Pharmaceutical preformulation

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The concept of preformulation

- Formulation is the process of developing a drug candidate into a drug product.
- Prior to the development of dosage forms, it is essential that certain physicochemical properties of the drug are determined.
- This information dictates many of the subsequent events and approaches in formulation development, and therefore this learning phase is termed preformulation.

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Examples formulation

Rx -----ml pediatric kaolin mixture B.P. 1980

Ingredients	Master formula	Scaled formula
Light kaolin	200gm	
Amaranth	10ml	
Benzoic acid	20ml	
Raspberry syrup	200ml	
Chloroform water(double strength)	500ml	
Water up to	1000ml	-----ml

S. No	Ingredients	Formulations			
		F1(mg)	F2(mg)	F3(mg)	F4(mg) (Ref)
1	Ibuprofen	400	400	400	400
2	Polyvinyl pyrollidone	30	30	30	30
3	Pectin	10	20	30	-
4	Starch	-	-	-	20
4	Di calcium phosphate	153	143	133	143
5	Talc	5	5	5	5
6	Magnesium stearate	2	2	2	2

Weight of each tablet = 600 mg

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Pharmaceutical preformulation

The concept of preformulation

Physicochemical properties can be split into:

- Intrinsic properties that are inherent to the molecule and so can only be altered by chemical modification.
- Derived properties are the result of intermolecular interactions and so can be affected by solid-state form, physical shape and environment among other factors.

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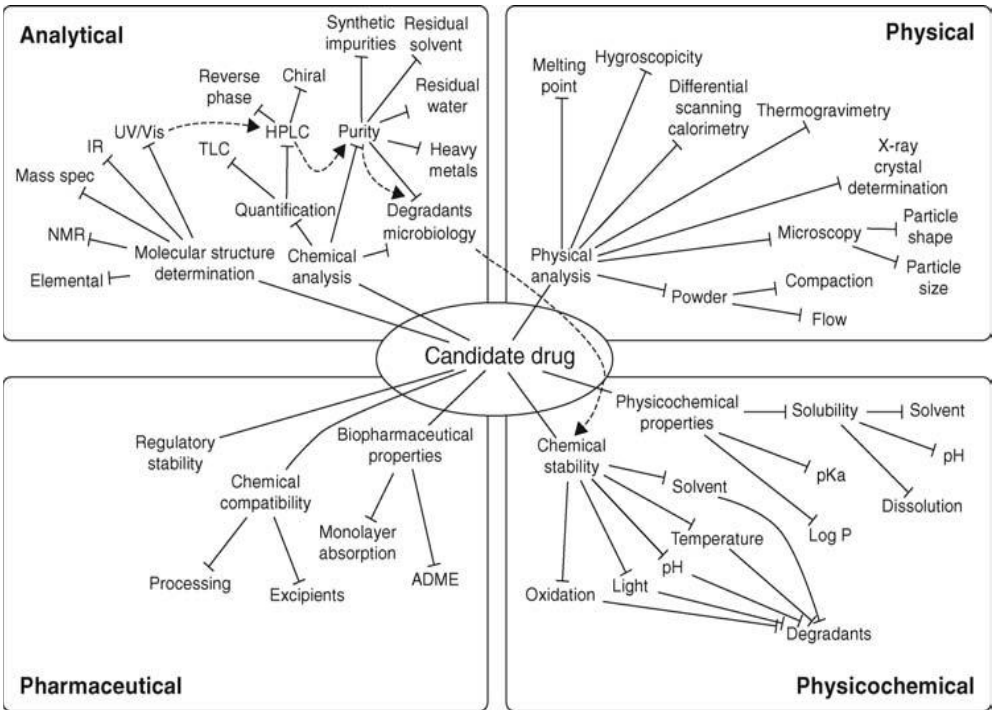

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Pharmaceutical preformulation

Analytical preformulation

- The first step in preformulation is to establish a simple analytical method.
- This is important for further steps such as determination of:
  1. Solubility
  2. pKa
  3. $P_{o/w}$
  4. Stability

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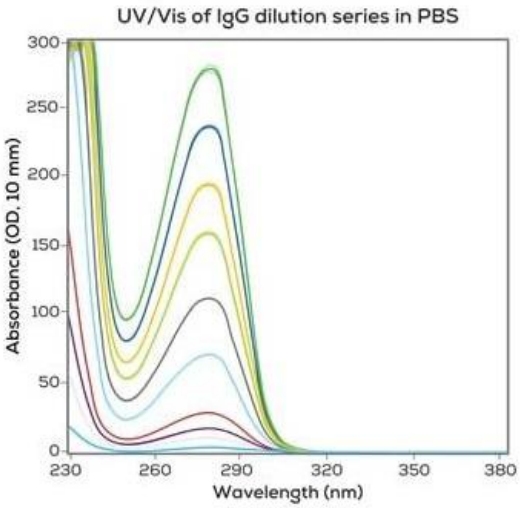
Analytical preformulation

- Most drugs absorb light in the UV region (190 -390 nm).
- UV spectroscopy is simple method and it is possible to choose an analytical wavelength suitable to quantify the amount of drug in solution.
- Other tests are suitable for identification, assay, purity and quality determination.



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Analytical preformulation

Identity	Nuclear magnetic resonance (NMR) Infrared spectroscopy (IR) UV spectroscopy Thin layer chromatography (TLC) Melting point Optical rotation, where applicable
Assay	High performance liquid chromatography (HPLC) Titration UV spectroscopy
Purity	Moisture Inorganic elements Heavy metals Organic impurities Enantiomers
Quality	**Organoleptic properties**: Appearance (texture), Odour, color, etc Solution color pH of slurry Melting point

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Analytical preformulation

Identification of drug

- A basic requirement is to ensure that the drug's molecular structure is identical to that proposed by the synthetic chemist.
- This should be performed before any form of testing

1. Nuclear magnetic resonance (NMR)
2. Infrared spectroscopy (IR)
3. UV spectroscopy
4. Thin layer chromatography (TLC)
5. Melting point
6. Optical rotation, where applicable

