

SECOND EDITION

Pharmaceutics

THE SCIENCE OF
DOSAGE FORM DESIGN

Edited by
M. E. Aulton



Contents

What is 'Pharmaceutics'? xiii	
1. The design of dosage forms 1	
<i>Peter York</i>	
PART ONE	
Scientific principles of dosage form design 13	
2. Dissolution and solubility 15	
<i>Michael Aulton</i>	
3. Properties of solutions 33	
<i>Michael Aulton</i>	
4. Rheology 41	
<i>Chris Marriott</i>	
5. Surface and interfacial phenomena 59	
<i>John Fell</i>	
6. Disperse systems 70	
<i>David Attwood</i>	
7. Kinetics and product stability 101	
<i>John Pugh</i>	
8. Pharmaceutical preformulation 113	
<i>James Wells</i>	
PART TWO	
Particle science and powder technology 139	
9. Solid-state properties 141	
<i>Graham Buckton</i>	
10. Particle-size analysis 152	
<i>John Staniforth</i>	
11. Particle-size reduction 166	
<i>John Staniforth</i>	
12. Particle-size separation 174	
<i>John Staniforth</i>	
13. Mixing 181	
<i>Andrew Twitchell</i>	
14. Powder flow 197	
<i>John Staniforth</i>	
PART THREE	
Biopharmaceutical principles of drug delivery 211	
15. Introduction to biopharmaceutics 213	
<i>Marianne Ashford</i>	
16. The gastrointestinal tract – physiology and drug absorption 217	
<i>Marianne Ashford</i>	
17. Bioavailability – physicochemical and dosage form factors 234	
<i>Marianne Ashford</i>	
18. Assessment of biopharmaceutical properties 253	
<i>Marianne Ashford</i>	
19. Dosage regimens 275	
<i>Stuart Proudfoot, (updated by John Collett)</i>	
20. Modified-release peroral dosage form 289	
<i>John Collett, Chris Moreton</i>	
PART FOUR	
Dosage form design and manufacture 307	
21. Solutions 309	
<i>Michael Billany</i>	
22. Clarification 323	
<i>Andrew Twitchell</i>	
23. Suspensions and emulsions 334	
<i>Michael Billany</i>	

8

Pharmaceutical preformulation: the physicochemical properties of drug substances

James Wells

CHAPTER CONTENTS

The concept of preformulation 114

Spectroscopy 114

Solubility 115

- Aqueous solubility 115
- Intrinsic solubility (C_0) 115
- pK_a from solubility data 116
- Salts 116
- Solvents 118
- Partition coefficient (K_{ow}) 119
- Solvent solubility 119
- Methodology and structure activity prediction 119
 - Choice of non-aqueous solvent (oil) 119
 - Structure–activity relationships 120
- Dissolution 122
 - Intrinsic dissolution rate 122
 - Measurement of intrinsic dissolution rate 123
 - Common ion effect 123

Melting point 124

- Techniques 124
 - Capillary melting 124
 - Hot-stage microscopy 124
 - Differential scanning calorimetry and thermal analysis 124
- Polymorphism 124
 - Pseudopolymorphism (solvates) 125
 - True polymorphism 126
- Crystal purity 126
- Solubility 126

Assay development 127

- UV spectroscopy 128
 - Molecular weight 128
 - pK_a 128
- Thin-layer chromatography 128
- High-performance liquid chromatography (HPLC) 128

- Normal-phase HPLC 129
- Reverse-phase HPLC 129

Drug and product stability 129

- Temperature 130
- Order of reaction 130
- Hydrolysis 130
- The influence of pH 130
- Solvolysis 131
- Oxidation 131
- Chelating agents 131
- Photolysis 131
- Solid-state stability 132
- Hygroscopicity 132
- Stability assessment 132

Microscopy 132

- Crystal morphology 133
- Particle size analysis 133

Powder flow properties 133

- Bulk density 133
- Angle of repose 134

Compression properties 134

- Plastic material 134
- Fragmentation 135
- Elastic material 135
- Punch filming (sticking) 136

Excipient compatibility 136

- Method 136
- Interpretation 136

Conclusions 138

References 138

Bibliography 138

THE CONCEPT OF PREFORMULATION

Almost all new drugs are marketed as tablets, capsules or both (Table 8.1). Although only a few are marketed as an injection (25% of those marketed as tablets) the intravenous route is always required during early toxicity, metabolic, bioavailability and clinical studies to provide a precise drug and dose deposition. Other dosage forms may be required (Table 8.1) but these are drug specific and depend to a large extent on the successful development of tablets, capsules and injections.

Prior to the development of these three major dosage forms, it is essential that certain **fundamental** physical and chemical properties of the drug molecule and other **derived** properties of the drug powder are determined. This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as **preformulation**.

A recommended list of the information required in preformulation is shown in Table 8.2. This is assembled, recognizing the relative importance and probable existence of only limited quantities of new bulk drug (mg rather than g). Investigators must be pragmatic and generate data of immediate relevance, especially if the likely dosage forms are known.

