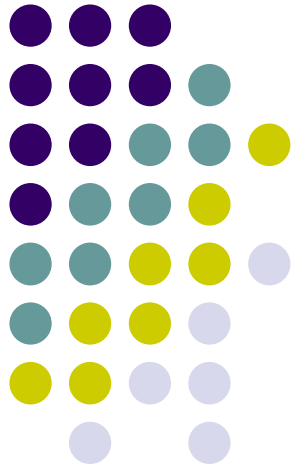
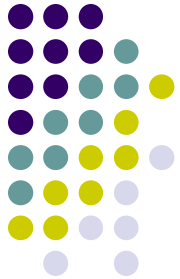
Pharmaceutical preformulation

The physicochemical properties of drug substances



THE CONCEPT OF PREFORMULATION



- Determine the ***fundamental*** physical and chemical properties of the drug molecule and other ***derived*** properties of the drug powder prior to the development of these the major dosage forms .

- This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as ***preformutation.***

Table 8.1 Frequency distribution of dosage form types manufactured in the UK

Dosage form	Frequency (%)
Tablets	46
Liquid oral	16
Capsules	15
Injections	13
Suppositories and pessaries	3
Topicals	3
Eye preparations	2
Aerosols (inhalation)	1
Others	1

Recommended list of the information required in preformulation

Table 8.2 Preformulation drug characterization

Test	Method/function/characterization
Spectroscopy	Simple UV assay
Solubility	Phase solubility, purity
aqueous	Intrinsic solubility, pH effects
pK_a	Solubility control, salt formation
salts	Solubility, hygroscopicity, stability
solvents	Vehicles, extraction
partition coeff K^{o}_{w}	Lipophilicity, structure activity
dissolution	Biopharmacy
Melting point	DSC – polymorphism, hydrates, solvates
Assay development	UV, TLC, HPLC
Stability (in solution and solid state)	Thermal, hydrolysis, oxidation, photolysis, metal ions, pH.
Microscopy	Morphology, particle size
Powder flow	Tablet and capsule formulation
bulk density	
angle of repose	
Compression properties	Tablet and capsule formation
Excipient compatibility	Excipient choice

- Two fundamental properties are mandatory for a new compound:

1. Intrinsic solubility (C0),

2. Dissociation constant *(pKa).*

- In addition analysts should generate data to confirm **structure** and **purity**, and this should be used to complement and confirm pharmaceutical data.

Analytical preformulation	
Attribute	Test
Identity	Nuclear magnetic resonance (NMR) Infra red spectroscopy (IR) Ultraviolet spectroscopy (UV) Thin-layer chromatography (TLC) Differential scanning calorimetry (DSC) Optical rotation, where applicable
Purity	Moisture (water and solvents) Inorganic elements Heavy metals Organic impurities Differential scanning calorimetry (DSC)
Assay	Titration Ultraviolet spectroscopy (UV) High-performance liquid chromatography (HPLC)
Quality	Appearance Odour Solution colour pH of slurry (saturated solution) Melting point

SPECTROSCOPY

- **The first step in preformulation is to establish a simple analytical method.**
- **Most drugs absorb light in the ultraviolet wavelengths (190-390 run) as they are generally aromatic and contain double bonds. The acidic or basic nature of the molecule can be predicted from functional groups .**
- **Using the UV spectrum of the drug, it is possible to choose an analytical wavelength (often Amax) suitable to quantify the amount of drug in a particular solution.**
- **The amount of light absorbed by a solution of drug is proportional to the concentration (C) and the path length of the solution (l) through which the light has passed.**

$$\text{Absorbance } (A) = \log_{10} (I_o/I) = eCl$$

- **Aqueous solubility**
- The availability of a drug is always limited and the preformulation scientist may only have 50 mg.

- As the compound is new the quality is invariably poor, so that a large number of impurities may be present and often the first crystals come down as a metastable polymorph.
- **Accordingly, as a minimum, the solubility and *pKa* must be determined.**

- **The *pKa* allows the informed use of pH to maintain solubility and to choose salts required to achieve good bioavailability from the solid state and improve stability and powder properties .**

- **Poorly soluble compounds** that have an aqueous solubility in less than 1% (10 mg/mL) over the pH range 1-7 at 37°C, shows potential bioabsorption problems may occur.