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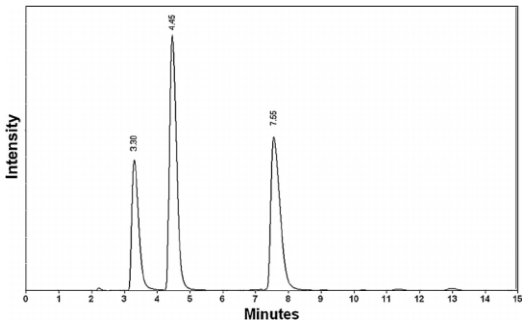
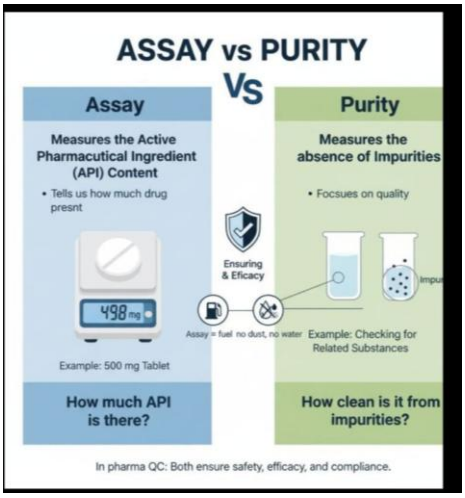
Analytical preformulation

Assay development

- In order to follow drug stability, it is important to have stability- indicating assays.
- In some cases UV spectroscopy can be used, but in general chromatography (**HPLC**) is used to separate the drug from its degradation products and any excipients





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Analytical preformulation

Assay development

Stability indicating methods:

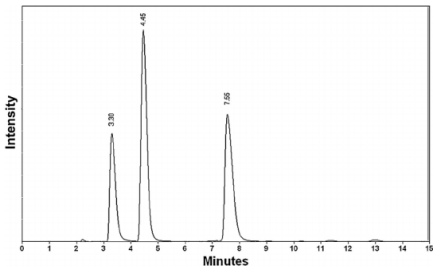
- These methods are able to separate and estimate the level of impurities (or degradation products) and are based mainly on chromatography.
- Common methods are:

High performance liquid chromatography (HPLC)

- Normal phase HPLC non-polar mobile)phase)
- Reverse phase HPLC polar mobile)phase)

Gas chromatography (GC)

- For volatile drugs.



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Analytical preformulation

Purity

- A key component of analytical development is purity determination, which is the actual percentage of the sample, usually by weight, that can be attributed to the drug
- Impurities however can range through:

1. moisture and residual solvents (quantified through KF titration for water and gas chromatographic methods for organic solvents)
2. inorganic impurities (heavy metals, salts, and catalysts detected by pharmacopoeial or other methods)
3. organic impurities (starting materials, intermediates, by-products, related impurities, and degradation products)
4. enantiomeric purity, if the drug is chiral
5. polymorphic purity

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Physical forms and solid state properties

Polymorphism

- Polymorphism is the ability of material to exist in more than one crystal structure (molecular arrangement).
- Polymorphs have different physical properties although they have identical chemical and structural formulas.
- These physical properties include: melting point, surface free energy, hygroscopicity, true density…
- These differences disappear in the liquid or the vapor state.
- The polymorph with the highest-melting point is generally the most stable, other polymorphs are metastable and convert to the stable form.

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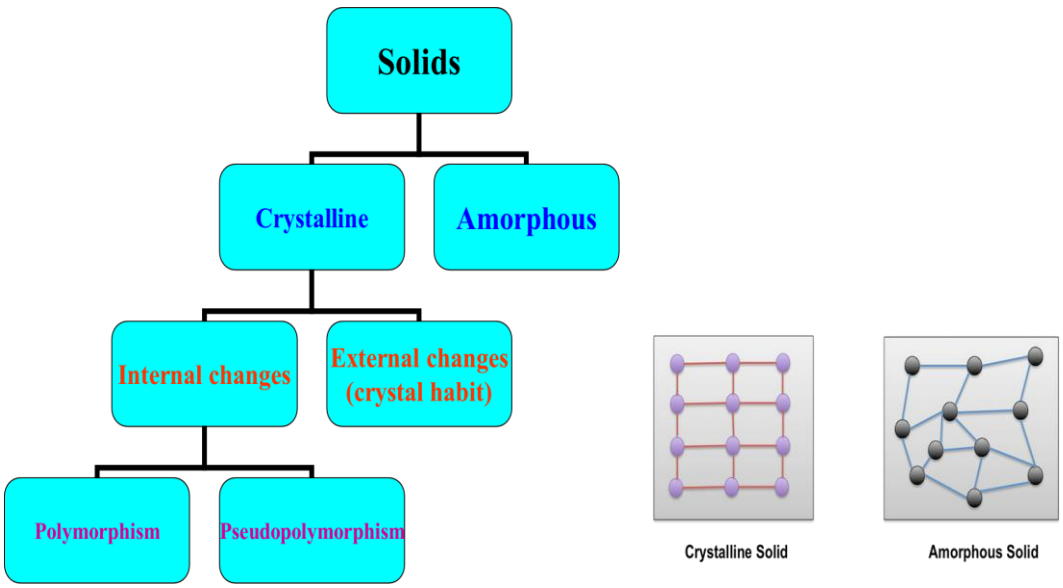

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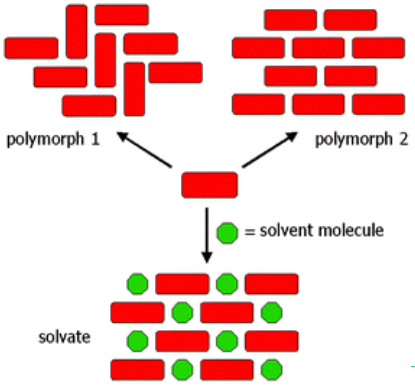

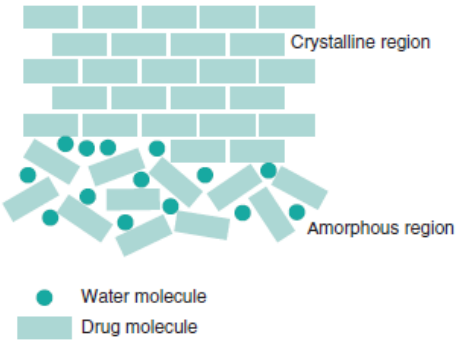

The disruption of a crystal giving the possibility for water vapor absorption in the amorphous region