Two fundamental properties are mandatory for a new compound:

1. Intrinsic solubility (C_0),
2. Dissociation constant (pK_a).

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

Independent of this pharmaceutical profiling (Table 8.2), analysts will generate data (Table 8.3) to confirm structure and purity, and this should be used to complement and confirm pharmaceutical data. Their greater training and knowledge in analysis will assist in the identification of suitable stability-indicating assays by high-performance liquid chromatography (HPLC).

SPECTROSCOPY

The first step in preformulation is to establish a simple analytical method. Most drugs absorb light in the ultraviolet wavelengths (190–390 nm) as they are

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	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

Table 8.3 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

generally aromatic and contain double bonds. The acidic or basic nature of the molecule can be predicted from functional groups (Perrin et al 1981). Using the UV spectrum of the drug, it is possible to choose an analytical wavelength (often $\lambda_{\max}$) suitable to quantify the amount of drug in a particular solution. Excitation of the molecule in solution causes a loss in light energy, and the net change from the intensity of the incident light (I_0) and the transmitted light (I) can be measured. 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. Equation 8.1 is the Beer–Lambert law, where ϵ is the molar extinction coefficient.

$$\text{Absorbance } (A) = \log_{10} (I_0/I) = \epsilon Cl \quad (8.1)$$

In pharmacy it is usual to use the **specific absorption coefficient** $E_1^{1\%}$ (E_1^1), where the pathlength is 1 cm and the solution concentration is 1% w/v (10 mg mL⁻¹), as doses of drugs and concentrations are generally in unit weights rather than molarity ($E_1^1 = 10\epsilon/MW$).

SOLUBILITY

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 pK_a must be determined. Solubility dictates the ease with which formulations for oral gavage and intravenous injection studies in animals are obtained. The pK_a allows the informed use of pH to maintain solubility and to choose salts required to achieve good bioavailability from the solid state (Chapter 9) and improve stability (Chapter 7) and powder properties (Chapter 13 and 14).

Kaplan (1972) suggested that unless a compound has an aqueous solubility in excess of 1% (10 mg mL⁻¹) over the pH range 1–7 at 37°C, potential bioabsorption problems may occur. If the intrinsic dissolution rate was greater than 1 mg cm⁻² min⁻¹ then absorption was unimpeded. Dissolution rates less than 0.1 mg cm⁻² min⁻¹ were likely to give dissolution rate-limited absorption. This tenfold difference in dissolution rate translates to a lower limit for solubility of 1 mg mL⁻¹. Under sink conditions, dissolution rate and solubilities are proportional.

A solubility of less than 1 mg mL⁻¹ indicates the need for a salt, particularly if the drug will be formulated as a tablet or capsule. In the range 1–10 mg mL⁻¹ serious consideration should be given to salt formation. When the solubility of the drug cannot be manipulated in this way (neutral molecules, glycosides, steroids, alcohols, or where the pK_a 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.

Intrinsic solubility (C_o)

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 (pK_a) 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 pK_a s, one acidic and one basic. No change in solubility suggests a non-ionizable neutral molecule with no measurable pK_a , 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 (C_o), 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 (Fig. 8.1). The data are obtained from a series of experiments in which the ratio of the amount of drug to the amount of dissolving solvent is varied.

Any deviation from the horizontal is indicative of impurities, which a higher drug loading and its inherent impurities either promotes or suppresses solubility. In cases where the observed result changes with the amount of solvent, the line is extrapolated to zero phase ratio, where solubility will be independent of solvent level and the true intrinsic solubility of the drug. The United States Pharmacopoeia uses this method to estimate the purity of mecamylamine hydrochloride.

pK_a from solubility data

Seventy-five per cent 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.

$$\text{For weak bases: } \text{pH} = \text{pK}_a + \log_{10}([B])/[BH^+]) \quad (8.2)$$

$$\text{and for weak acids: } \text{pH} = \text{pK}_a + \log_{10}([A^-])/[HA]) \quad (8.3)$$

Equations 8.2 and 8.3 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_0) and pK_a are known
3. to facilitate the selection of suitable salt-forming compounds and predict the solubility and pH properties of the salts.

Albert and Serjeant (1984) give a detailed account of how to obtain precise pK_a values 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 8.4. As an example, the consequence of changing chlorthalidone to various salt forms is shown in Table 8.5.

