = \frac{0.3 \times 0.082 \times 373}{1 \times 0.2} = 46\,\frac{\mathrm{g}}{\mathrm{mole}}$$

Ideal gas

Kinetic Molecular Theory

Kinetic molecular theory explains the behavior of gases according to the ideal gas law:

- Gases are composed of particles called atoms or molecules, the total volume of which is so small (negligible) in relation to the volume of the space in which the molecules are confined.
- Gas molecules exert neither attractive nor repulsive forces on one another
- The particles exhibit continuous random motion. The average kinetic energy, E, is directly proportional to the absolute temperature of the gas, or **E=(3/2)RT.**
- The molecules exhibit perfect elasticity; there is no net loss of speed or transfer of energy after they collide with one another and with the walls of the confining vessel.

Real gas

- Real gases do not interact without energy exchange, and therefore do not follow the laws of Boyle, Charles, and Gay-Lussac.
- Real gases are not composed of infinitely small and perfectly elastic non-attracting spheres.
- They are composed of molecules of a finite volume that tend to attract one another.
- The significant molecular volume and the intermolecular attractions between gas molecules affect both the volume and the pressure of a real gas respectively.

Real gas: van der Waals equation

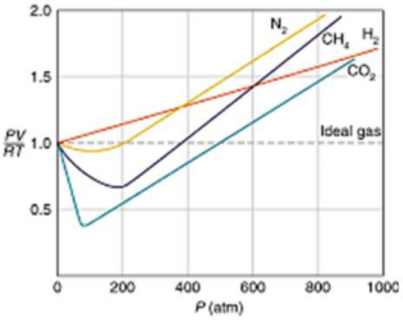
- The van der Waals equation is a modified ideal gas equation that takes into account the factors that affect the volume and pressure of a real gas.

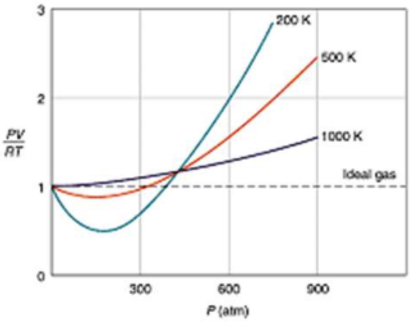
For n mole of gas: $\left(\boldsymbol{P}+\frac{\boldsymbol{a}\boldsymbol{n}^2}{\boldsymbol{V}^2}\right)(\boldsymbol{V}-\boldsymbol{n}\boldsymbol{b})=\boldsymbol{n}\boldsymbol{R}\boldsymbol{T}$

- where *a and b are constants for a particular* gas.
- Around each molecule of a gas is a particular volume from which other molecules are excluded for purely physical reasons. The bulk molar volume, *V, of the gas is consequently an* overestimation of the true molar volume.

Real gas: van der Waals equation

- The influence of non-ideality is greater when the gas is compressed (At high pressure and low temperature).
- When the volume of a gas is large (At low pressure and high temperature), the molecules are well dispersed and far apart. Under these conditions, **a/V^2** and **b** become insignificant with respect to **P** and **V**, respectively, and the van der Waals equation for the real gas reduces to the ideal gas equation: **PV = nRT**
- At these conditions, real gases behave in an ideal manner.
- A convenient means of expressing departure from ideality is by a plot of PV/RT as a function of pressure for 1 mole of each gas



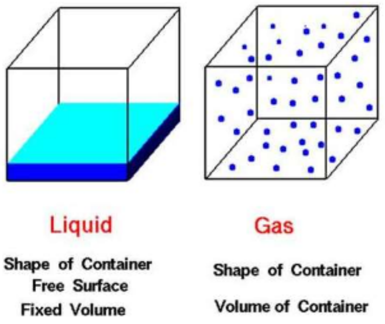


The liquid state

- The transitions from a gas to a liquid and from a liquid to a solid depend on both temperature and pressure.
- When a gas is cooled, it loses some of its kinetic energy in and the velocity of the molecules decreases.
- If pressure is applied to the gas, the molecules are brought within the range of the van der Waals forces and pass into the liquid state.

The liquid state

- Liquids are denser than gases and occupy a definite volume and density due to the presence of van der Waals forces.
- Liquids are relatively incompressible.
- Liquid are fluids (have no definite shape) like gases.

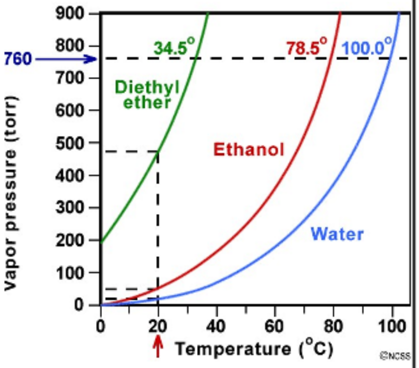


Vapor pressure of liquids

- When a liquid is placed in an evacuated container at a constant temperature, the molecules with the highest energies break away from the surface of the liquid and pass into the gaseous state (evaporate), and some of the molecules subsequently return to the liquid state (condense).
- When the rate of condensation equals the rate of vaporization at a definite temperature, the vapor becomes saturated and a dynamic equilibrium is established.
- The pressure of the saturated vapor above the liquid is then known as the *equilibrium vapor pressure*.

Vapor pressure of liquids

- As the temperature of the liquid is elevated, more molecule approach the velocity necessary for escape and pass into the gaseous state.
- As a result the vapor pressure increases with rising temperature.
- Any point on one of the curves represents a condition in which the liquid and the vapor exist together in equilibrium.