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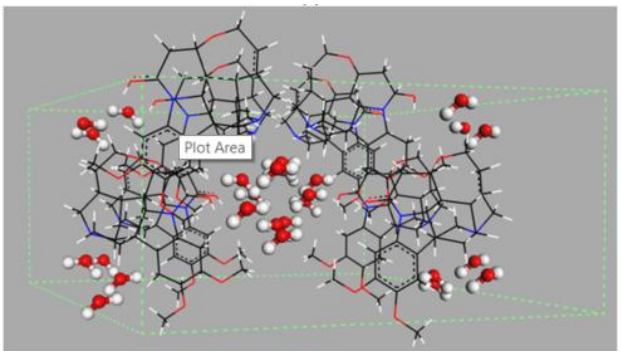
Physical forms and solid state properties

Solvates (pseudopolymorphism)

- This is the case when solvent becomes part of the crystal structure.
- If the solvent is water , then it is called hydrates.
- These states can dehydrate or change (e.g.. from dihydrate to monohydrate) by heating.



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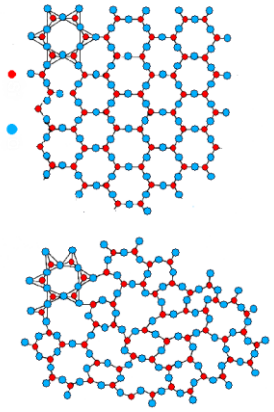
Physical forms and solid state properties

Amorphous state



•Amorphous solids have no long-range order of molecular packing.

•In case of pharmaceutical materials, the importance of amorphous solids is due to:

Useful properties. Amorphous solids have higher solubility, higher dissolution rate, and sometimes better compression properties than corresponding crystals.

Instability. Amorphous solids are generally less stable chemically and physically and more hygroscopic than corresponding crystals.

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Physical forms and solid state properties

Common occurrence. Amorphous solids are the common form of certain materials (ex. Proteins. Peptides, some sugars and polymers)

The main properties of concern are:

- Solubility → may affect bioavilability
- Stability (Chemical and physical stability)
- Compression properties

High melting point = strong lattice
= hard to remove a molecule
= low dissolution rate

Low melting point = weak lattice
= easy to remove a molecule
= high dissolution rate

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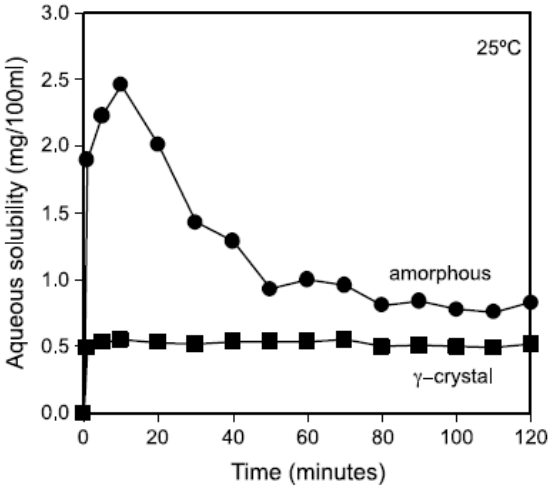
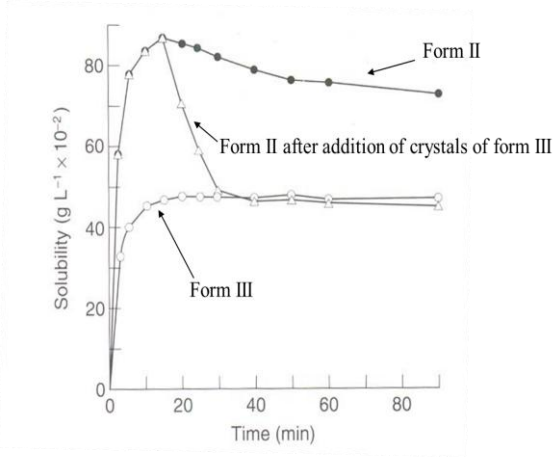


Aqueous solubility of the amorphous and crystalline forms of indomethacin.



The solubility time relationship for sulphamethoxydiazine

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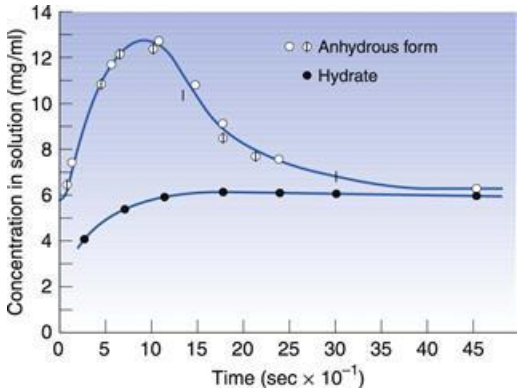

The dissolution of theophylline monohydrate rising to an equilibrium solubility, compared with that for theophylline anhydrous which forms a supersaturated solution with a peak over twice that of the dissolving hydrate, before crystallizing to form the true equilibrium solubility

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Physical forms and solid state properties

- In the preformulation the following should be considered
  A. How many polymorphs exist?
  B. How many hydrates exist?
  C. Is there an amorphous structure?
  D. What is the solubility of each form?
  E. How stable are the physical forms?
  F. Can a more soluble physical form be stabilized?

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Physical forms and solid state properties

Screening of polymoprhs and solvates

- Basic screening is achieved by <u>crystallizing</u> the drug candidate from a number of solvent or solvent mixtures of varying polarity:
  A. A small amount of drug (around 0.5 mg) is added into each well of a 96-well plate.
  B. To each well is added a small volume of each solvent or solvent mixture.
  C. The formation of crystals is monitored and further analysis performed to determine the crystal form resulting.