- **solubility of less than 1 mg /mL indicates the need for a salt, particularly if the drug will be formulated as a tablet or capsule.**

- **When the solubility of the drug cannot be manipulated** in this way (neutral molecules, glycosides, steroids, alcohols, or where the *pKa* is less than 3 for a base or greater than 10 for an acid) then **liquid filling in soft or hard gelatin capsules may be necessary .**

- **An increase in solubility in acid compared to aqueous solubility suggests a weak base**, and an **increase in alkali a weak acid**. In both cases a dissociation constant ***(pKa*** **can be measured and salts should form.**

- **An increase in acidic and alkaline solubility suggests either amphoteric or zwitterion behaviour**. In this case **there will be two *pKas*,** one acidic and one basic.

- **No change in solubility suggests a non-ionizable neutral molecule with no measurable *pKa*,** and **solubility manipulation will require either solvents or complexation.**

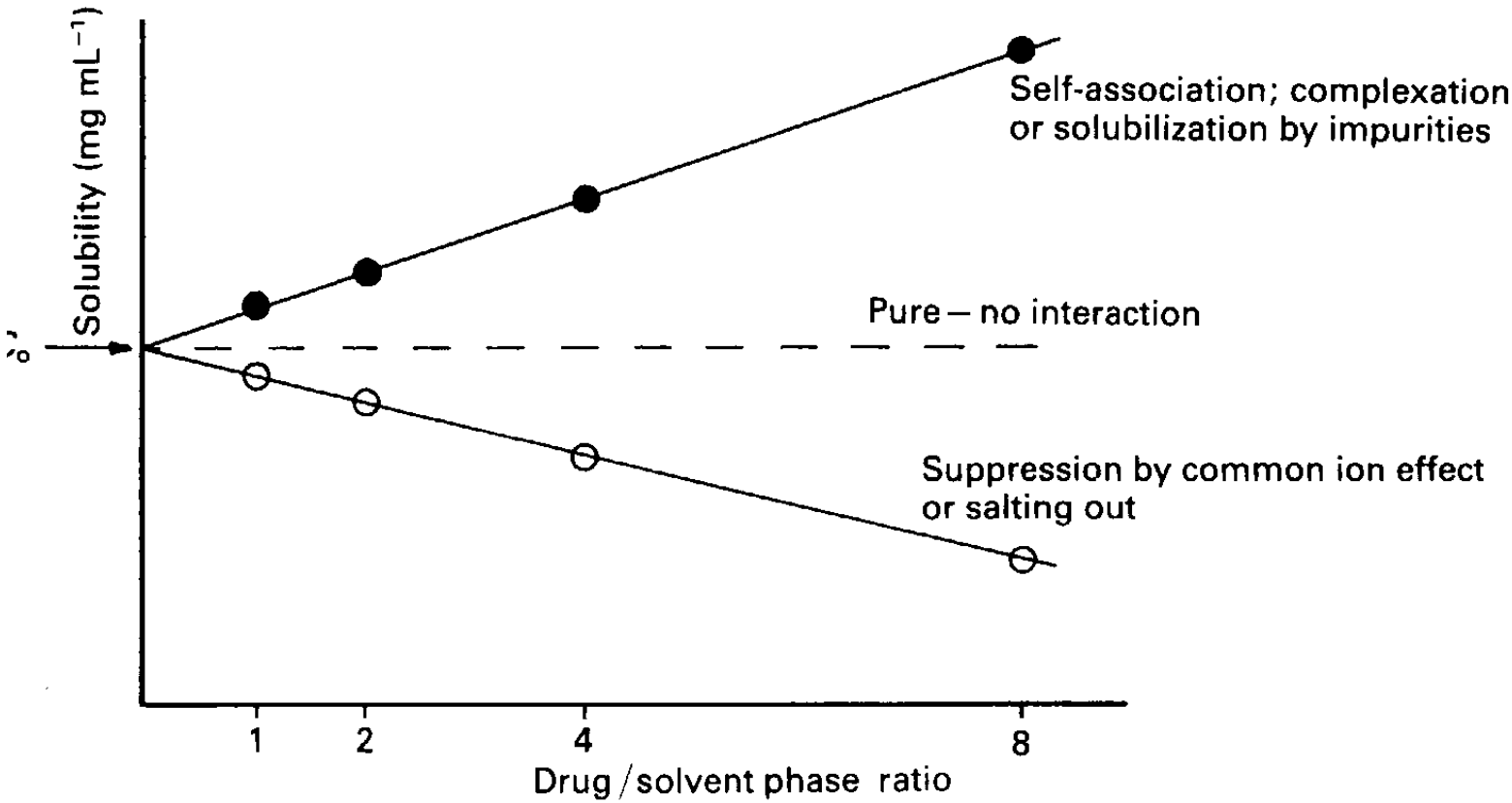
- **When the purity of the drug sample can be assured**, the solubility value obtained in acid for a weak acid or alkali for a weak base can be assumed to be the intrinsic solubility (C0), **ie. the fundamental solubility when completely unionized.**

- The solubility should ideally be measured at two temperatures:

1. 4°C to ensure physical stability and extend short-term storage and chemical stability until more definitive data are available. The maximum density of water occurs at 4°C.This leads to a minimum aqueous solubility.