Vapor pressure of liquids

- **Clausius–Clapeyron equation** expresses the relationship between the vapor pressure and the absolute temperature of a liquid:

$$\ln\frac{P_2}{P_1} = \frac{\Delta H_v(T_2 - T_1)}{RT_1T_2}$$

- P_1 and P_2: vapor pressures at absolute temperatures T_1 and T_2.
- ΔHv: the molar heat of vaporization (the heat absorbed by 1 mole of liquid when it passes into the vapor state).
- R: molar gas constant

Vapor pressure of liquids

Example: Application of **Clausius–Clapeyron equation**

- Compute the vapor pressure of water at 120 °C. The vapor pressure of water at 100°C is 1atm, and ΔHv is 9720 cal/mole.

$$\ln\frac{P_2}{P_1} = \frac{\Delta H_v(T_2 - T_1)}{RT_1T_2}$$

$$\ln\frac{P_2}{1} = \frac{9720(393 - 373)}{1.987 \times 393 \times 373}$$

$$P_2 = 1.95 \text{ atm}$$

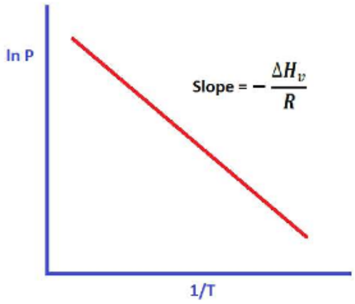
Vapor pressure of liquids

- The Clausius–Clapeyron equation can be written in a more general form:

$$lnP = -\frac{\Delta H_v}{R}\frac{1}{T} + Constant$$

or

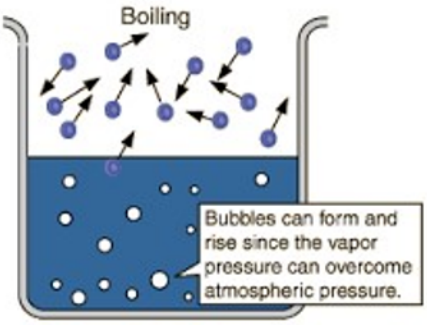
$$logP = -\frac{\Delta H_v}{2.303\,R}\frac{1}{T} + Constant$$



- A plot of ***lnP*** (or ***logP***) against **1/T** results in a straight line. The heat of vaporization of the liquid can be calculated from the slope of the line.

Boiling point

- If a liquid is placed in an open container and heated until the vapor pressure equals the atmospheric pressure, the liquid starts to boil and escape into the gaseous state.
- The temperature at which the vapor pressure of the liquid equals the external or atmospheric pressure is known as the *boiling point*
- The absorbed heat used to change the liquid to vapor is called the *latent heat of vaporization.*



Boiling point

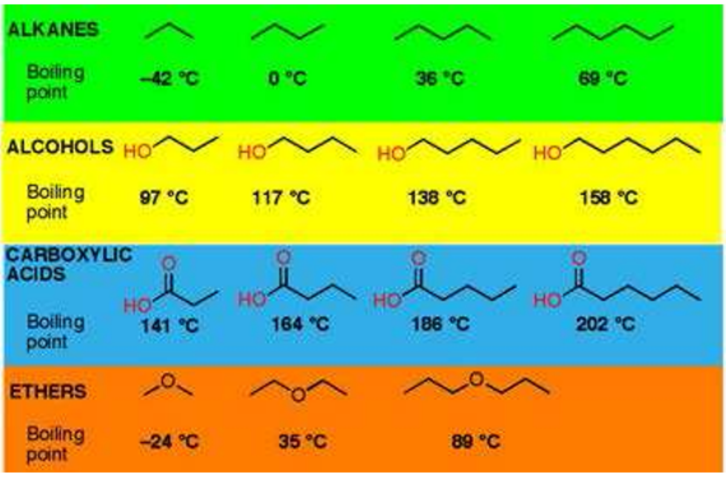
- The temperature at which the vapor pressure of the liquid equals an atmospheric pressure of 1 atm is called *normal boiling point*
- At higher elevations, the atmospheric pressure decreases and the boiling point is lowered.
- At a pressure of 700 mm Hg, water boils at 97.7°C; at 17.5 mmHg, it boils at 20°C.
- The change in boiling point with pressure can be computed by using the **Clausius–Clapeyron equation.**

Boiling point

- The boiling point can be considered the temperature at which thermal agitation can overcome the attractive forces between the molecules of a liquid.
- The boiling point of a compound, like the heat of vaporization and the vapor pressure, depends on the magnitude of the attractive forces.
- Nonpolar substances have low boiling points and low heats of vaporization because the molecules are held together predominantly by the weak London forces.
- Polar molecules (e.g. water) exhibit high boiling points and high heats of vaporization because they are associated through hydrogen bonds.

Boiling point

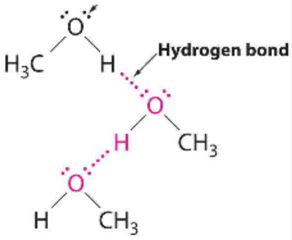
- The boiling points of normal hydrocarbons, simple alcohols, and carboxylic acids increase with molecular weight because van der Waals forces become greater with increasing numbers of atoms.

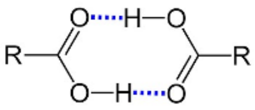


ALKANES Boiling point	−42 °C	0 °C	36 °C	69 °C
ALCOHOLS Boiling point	97 °C	117 °C	138 °C	158 °C
CARBOXYLIC ACIDS Boiling point	141 °C	164 °C	186 °C	202 °C
ETHERS Boiling point	−24 °C	35 °C	89 °C	

Boiling point

- Alcohols boil at a much higher temperature than saturated hydrocarbons of the same molecular weight because of association of the alcohol molecules through hydrogen bonding.
- The boiling points of carboxylic acids are higher than that of alcohols because the acids form dimers through hydrogen bonding. That can persist even in the vapor state





Boiling point

- Branching of the chain produces a less compact molecule with reduced intermolecular attraction, and a decrease in the boiling point.