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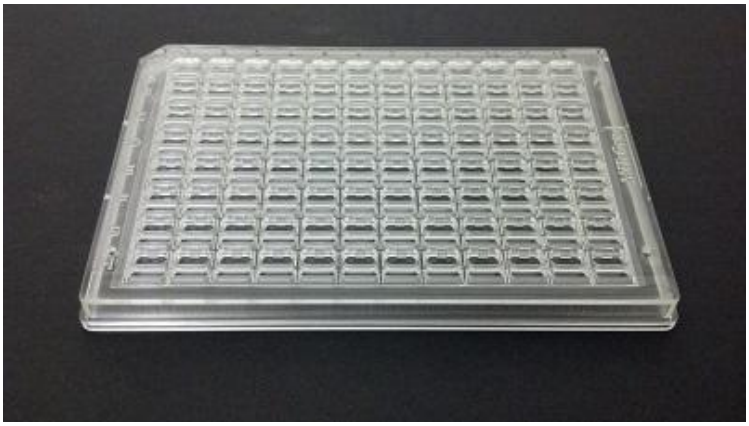

a 96-well plate

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Methods for the Characterization of solid state

X-Ray Powder Diffraction

- The defining criterion for the existence of polymorphic types must always be non-equivalent X-ray powder diffraction pattern.
- All other methodologies must be considered as sources of supporting and auxiliary information, but cannot be taken as definitive proof for the existence of polymorphism by themselves.
- The 2θ angles or each peak provide a 'fingerprint' of each form, while the intensities of each peak can be used as the basis or a quantitative assay or each form.

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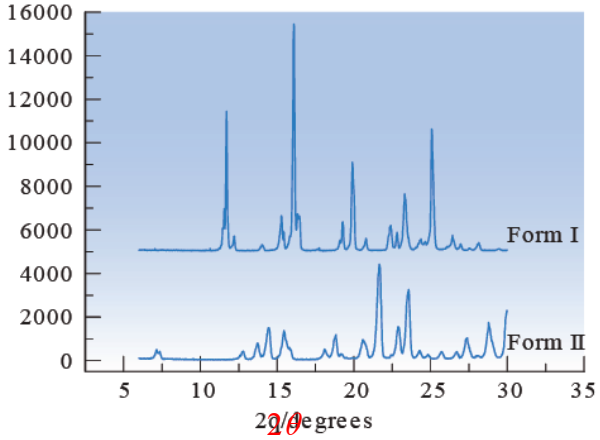
Methods for the Characterization of solid state

X-Ray Powder Diffraction (XRPD)



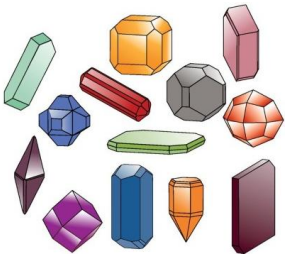


Fig. 23.13 • XRPD diffractograms for two polymorphs of sulfapyridine.

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Methods for the Characterization of solid state

X-Ray Powder Diffraction (XRPD)

The diffraction pattern of an amorphous solid corresponds to a broad peak or peaks, often referred to as an amorphous **halo** because amorphous systems have little long-range order.

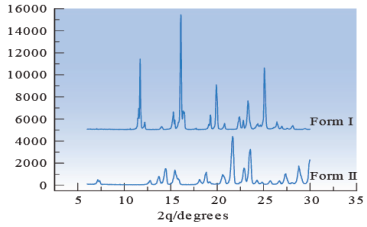

Fig. 23.13 • XRPD diffractograms for two polymorphs of sulfapyridine.

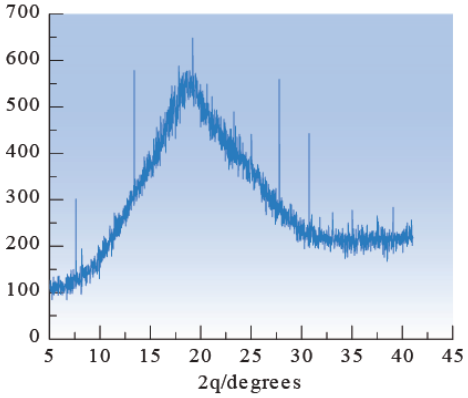

Fig. 23.15 • XRPD diffractogram for amorphous trehalose.

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Methods for the Characterization of solid state

Melting point and thermal analysis techniques

- The melting point of a drug can be measured using three techniques:

1) *capillary melting*

- This involves the observation of melting in a capillary tube in a heated metal block
- It gives information about melting range but it is difficult to assign an accurate melting point.

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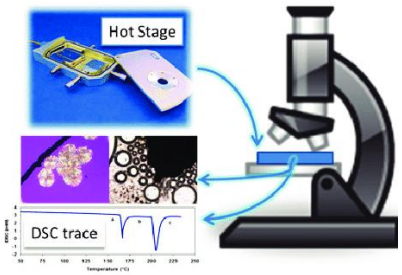
Methods for the Characterization of solid state

Melting point and thermal analysis techniques

2) *Hot stage microscopy*

- This is the visual observation of melting under a microscope equipped with a heated and lagged sample stage
- It is more accurate than capillary method because of high magnification.
- Changes other than melting can be observed.



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Methods for the Characterization of solid state

Melting point and thermal analysis techniques

3) *Thermal analysis*

- This is more versatile and accurate than the above two methods.
- The two common techniques for melting point determination are:

a) Differential thermal analysis (DTA)

- DTA measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate.

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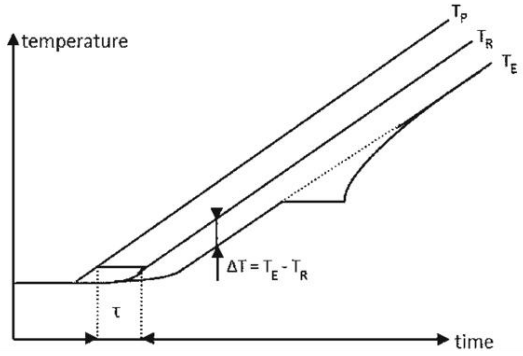

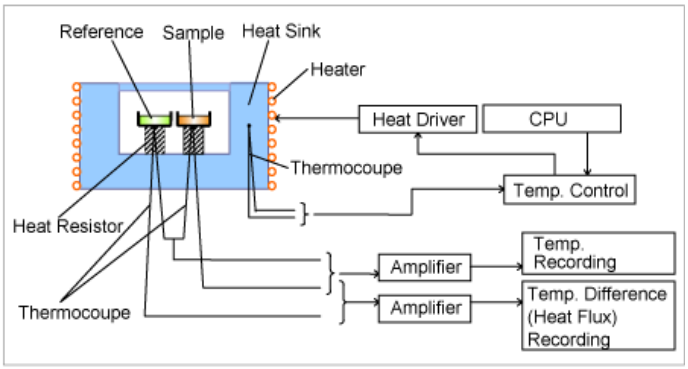

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Methods for the Characterization of solid state

Melting point and thermal analysis techniques

3) *Thermal analysis*

b) Differential scanning calorimetry (DSC)

- DSC measures the amount of energy required to keep the sample at the same temperature as the reference, i.e. it measures the enthalpy of transition.
- When a phase change (like melting) occurs then latent heat suppresses a temperature change and the isothermal energy required registers as an electrical signal generated by thermocouples.