2. 37°C to support biopharmaceutical evaluation.

However, as absolute purity is often in doubt it is more accurate to determine this crucial solubility by the use of a phase-solubility diagram



pKa *from solubility data*

- **75% of all drugs are weak bases; 20% are weak acids and only 5% are non- ionic, amphoteric or alcohols.**
- **It is therefore appropriate to consider the Henderson-Hasselbalch equations for weak bases and acids.**

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

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

- **Henderson-Hasselbalch equations can be used:**

1. to determine *pKa* by following changes in solubility

2. to predict solubility at any pH, provided that the intrinsic solubility (C0) and *pKa* are known

3. to facilitate the selection of suitable salt-forming compounds and predict the solubility and pH properties of the salts.

- ***pKa* values obtain precise by potentiometry, spectroscopy and conductivity.**

Salts

- *A* major improvement in solubility can be achieved by forming a salt. Acceptable **pharmaceutical salt counter-ions** are shown in Table

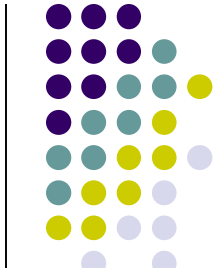
Table 8.4 Potential pharmaceutical salts

Basic drugs			Acidic drugs		
Anion	pK_a	% Usage	Cation	pK_a	% Usage
Hydrochloride	−6.10	43.0	Potassium	16.00	10.8
Sulphate	−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, 12.38	3.2	Magnesium	11.42	1.3
Salicylate	3.00	0.9	Diethanolamine	9.65	1.0
Tartrate	3.00	3.5	Zinc	8.96	3.0
Lactate	3.10	0.8	Choline	8.90	0.3
Citrate	3.13, 4.76, 6.40	3.0	Aluminium	5.00	0.7
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		31.4	Others		8.8

- In some cases, salts prepared from strong acids or bases are freely soluble but very hygroscopic. **This does lead to instability in tablet or capsule formulations,** as some drug will dissolve in its own adsorbed films of moisture.

- **It is often better to use a weaker acid or base to form the salt, provided any solubility requirements are met.**

- A less soluble salt will generally be less hygroscopic and form less acidic or basic solutions .



- Injections should ideally lie in the pH range 3-9 to prevent vessel or tissue damage and pain at the injection site.

- Oral syrups should not be too acidic, to enhance palatability.

- Packaging may also be susceptible: undue alkalinity will attack lass, and hydrochloride salts should not be used in aerosol cans as a propellant-acid reaction will corrode the canister.

The dissolution rate of a particular salt is usually much greater than that of the parent drug. Sodium and potassium salts of weak acids dissolve much more rapidly than do the parent acids, and some comparative data are shown in Table below .

On the basis of bulk pH these salts would be expected to have lower dissolution rates in the stomach.

Table 8.6 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	
			0.1 M 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
Sulphathiazole	7.3	4.97	<0.1	0.5
Sodium sulphathiazole		10.75	550	810

Common ion effect

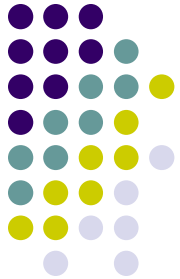
- An often overlooked interaction is the common ion effect.
- **A common ion often significantly reduces the solubility of a slightly soluble electrolyte.**
- The **'salting out'** results from the removal of water molecules as solvent owing to the competing hydration of other ions.
- The reverse process, **'salting in**', arises with larger anions, e.g. benzoate, salicylate, which open the water structure. These hydrotropes **increase the solubility of poorly water-soluble compounds such as diazepam.**
- **Hydrochloride salts often exhibit suboptimal solubility in gastric juice owing to the abundance of Cl ions**

- *Solvents*

Table 8.7 Recommended solvents for preformulation screening

Solvent	Dielectric constant (ϵ)	Solubility parameter (δ)	Application
Water	80	24.4	All
Methanol	32	14.7	Extraction, separation
0.1 M HCl (pH 1.1)			Dissolution (gastric), basic extraction
0.1 M NaOH (pH 13.1)			Acidic extraction
Buffer (pH 6–7)			Dissolution (intestinal)
Ethanol	24	12.7	Formulation
Propylene glycol	32	12.6	
Glycerol	43	16.5	
PEG 300 or 400	35		