Name	Formula	Boiling point (°C) at 1 atm. (~101.33 kPa)
Methanol	CH_3OH	~64.7
Ethanol	CH_3CH_2OH	~78.3
Propanol	$CH_3CH_2CH_2OH$	~97.2
Isopropanol	$CH_3CH(OH)CH_3$	~82.3
Butanol	$CH_3CH_2CH_2CH_2OH$	~117.7
Isobutyl alcohol	$CH_3CH(CH_3)CH_2OH$	~108
sec-Butanol	$CH_3CH_2CH(OH)CH_3$	~99.5
tert-Butanol	$(CH_3)_3COH$	~82.5

Solid state

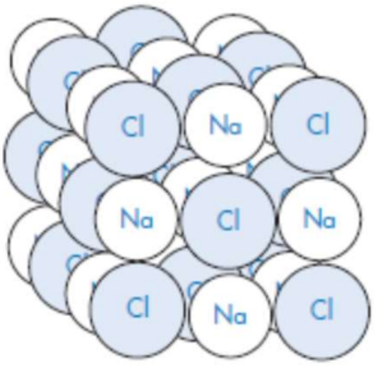
- Solid particles are made up of molecules, atoms or ions that are held in close proximity to each other.
- They are much denser than both gases and liquids due to the presence of very strong forces between molecules, atoms or ions.
- Solids are unique because their physical form (the packing of molecules and the size and shape of particles) can have an influence on the way the material will behave.
- Solids may be crystalline or amorphous (or a combination of both).

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.

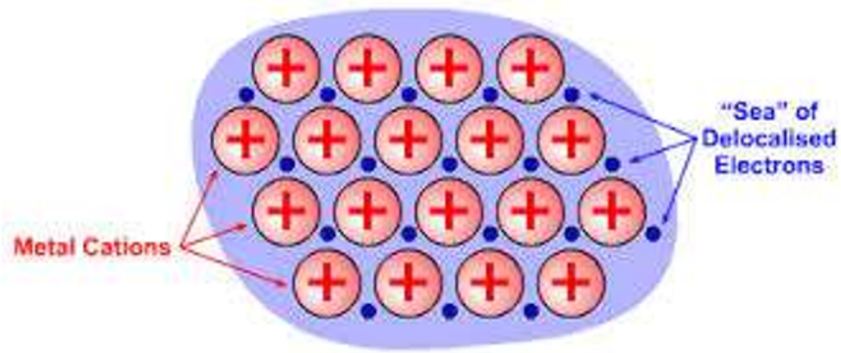
- The forces of interaction between units include:
  - metallic bonds
  - covalent bonds (e.g. Diamond)
  - ionic bonds (between ions in salts such as NaCl crystals)
  - hydrogen bonds (between molecules),
  - van der Waal's forces

Ionic bonds



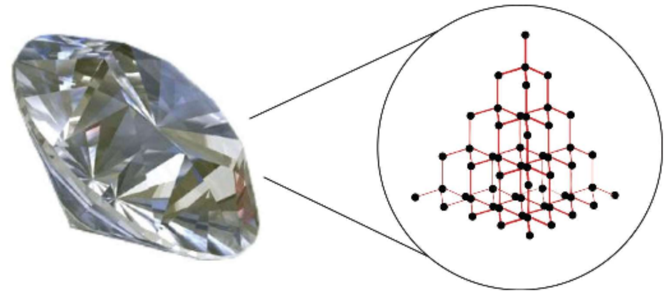
Space lattice of sodium chloride crystal. Each sodium ion is octahedrally surrounded by six chloride ions and each chloride ion is octahedrally surrounded by six sodium ions.

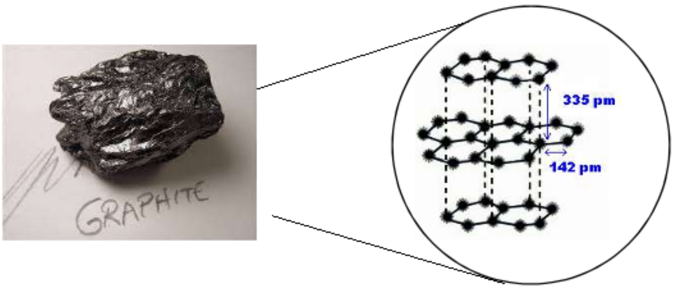
Metallic bonds



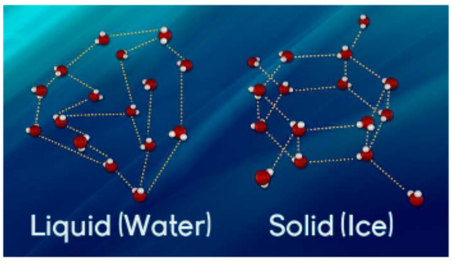
Electrons are not bonded to any particular atom and are free to move about in the solid