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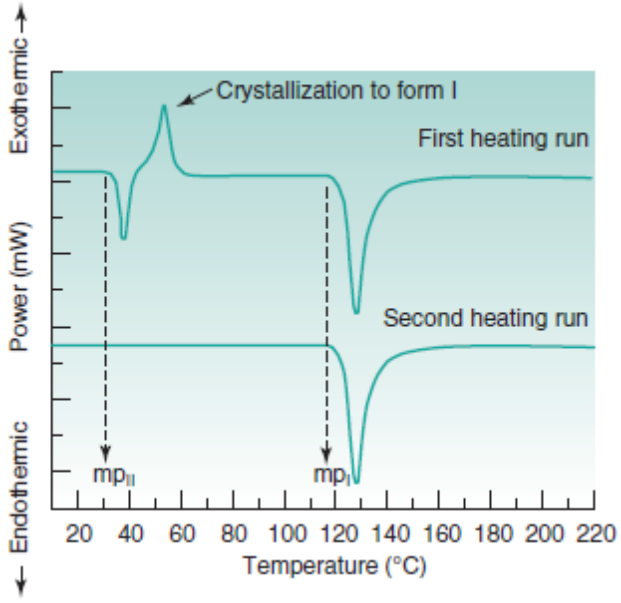
Differential scanning calorimetry thermal curves for a metastable polymorph on its first *(top)* and second *(bottom)* heating runs. *mp,* melting point



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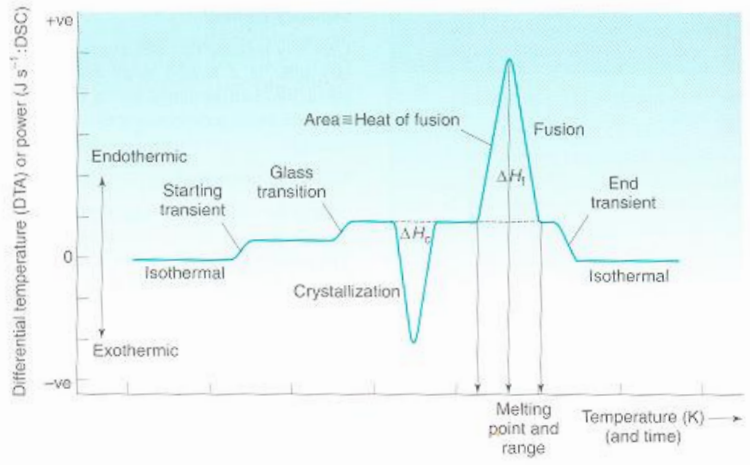

Fig. 24.3 Schematic differential scanning calorimeter thermogram.

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Methods for the Characterization of solid state

Melting point and thermal analysis techniques

3) *Thermal analysis*

c) Thermogravimetry (TG)

- In this technique, the change of weight as temperature increases is determined using a sensitive microbalance.
- TG analysis is restricted to transitions that involve either a gain or a loss of mass, and it is most commonly used to study desolvation processes and compound decomposition.

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Methods for the Characterization of solid state

- The distinction between hydrates and anhydrous state can be done by:

Hot-stage microscopy

- By observing the melting behavior of the powder dispersed in silicone oil (with heating hydrates, solvent vapor is detected as bubbles)

Thermogravimetry (TG)

- A hydrates (or solvate) looses its water (or solvent), showing a sharp decrease in weight, at a certain temperature.

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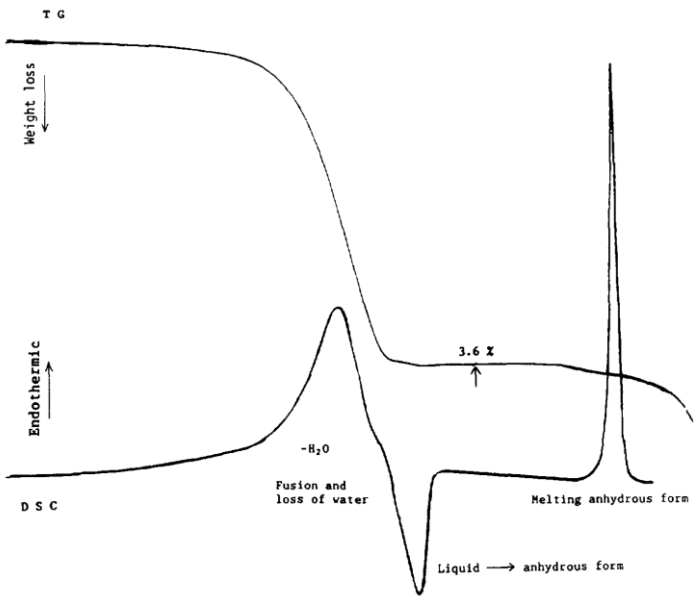

Fig. 13. DSC and TG scans of a substance in which dehydration occurs just after melting and the anhydrous form crystallises from the melt.