Partition coefficient (LogP)

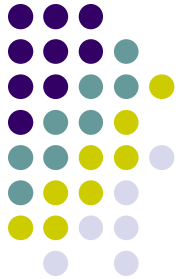


Partition coefficient (the solvent: water quotient of drug distribution) has **a number of applications which are relevant to preformulation:**

1. **Solubility**: both aqueous and in mixed solvents
2. **Drug absorption in vivo**: applied to a homologous series for structure activity relationships (SAR)
3. **Partition chromatography**: choice of column (HPLC) or plate (TLC) and choice of mobile phase (eluant).

- A drug's partition coefficient **is a measure of its distribution in a lipophilic –hydrophilic phase system** and indicates its ability to penetrate biological multiphase systems to produce a pharmacological effect .

PARTITION COEFFICIENT

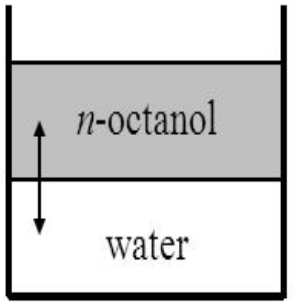


- The most useful scale of polarity for a solute is $K_{o/w}$ (oil:water partition coefficient).

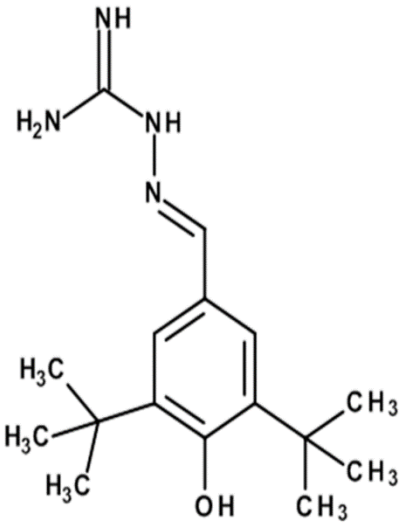
- **For a wide range of drugs it is possible to relate solvent solubility and the partition coefficient (log $K_{o/w}$ = log P).**

- Many partition solvents have been used. The largest database has been generated using **n-octanol.**

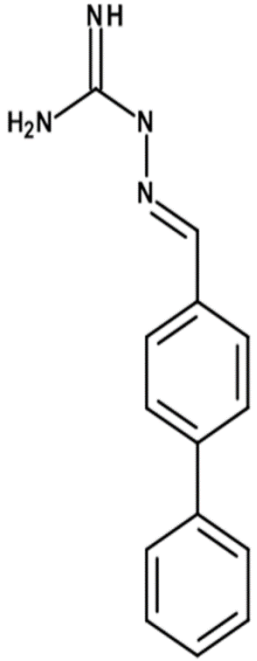
Expermintal determination of Octanol-Water Partition Coefficient (LogP Values)



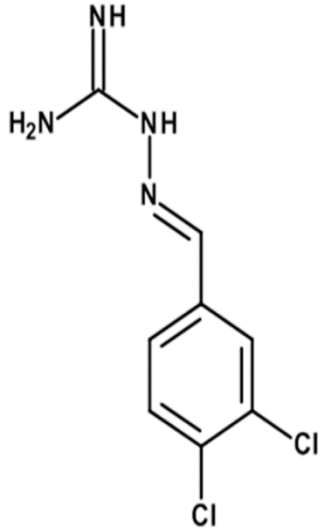
- In the ***shake flask method:***
- the drug, dissolved in one of the phases, is shaken with the other partitioning solvent for 30 minutes, allowed to stand for 5 minutes,
- then the majority of the lower aqueous phase is run off and centrifuged for 60 minutes at 2000 rpm.
- The aqueous phase is assayed before *(∑C)* and after partitioning (Cw) [the aqueous concentration] to give $K_{octanol/water} = (\sum C - Cw)/Cw$.