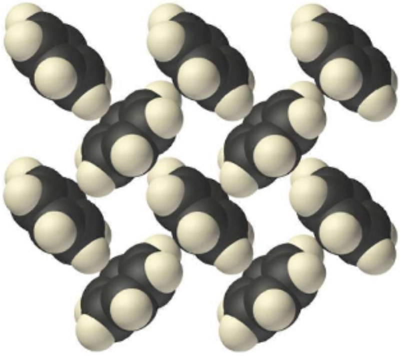
Covalent bonds





Hydrogen and Van der Waals bonds

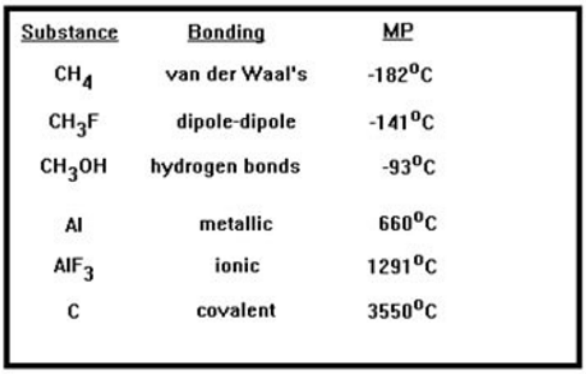




The structure of solid benzene

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.

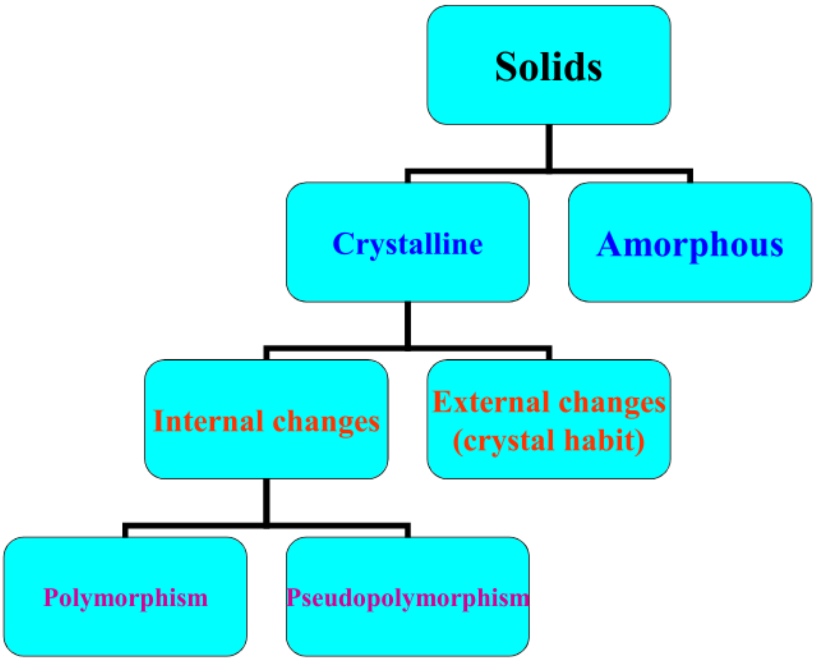
Crystallization from solution

- 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.



Solids

Crystalline

Amorphous

Internal changes

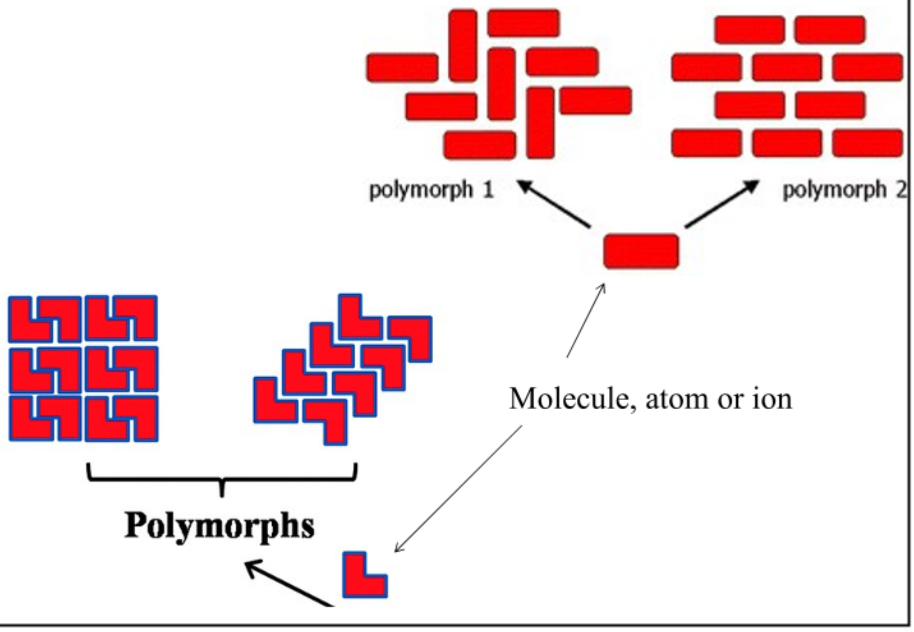
External changes (crystal habit)

Polymorphism

Pseudopolymorphism

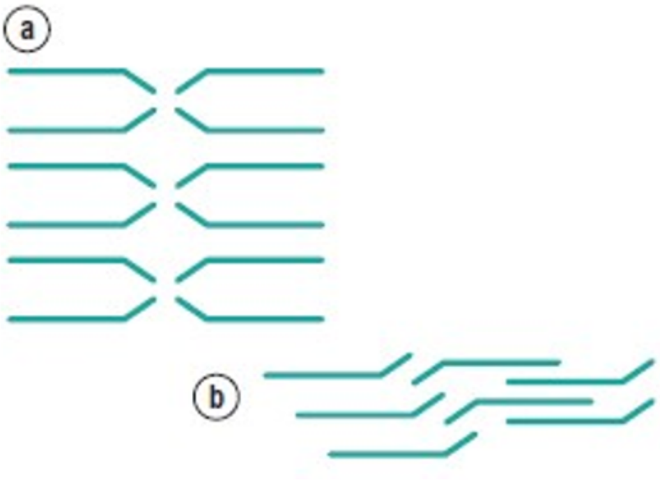
Polymorphism

- 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
- 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
  - Change in the stirring
  - Different cooling conditions
  - Different impurities in the crystallization liquid