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Methods for the Characterization of solid state

Melting point and thermal analysis techniques

In addition to characterization of solid state (polymorphism, amorphous,..), thermal analysis techniques and melting point determination have application in:

- Identification of drug
- Determination of purity of raw material
- Detection of drug-excipient incompatibility

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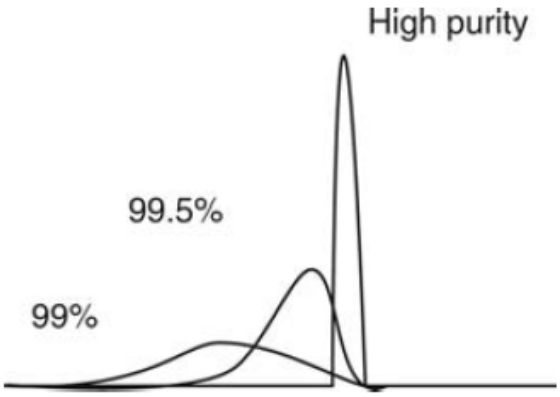

Schematic (and exaggerated to demonstrate the point) indication of how a melting point peak would tend to alter as purity is reduced.

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Powder properties

Particle size and shape

- Microscopy is particularly useful in the performulation stage because of:
  - It needs small sample amount for analysis
  - It can be used to determine shape in addition to size

Powder flow properties

- Powder flow is of primary importance when handling a drug.
- Changes of particle size and shape (possibly due to changes in batches or source of raw material) affect powder flow.

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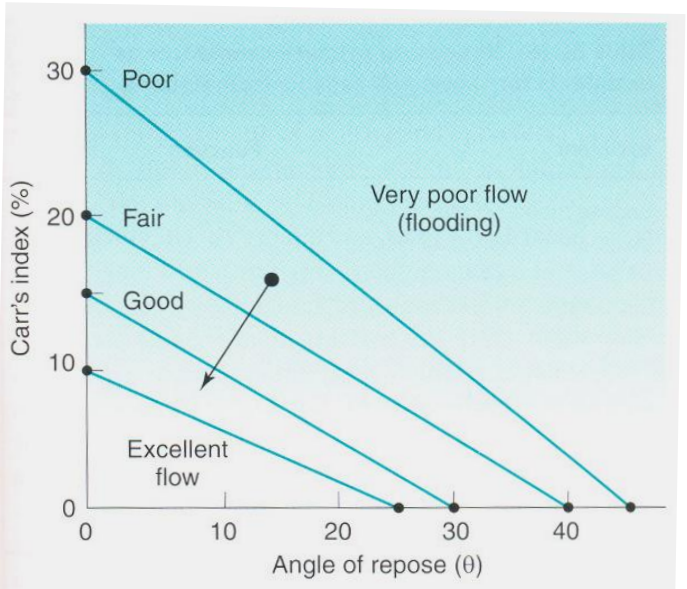

Fig. 24.7 Relationship between Carr's Index and angle of repose of a powder and its flow characteristics.

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Pharmaceutical preformulation

Compression properties

- The compression properties of most drug powders are poor and necessitates the addition of compression aids.
- The effect of compression properties of the pure drug, on the behavior of formula during compression increases as dose is increased.
- Drug with dose lower than 50 mg can often be prepared by direct compression with the addition of modern direct compression diluents.

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Pharmaceutical preformulation

Compression properties

Three distinct behaviors can be identified regarding compression of powders:

Plastic deformation

- The deformation due to pressure is irreversible after pressure removal

Fragmentation

- The particles break under pressure to smaller particles

Elastic deformation

- The deformation is reversible, i.e the particle retain their previous shape after pressure removal.

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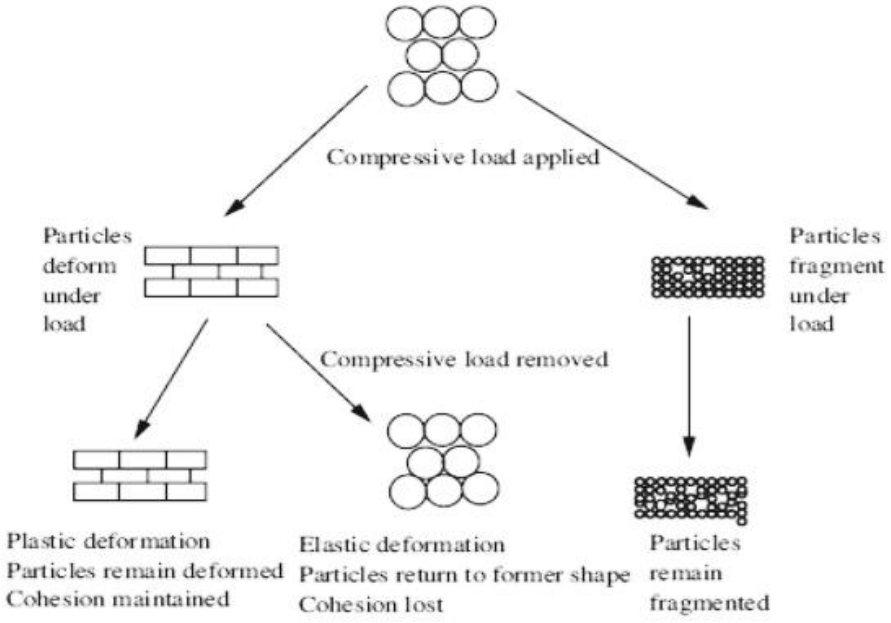

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	500 mg drug+ 1% magnesium stearate		
Sample	A	B	C
Blend in a tumble mixer for	5 min	5 min	30 min
Compress in a hydraulic press at 75 MPa for	2 s	30 s	2 s
After 24 hrs, perform crushing strength and record load	A N	B N	C N

Plastic materials B>A>C

Fragmenting material A=B=C

Elastic material A & C: capping or lamination , B very weak

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Pharmaceutical preformulation

Drug and Product stability

- The commercial pharmaceutical products have a certain shelf-life within which the potency should not fall below 95%.
- This shelf-life should be 3 years wherever possible.
- By investigating the intrinsic stability of drug it is possible to suggest the following in order to improve stability of product:
  - formulation approaches (eg. Dry instead of wet granulation)
  - types of excipient
  - specific protective additives (eg. Antioxidant)
  - packaging

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Pharmaceutical preformulation