LQM010
$C_{16}H_{26}N_4O$
MM = 290.37 g/mol
Log P = 3.75



LQM014
$C_{14}H_{14}N_4$
MM = 238.29 g/mol
Log P = 2.61

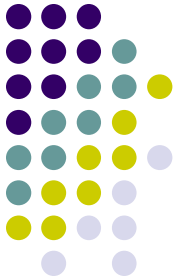


LQM017
$C_8H_8Cl_2N_4$
MM = 231.08 g/mol
Log P = 2.18

High log p …. High lipophilicity

log p value typically range -3 (very hydrophilic) to 10 (very Lipophlic)

High Ko/w value …. Less polarity



- log *P* differs between 3 and 4
- $K_{o/w}$ from ---------- to ----------

Table 8.9 The effect of salt formation on the log *P* of some weakly basic drugs

Free base and hydrochloride salt	log *P*	Δlog *P*
Chlorpromazine	5.35	3.84
Chlorpromazine HCl	1.51	
Promazine	4.49	3.58
Promazine HCl	0.91	
Trifluopromazine	5.19	4.28
Trifluopromazine HCl	1.78	
Trifluoperazine	5.01	3.34
Trifluoperazine HCl	1.69	
Diphenylhydramine	3.30	3.42
Diphenylhydramine HCl	–0.12	

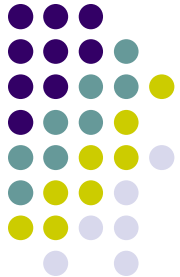
Salts increase polarity

↓

Decreases log p

Negative sign very high polarity

Polymorphism



- A polymorph is a solid material with at least two different molecular arrangements that give distinct crystal species.These differences disappear in the liquid or the vapour state.
- Of concern are their relative stabilities and solubility.

- The highest-melting species is generally stable; other polymorphs are metastable and convert to the stable form. There are also potentially large differences in their physical properties .

- Solubility (particularly important in suspensions and biopharmaceutically), melting point, density, crystal shape, optical and electrical properties and vapour pressure are often very different for each polymorph.

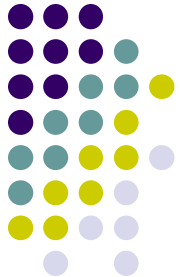
- Polymorphism is remarkably common, particularly within certain structural groups: 63% of barbiturates, 67% of steroids and 40% of sulphonamides exhibit polymorphism.

- The **steroid progesterone has five polymorphs**, whereas the sulphonamide sulphabenzamide has four polymorphs and three solvates.

- In preformulation the following should be considered.

• How many polymorphs exist?
• How stable are the metastable forms?
• Is there an amorphous glass?
• Can the metastable forms be stabilized
• What is the solubility of each form?
• Will a more soluble form survive processing and storage?

Pseudopolymorphism (solvates)



- the presence of solvates or false polymorphs, sometimes (incorrectly and confusingly)
- called pseudopolymorphs, should be identified, as most polymorphs can be obtained by changing the recrystallizing solvent.

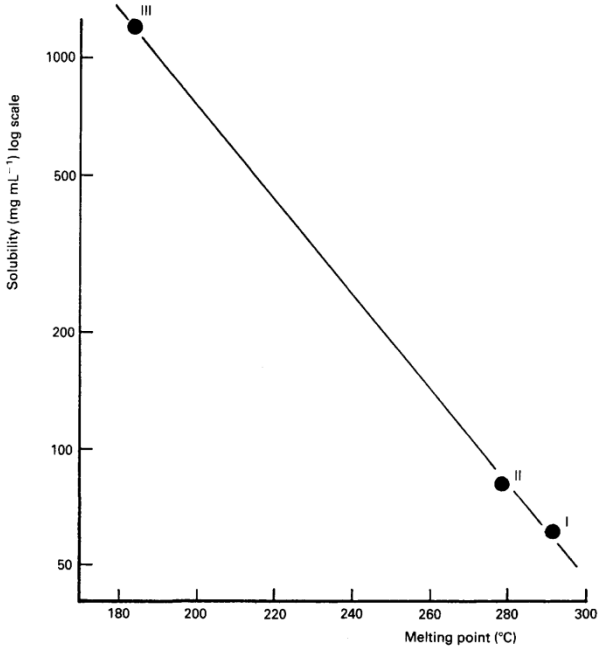
- Typical solvents inducing polymorphic change are water, methanol, ethanol, acetone, chloroform, n-propanol, isopropanol alcohol, n-butanol, n-pentanol, toluene and benzene.

- These can become molecular additions to the crystal and change habit. These hydrates (water) and solvates (e.g. methanolate, ethanolate) have been confused with true polymorphism and have led to the term pseudopolymorphism.

True polymorphism

- Most polymorphs are obtained by solvent manipulation. Others can be produced without the presence of solvent by thermal techniques,
- The difference in melting point *(ΔTm)* between polymorphs is a measure of the metastable polymorph stability.

The relationship between melting point and solubility for three polymorphs of riboflavine.



ig. 8.5 The relationship between melting point and solubility for three polymorphs of riboflavine.