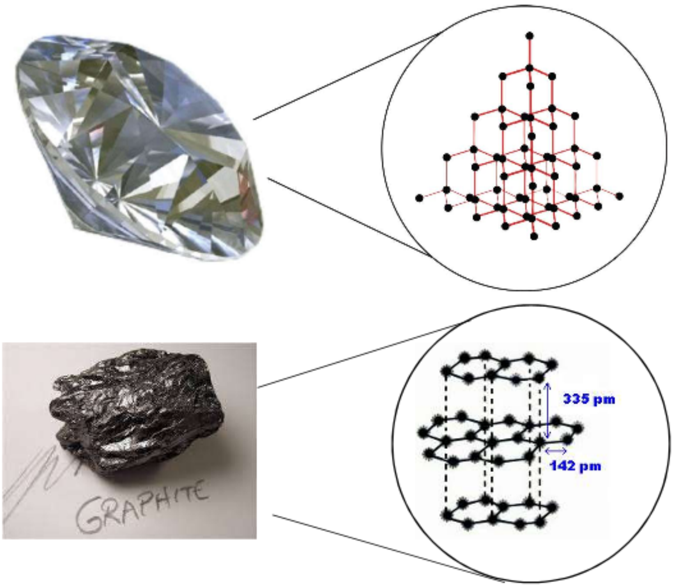
Molecule, atom or ion

Polymorphs



A representation of two polymorphic forms of a crystal consisting of a molecule shown as a 'hockey stick' shape.

Covalent bonds



Polymorphism

- Many drugs and excipients exhibit polymorphism.
- Different polymorphs have different physcial properties such as: true density, melting point, apparent solublity, 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
- Transformation of the metastable polymorph(s) to the stable one may occur and may be catalyzed by:
  - Energy (heating, milling)
  - Presence of solvent

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

- 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)

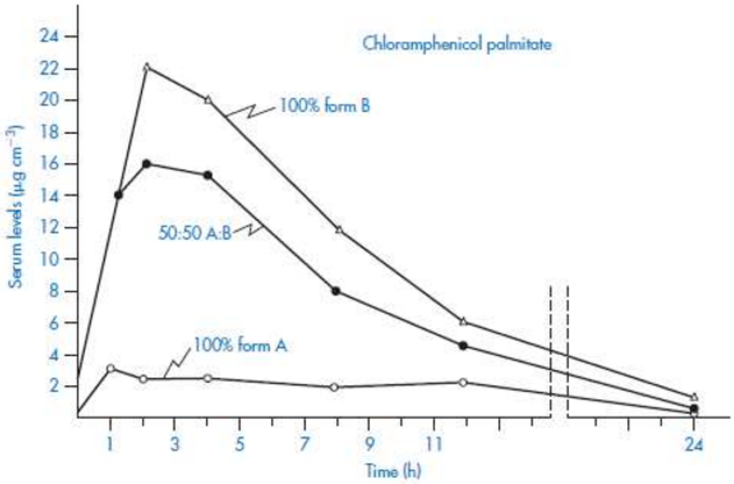
- The stable form has the highest melting point → slowest dissolution.

- 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).

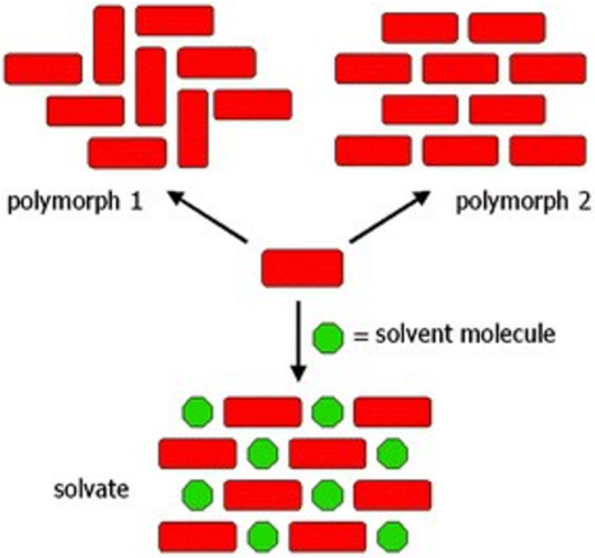
- Importance of polymorphism in bioavailability is related to different solubility and dissolution rate for different polymorphs, which might be significant (e.g. chloramphenicol palmitate).



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.

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.
- 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)

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

- 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.