The Influence of pH

- The degradation of most drugs is catalyzed by extremes of pH, and most drugs have better stability at pH between 4 and 8.
- Weakly acidic and basic drugs are most soluble when ionized, while instability is most likely to occur as they are charged. Therefore a compromise between optimum pH for solubility and pH for stability should be considered.
- In some cases the inclusion of a water-miscible solvent in the formulation will increase stability by:
  - Suppressing ionization
  - reducing the extreme of pH required to achieve solubility
  - reducing water activity by reducing polarity of the solvent

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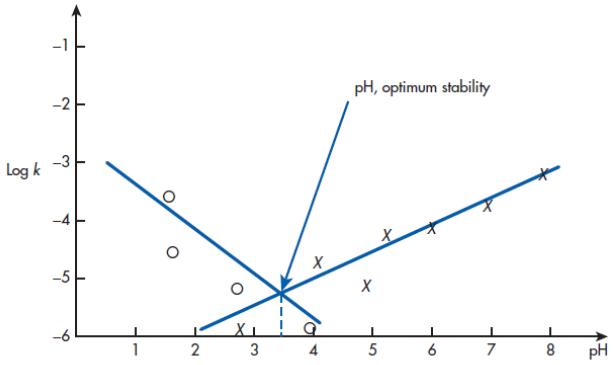
Effect of pH on stability can be studied by monitoring degradation rates against pH keeping constant:

1. temperature,
2. ionic strength and
3. solvent concentration.



Determination of the optimal pH for a drug.

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Pharmaceutical preformulation

Hygroscopicity

- Most pharmaceutical compounds are either:
  - Impassive to the water available in the surrounding atmospheres (nonhygroscopic) or,
  - Lose or gain water from the atmosphere depending on the relative humidity (RH) (hygroscopic).
- Ambient RH can vary widely and continually depending on the weather and air temperature.
- Hygroscopicity can be evaluated by monitoring moisture sorption by solid at certain fixed RH values.

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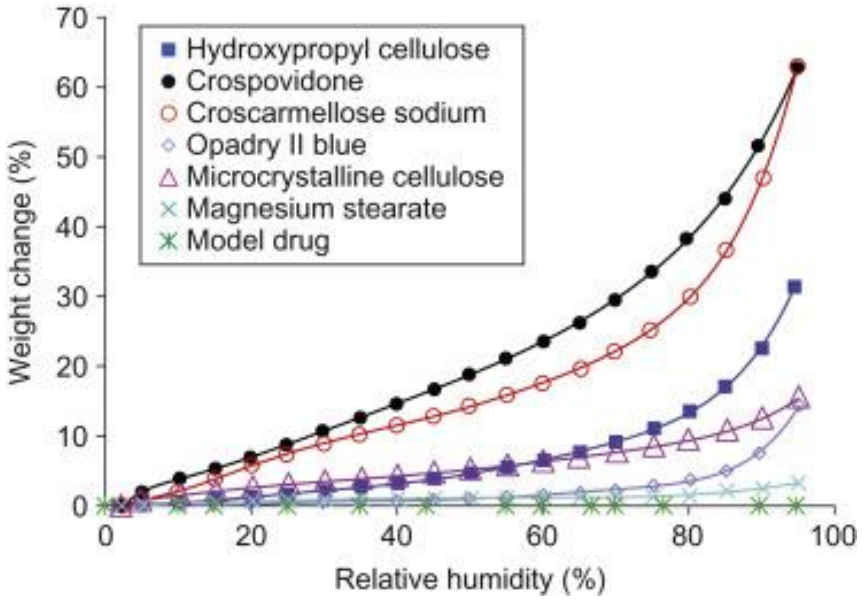

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Pharmaceutical preformulation

Stability assessment

- If the same drug will be used in both solid and liquid (i.e. solution) dosage forms, the testing protocol used in preformulation to ascertain the stability of formulated products must be performed

1. in solution and
2. in the solid state

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Pharmaceutical preformulation

Excipient compatibility

- Ordinary method depends on making binary mixtures of drug and different excipients, and testing for interaction using suitable analytical method (TLC, HPLC).
- The interaction may be accelerated by putting the samples at exaggerated conditions (high temperature and moisture).

- Thermal analysis can be used to investigate and predict any physicochemical interactions between components in a formulation and can be applied for selection of suitable and compatible excipients.

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Pharmaceutical preformulation

Determination of excipient compatibility by thermal analysis

Method

- The preformulation screening of drug-excipient interactions requires 5 mg of drug, in a 50% mixture with the excipient.
- Mixtures should be examined under nitrogen to eliminate oxidative and pyrrolytic effects at a standard heating rate (2, 5, or10 ^{o}C /min).
- The melting range and any other transitions of the drug will be known from earlier investigation and so the thermogram of drug alone

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Pharmaceutical preformulation

Determination of excipient compatibility by thermal analysis

Interpretation

- The thermogram is compared with those of drug and the excipient alone.
- An interaction on DSC will show as changes in melting point, peak shape (eg. gross broadening or elongation), and area or by the appearance of transition.
- Where an interaction is suspected but the thermal changes are small, the incompatibility should be confirmed by TLC.

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Table 24.16 Suggested primary candidates as excipients for tablet and capsule formulations

Excipient	Function*
Lactose monohydrate	F
Dicalcium phosphate dihydrate	F
Dicalcium phosphate anhydrous	F
Microcrystalline cellulose	F
Maize starch	D
Modified starch	D
Polyvinylpyrrolidone	B
Sodium starch glycollate	D
Sodium croscarmellose	D
Magnesium stearate	L
Colloidal silica	G

* B, binder; D, disintegrant; F, filler/diluent; G, glidant; L, lubricant.

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Pharmaceutical preformulation

Solubility

- The dissolution of drug is a prerequisite for absorption.
- Solubility in body fluids indicates the upper limit of concentration (ex. GIT fluids) that will be ready for absorption.
- Kaplan (Drug Metab. Rev,1, 15-32, 1972) suggested that unless a compound has an aqueous solubility in excess of 1 % (10 mg/ml) over the pH range 1 -7 at 37 ^{o}C, potential bioabsorption problems may occur.
- A solubility of less than 1 mg/ml indicates the need for a salt.
- In the range 1-10 mg/ml, serious consideration should be given to salt formation.