- **Crystal purity**
- Thermal analysis has been widely used as a method of purity determination and the USP includes an appendix describing the methods.
- This is particularly pertinent at the preformulation stage, because early samples of a new drug are inevitably 'dirty' while improvements in synthetic route are made.
- Thermal analysis is rapid and will discriminate 0.002 mole% of impurity.
- Solubility
- The most important reason to determine melting point during preformulation is crystalline solubility.

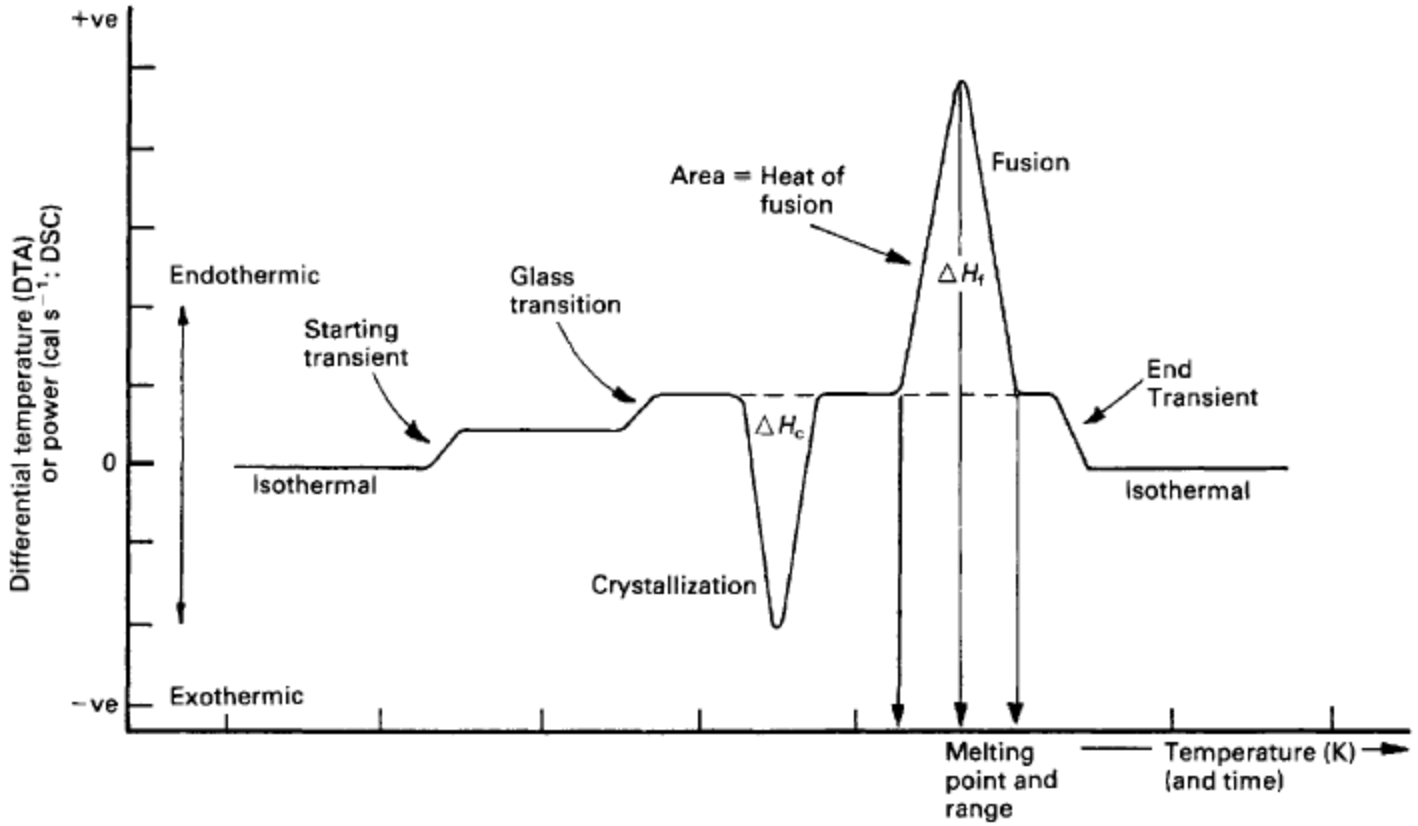
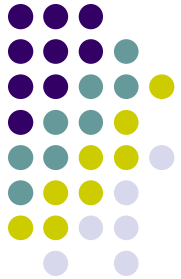


Fig. 8.3 Schematic differential scanning calorimeter thermogram.