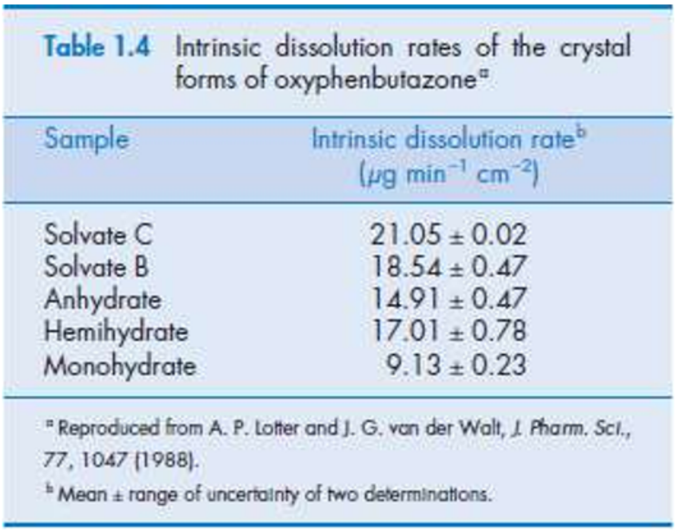
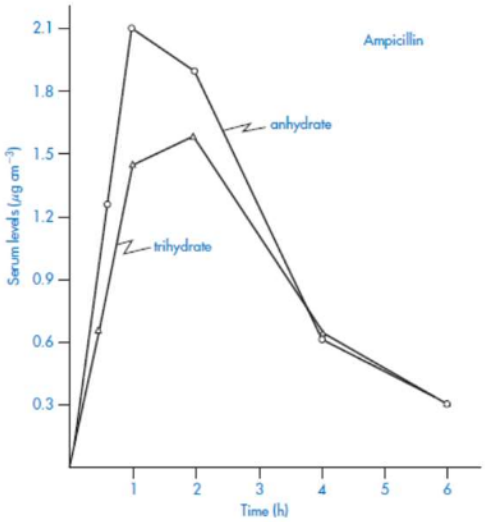


Table 1.4 Intrinsic dissolution rates of the crystal forms of oxyphenbutazone[a]

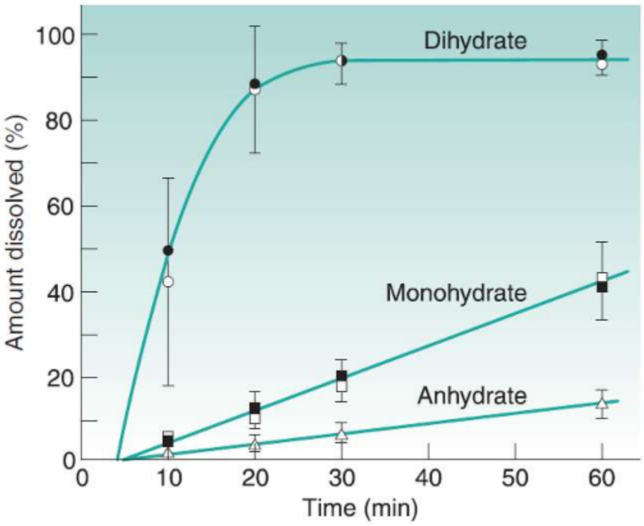
Sample	Intrinsic dissolution rate[b] (μg min^{-1} cm^{-2})
Solvate C	21.05 ± 0.02
Solvate B	18.54 ± 0.47
Anhydrate	14.91 ± 0.47
Hemihydrate	17.01 ± 0.78
Monohydrate	9.13 ± 0.23

[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 (*μg cm^{-3}) obtained after oral administration of a suspension containing 250 mg ampicillin as* the anhydrate and as the trihydrate.



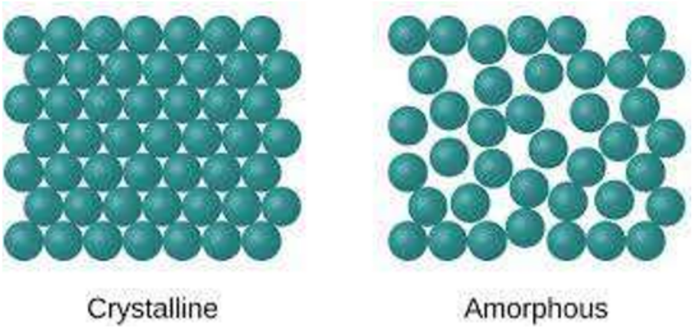
The dissolution behaviour for erythromycin as the anhydrate, monohydrate and dihydrate, showing a progressively faster dissolution rate as the level of hydrate is increased. Adapted from Allen et al., 1978

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.