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Pharmaceutical preformulation

Intrinsic solubility

- Weak acids have higher solubility in bases than in water while weak bases have higher solubility in acids than in water.
- An increase in acidic and alkaline solubility suggests either amphoteric or zwitterion behavior.
- No change in solubility suggests a non-ionizable neutral molecule.
- The solubility in acid for weak acid or alkali for weak base can be assumed to be the intrinsic solubility, i.e. the solubility when completely unionized.

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Pharmaceutical preformulation

pK_a from solubility data

- 75% of all drugs are weak bases, 20% are weak acids and only 5% are non-ionic, amphoteric or alcohols (R-OH).

Handerson-Hasselbalch equation:

For weak bases: $pH = pK_a + \log_{10}([B]/[BH+])$

For weak acids: $pH = pK_a + \log_{10}([A-]/[HA])$

This equation can be used:

1. To determine pK_a by following changes in solubility
2. To predict solubility at any pH, provided that the intrinsic solubility (C_u) and pK_a are known

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Pharmaceutical preformulation

Salts

- A major improvement in solubility can be achieved by forming a salt.
- In some cases, salts prepared from strong bases or acids are freely soluble but very hygroscopic leading to instability.
- Changes in hygroscopicity and stability influence formulation and changes in dissolution rate and solubility affect the rate and extent of absorption.
- Different salts of drug rarely change pharmacology, but only physical properties

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Table 24.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pKa	% Usage	Cation	pKa	% Usage
Hydrochloride	–6.10	43.0	Potassium	16.00	10.8
Sulfate	–3.00, +1.96	7.5	Sodium	14.77	62.0
Mesylate	–1.20	2.0	Lithium	13.82	1.6
Maleate	1.92, 6.23	3.0	Calcium	12.90	10.5
Phosphate	2.15, 7.20,	3.2	Magnesium	11.42	1.3
Salicylate	12.38	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.00	0.8	Choline	8.90	0.3
Citrate	3.10	3.0	Aluminium	5.00	0.7
Succinate	3.13, 4.76, 6.40	0.4	Others		8.8
Acetate	4.21, 5.64	1.3			
Others	4.76	31.4			

R-COO- K+, Na+, Al3+, etc

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Table 24.6 Dissolution rates of weak acids and their sodium salts

Drug	pK_a	pH (at C_s)	Dissolution rate (mg cm^{-2} min^{-1}) × 10^2	
			Dissolution media	
			0.1M HCl (pH 1.5)	Phosphate (pH 6.8)
Salicylic acid	3.0	2.40	1.7	27
Sodium salicylate	–	8.78	1870	2500
Benzoic acid	4.2	2.88	2.1	14
Sodium benzoate	–	9.35	980	1770
Sulfathiazole	7.3	4.97	<0.1	0.5
Sodium sulfathiazole	–	10.75	550	810

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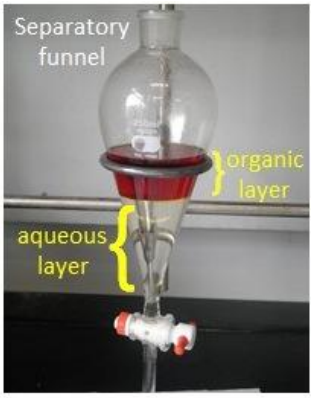
Pharmaceutical preformulation

Partition coefficient (K^o_w)

- A measurement of drug's lipophilicity and an indication of its ability to cross cell membrane is the oil/water partition coefficient in systems such as octanol/water and chloroform/water.

- The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.



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Pharmaceutical preformulation

Dissolution

Intrinsic dissolution rate (IDR)

- This is the dissolution rate of drug, under sink conditions, where the exposed surface area is constant.
- IDR is independent on formulation effects and measures the intrinsic properties of the drug and salts as a function of dissolution media, ex. pH, ionic strength and counter-ions.

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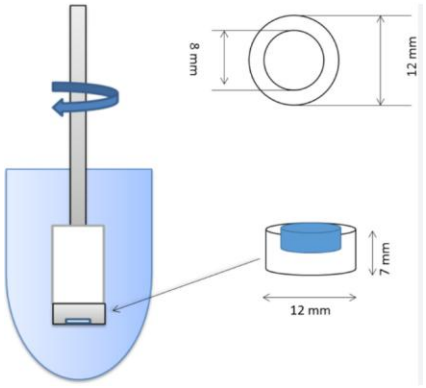
Pharmaceutical preformulation

Measurement of Intrinsic Dissolution Rate (IDR)

- A compressed disk of material can be made by compressing 500 mg of drug at high pressure to ensure zero porosity.
- The compressed disk is fixed to the holder of the rotating basket apparatus using a low-melting paraffin wax and successfully dipped so that the top and sides of the disk are coated and dissolution is possible only from the lower surface.



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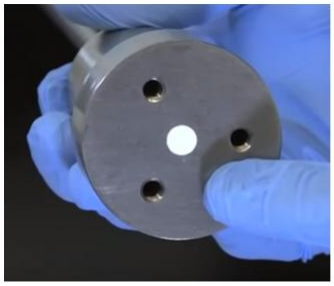
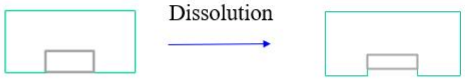


Constant surface area

t = 0



Decreasing surface area

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Pharmaceutical preformulation

Common ion effect

- A common ion often significantly reduces the solubility of a slightly soluble electrolyte.
- The salting out results from the removal of water molecules as solvent owing to the competing hydration of other ions.
- Hydrochloride salts often exhibit suboptimal solubility in gastric juice due to the abundance of Cl^-.

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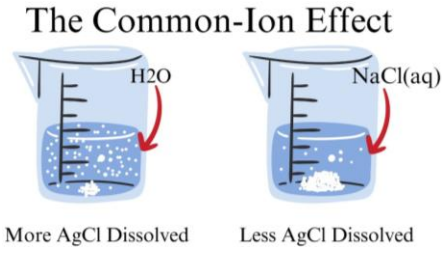
Pharmaceutical preformulation

Common ion effect

- To identify common ion interaction, the IDR of the hydrochloride (or inorganic salt) should be compared between
  - (a) water, and water containing 1.2 % w/v NaCl, and
  - (b) 0.05 M HCl and 0.9 % w/v NaCl in 0.05 M HCl.



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