Dissolution



- The dissolution rate of a drug is only important where it is the **rate-limiting step in the absorption process.**

- Provided the solubility of a drug exceeded 10 mg /mL at pH <7, no bioavailability- or dissolution-related problems were to be expected.

- Below 1 mg /mL such problems were quite possible, and salt formation could improve absorption and solubility by controlling the pH of the microenvironment independently of the drug and dosage forms' position within the GI tract.

Intrinsic dissolution rate

- The *Intrinsic dissolution rate (* IDR) is independent of formulation effects and measures the intrinsic properties of the **drug and salts** **as a function of dissolution media**, e.g. pH, ionic strength and counter-ions.

- **If the IDR was greater than 1mg /cm.min , then absorption was unimpeded**

- **the IDR was less than 1mg /cm.min , were likely to give dissolution rate –limited absorption**

Determination of Intrinsic Dissolution Rate

- **IDR is defined as the dissolution rate of a pure compound under the condition of constant surface area.**

- IDR is determined according to the equation:

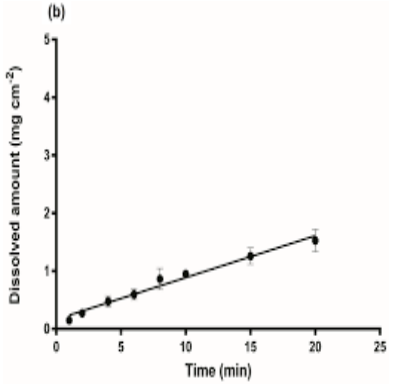
$$IDR = (dm/dt)_{max}/A$$

where $(dm/dt)_{max}$) is the maximum slope in the dissolution curve evaluated at the start of the dissolution process, A is the area of the drug disk (cm^2). the units of IDR are $mg/min/cm^2$,

- IDR is affected by the solid-state properties of a drug substance and is also influenced by external factors, such as compression force and hydrodynamics (e.g., dissolution vessel, dissolution medium volume, die position, and rotation speed).

Evaluation of the intrinsic dissolution rate

- **Fixed-disc method** is used for determination of the intrinsic dissolution rate.
- The backs of tablets is covered with a layer of molten hard paraffin which was permitted to solidify inside a plastic holder before immersion into the dissolution medium.
- This test is performed using dissolution system as paddle dissolution apparatus medium.
- A plot of the amount of drug released versus time is constructed and the IDR is determined from the curve.

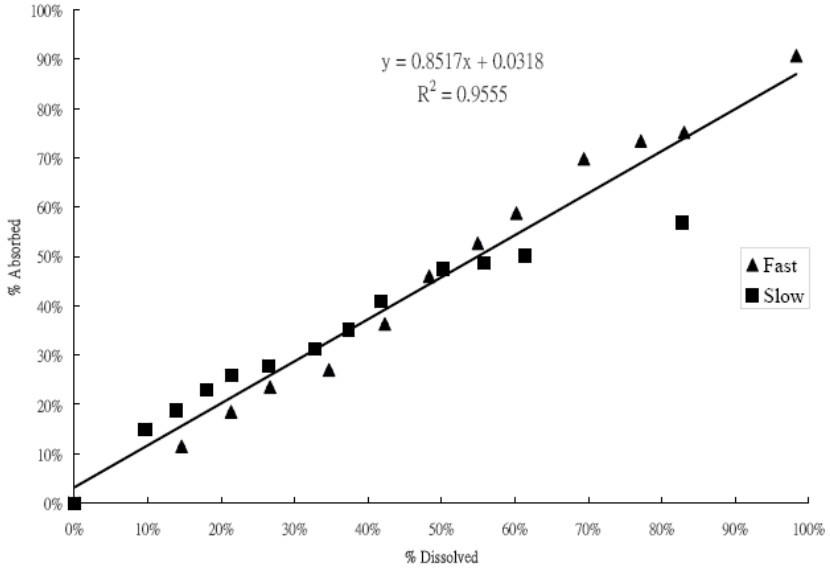


- The IDR of a drug is determined dividing the slope of the regression line by the area of the drug disk (cm^2).