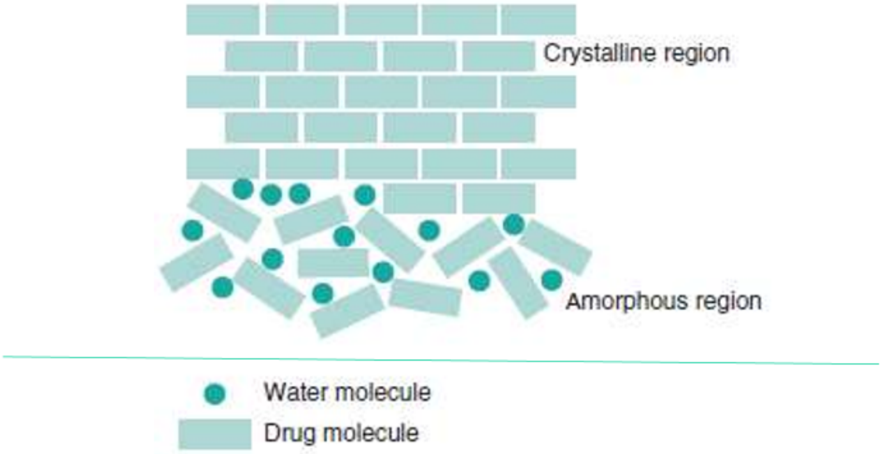


The amorphous state

- 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

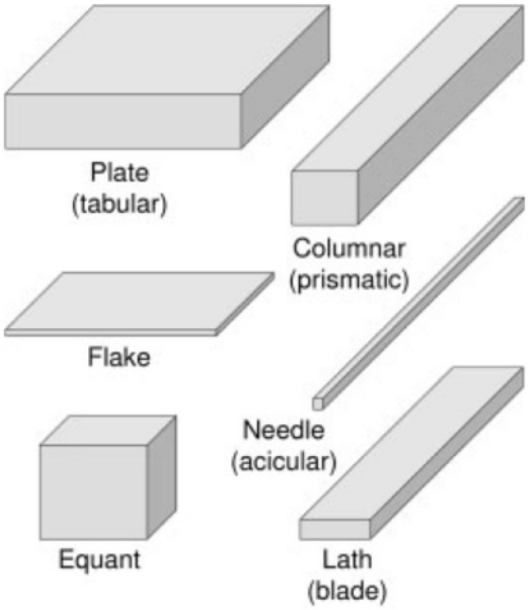
Degree of crystallinity

- 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

- 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



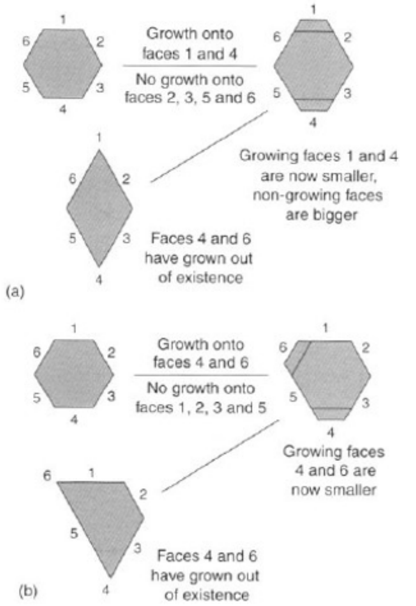


Fig. 9.10 (a) Demonstration of how growth on to faces 1 and 4 of a hexagonal crystal form result in the formation of a diamond. (b) Demonstration of how growth on to faces 4 and 6 of a hexagonal crystal result in the formation of a trapezium.

Crystal habit

- Changes in internal structure usually give different habits.
- However, it is also possible to change the external shape for the same crystal packing by changing the crystallization conditions.

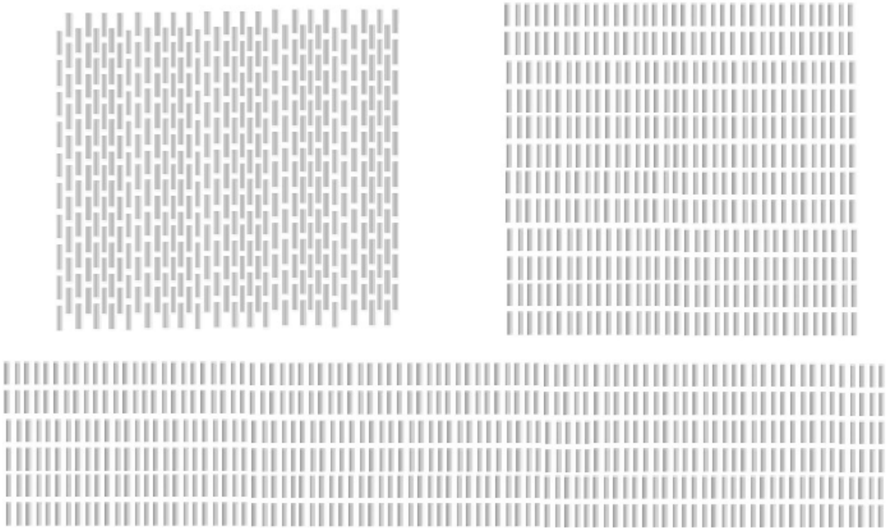
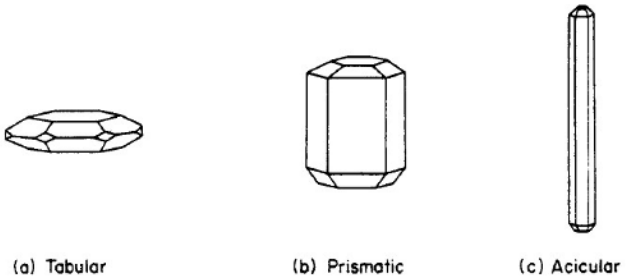


Diagram showing molecule packing effect on crystal external shape. Different external shape does not necessarily indicate different internal structure

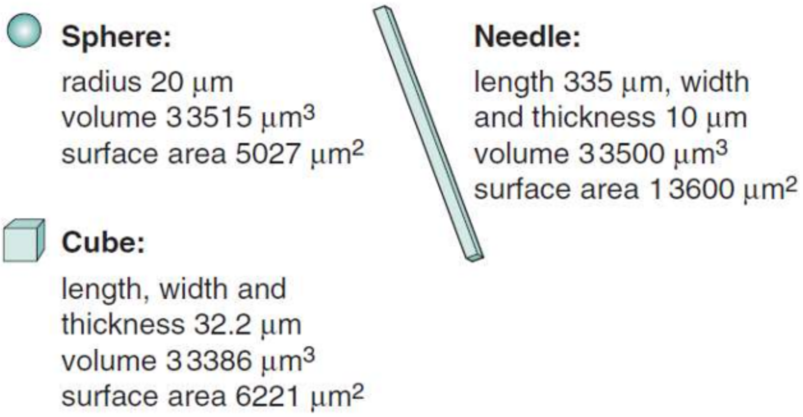


Crystal habit illustrated on a hexagonal crystal

Crystal habit

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

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

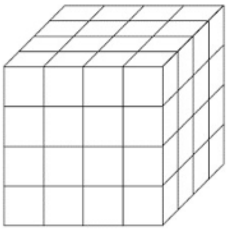


Sphere:
radius 20 μm
volume 33515 μm^3
surface area 5027 μm^2

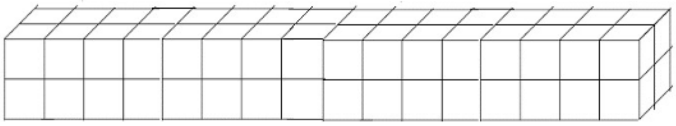
Cube:
length, width and thickness 32.2 μm
volume 33386 μm^3
surface area 6221 μm^2