IVIVC - A Tool for *in vitro- in vivo* Correlation

- **IVIVC defined as "a predictive mathematical model describing the relationship between an in vitro property**

- **Correlations between in vitro and in vivo data (IVIVC) are often used during pharmaceutical development**



Purpose of IVIVC

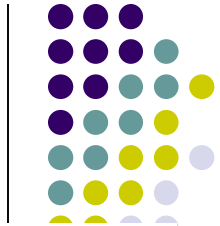
- **The optimization of formulations**
  - *optimization with the fewest possible trials in man*
  - *m*ay require changes in the composition, manufacturing process, equipment, and batch sizes.
  - In order to prove the validity of a new formulation, which is bioequivalent with a target formulation, a considerable amount of efforts is required to study bioequivalence (BE)/bioavailability(BA).
- ***Predicting In- Vivo results***
  - *to utilize in vitro dissolution profiles as a surrogate for in vivo bioequivalence*
  - *Data analysis of IVIVC attracts attention from the pharmaceutical industry.*
- ***IVIVC recommended by regulatory authorities***

- Bases on the type of data used to establish the relationship,
- three main levels are defined by the FDA:

Table 1. Various parameters used in IVIVC depending on the level.

Level	In vitro	In vivo
A	Dissolution curve	Input (absorption) curves
B	Statistical moments: MDT	Statistical moments: MRT, MAT, etc
C	Disintegration time, Time to have 10, 50, 90% dissolved, Dissolution rate, Dissolution efficiency	C_{max}, T_{max}, K_a, Time to have 10, 50, 90% absorbed, AUC (total or cumulative),

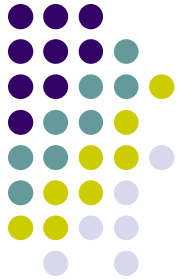
Level A



- A correlation of this type is generally linear and represents a point-to-point relationship between in vitro dissolution and the in vivo input rate (e.g., the in vivo dissolution of the drug from the dosage form).

- In a linear correlation, the in vitro dissolution and in vivo input curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor.

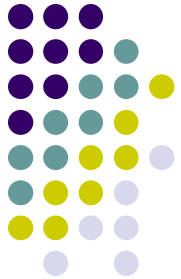
Level B



- A Level B IVIVC uses the principles of statistical moment analysis. The mean in vitro dissolution time is compared either to the mean residence time or to the mean in vivo dissolution time…. A

- Level B correlation does not uniquely reflect the actual in vivo plasma level curve,because a number of different in vivo curves will produce similar mean residence time values.

Level C



- A Level C IVIVC establishes a single point relationship between a dissolution parameter, for example, t50%,percent dissolved in 4 hours and a pharmacokinetic parameter (e.g.,AUC,Cmax,Tmax).

- A Level C correlation does not reflect the complete shape of the plasma concentration-time curve, which is the critical factor that defines the performance of ER products.

- A Level A IVIVC is considered the most informative and is recommended , if possible.

- Multiple Level C correlations can be as useful as Level A correlations.

- Level C correlations can be useful in the early stages of formulation development when pilot formulations are being selected. Level B correlations are least useful for regulatory purposes.

DRUG AND PRODUCT STABILITY

- Wherever possible, commercial pharmaceutical products should have a shelf-life of 3 years.
- The potency should not fall below 95% under the recommended storage conditions and the product should still look and perform as it did when first manufactured.
- **By investigating the intrinsic stability of the drug it is possible to advise on formulation approaches and indicate types of excipient, specific protective**
- additives and packaging which are likely to improve the integrity of the drug and product.
- Drug degradation occurs by four main processes:

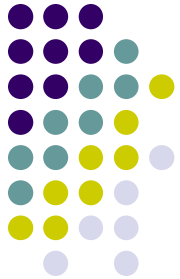
• Hydrolysis

• Oxidation

• Photolysis

• Trace metal catalysis.

Stability assessment



- **The testing protocols used in preformulation to ascertain the stability of formulated products.**
- In every case drug stability testing at various temperatures , relative humidity , effect of environmental factors and packaging .

- **Such information is vital in :**
- Developing label instructions for use
- Instructions for storage
- Assigning product pharmacokinetics
- Packaging and shipment

Table 8.11 Stress conditions used in preformulation stability assessment

Test	Conditions
Solid	
Heat (°C)	4, 20, 30, 40, 40/75% RH, 50 and 75
Moisture uptake	30, 45, 60, 75 and 90% RH at RT[a,b]
Physical stress	Ball milling
Aqueous solution	
pH	1, 3, 5, 7, 9 and 11 at RT and 37°C. Reflux in 1 M HCl and 1 M NaOH
Light[c]	UV (254 and 366 nm) and visible (south-facing window) at RT
Oxidation[c]	Sparging with oxygen at RT; UV may accelerate breakdown

[a] RT is ambient room temperature. Can vary between 15 and 25°C.
[b] Saturated solutions of $MgBr_2$, KNO_2, NaBr, NaCl and KNO_3 respectively.
[c] At pH of maximum stability in simple aqueous solution.