Needle:
length 335 μm, width and thickness 10 μm
volume 33500 μm^3
surface area 13600 μm^2

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



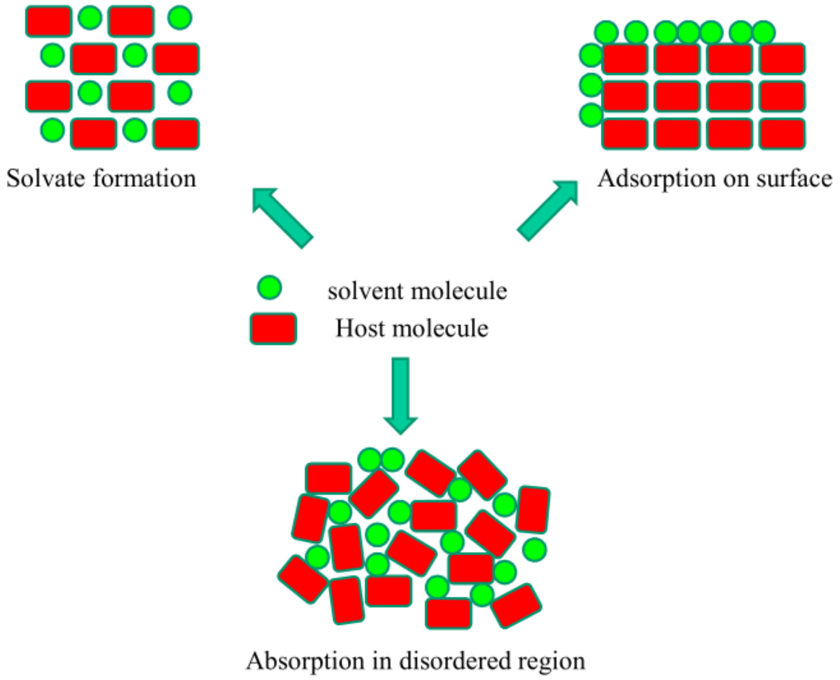
Volume = $4 \times 4 \times 4 = 64\ \mu m^3$
Area = $4 \times 4 \times 6 = 96\ \mu m^2$
Specific surface area = $1.5\ \mu m^{-1}$



Volume = $2 \times 2 \times 16 = 64\ \mu m^3$
Area = $(2 \times 16 \times 4) + (2 \times 2 \times 2) = 136\ \mu m^2$
Specific surface area = $2.125\ \mu m^{-1}$

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.



Solvate formation

Adsorption on surface

● solvent molecule

🟥 Host molecule

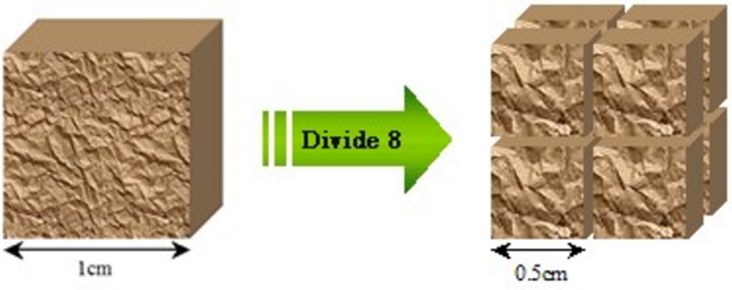
Absorption in disordered region

Importance of particle size

Particle size influence

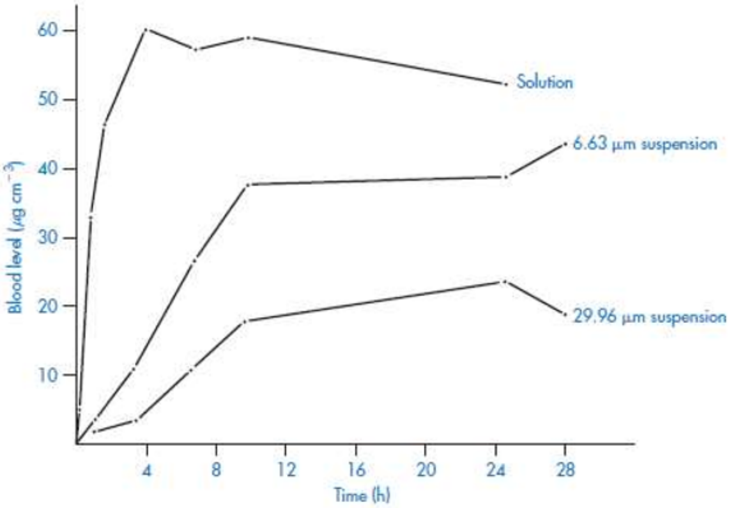
- Drug dissolution
  - Important for poorly-soluble drugs (e.g. griseofulvin, tolbutamide, spironolactone, indomethacin and nifidipine)
- Mixing of powders (content uniformity for potent drugs, segregation)
- Hygroscopicity

Cubic with 1 cm



Surface area   S=6cm^2

Surface area   S=12cm^2



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)