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 gener-

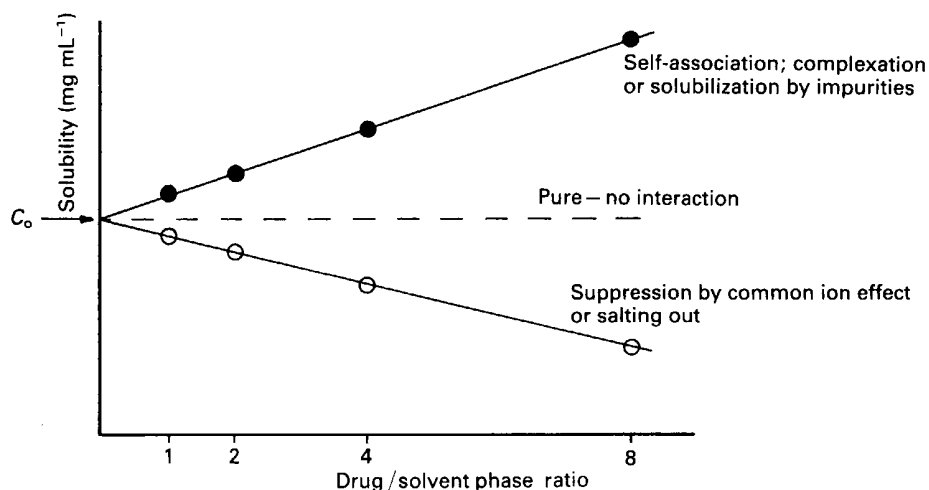


Fig. 8.1 Effect of drug: solvent ratio on solubility when the drug is impure. Assuming the compound is a base and the estimate of its solubility in 0.1 M NaOH was 1 mg mL⁻¹, four solutions of 3 mL should be set up containing 3, 6, 12 and 24 mg of drug. These give the phase ratios shown here. 3 mL is the smallest volume that can be manipulated for either centrifugation or filtration and dilution of UV analysis. The vials should be agitated continuously overnight and then the concentration in solution determined.

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

Table 8.5 Theoretical solubility and pH of salts of chlordiazepoxide			
Salt	pK_a	Salt pH	Solubility (mg mL ⁻¹)
Base	4.80	8.30	2.0
Hydrochloride	-6.10	2.53	<165 ^a
Maleate	1.92	3.36	57.1
Tartrate	3.00	3.90	17.9
Benzoate	4.20	4.50	6.0
Acetate ^b	4.76	4.78	4.1

^a Maximum solubility of chlordiazepoxide hydrochloride, achieved at pH 2.89, is governed by crystal lattice energy and common ions.

^b Chlordiazepoxide acetate may not form; pK_a of acetate too high and too close to that of drug ion.

ally be less hygroscopic and form less acidic or basic solutions (Table 8.5). 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 glass, and hydrochloride salts should not be used in aerosol cans as a propellant–acid reaction will corrode the canister.

From Table 8.5, not only does the intrinsic pH of the base solution fall significantly if salt forms are produced but, as a consequence, the solubility

increases exponentially (Eqns 8.2 and 8.3). This has important implications in vivo. A weak base with an intrinsic solubility greater than 1 mg mL⁻¹ will be freely soluble in the gastrointestinal tract, especially in the stomach. However, it is usually better to formulate with a salt, as it will control the pH of the diffusion layer (the saturated solution immediately adjacent to the dissolving surface, known as the pH microenvironment). For example, although chlordiazepoxide base ($C_s = 2$ mg mL⁻¹ at pH_{sat} 8.3) meets the requirements for in vivo ‘solubility’ (Kaplan, 1972); commercial capsules contain chlordiazepoxide hydrochloride ($C_s = 165$ mg mL⁻¹ at pH_{sat} 2.53).

A weak base will have a high dissolution rate in the stomach, but as it moves down the gastrointestinal tract the pH rises and dissolution rate falls. Conversely, a weak acid has minimal dissolution in the stomach but becomes more soluble and dissolution rate increases down the gut. Paradoxically, as dissolution rate increases so absorption falls because the drug is ionized.

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 8.6. On the basis of bulk pH these salts would be expected to have lower dissolution rates in the stomach. However, the pH of the diffusion layer (found by measuring the pH of a saturated bulk solution) is

higher than that of gastric fluid (which is approximately 1.5) because of its buffering action. The pH is the saturated unbuffered aqueous solution (calculated pH in Table 8.6) and the dissolution rate is governed by this pH and not the bulk medium pH.

In the intestine the salt does not depress the pH, unlike the acid which is neutralized, and the diffusion layer pH is again raised to promote dissolution. Providing that the acid forming the salt is strong, the pH of the solution adjacent to the dissolving surface will be that of the salt, whereas for the dissolving free base it will be the pH of the bulk dissolving medium. With weak bases, their salts dissolve rapidly in the stomach but there is no absorption, as the drug is ionized and absorption is delayed until the intestine. Any undissolved drug, as salt, rapidly dissolves, as the higher diffusion layer pH compensates for the higher bulk pH, which would be extremely unfavourable to the free base. Data for chlordiazepoxide are shown in Table 8.5. The maleate salt has a predicted solubility of 57 mg mL⁻¹ but, more importantly, reduces the pH by 5 units. By controlling diffusion layer pH the dissolution rate can increase manifold, independently of its position in the gastrointestinal tract. This is particularly important in the development of controlled-release products.

Different salts of a drug rarely change pharmacology, but only physical properties. This statement has been qualified to acknowledge that salts do affect the intensity of response. However, the salt form does change the physicochemical properties of the drug. Changes in dissolution rate and solubility affect the rate and extent of absorption (bioavailability), and changes on hygroscopicity and stability influence formulation.

Consequently each new drug candidate has to be examined to choose the most suitable salt, because

each potential salt will behave differently and require separate preformulation screening. The regulatory authorities also treat each salt as a different chemical entity, particularly in the context of toxicity testing.

Solvents

It is generally necessary to formulate an injection even if there is no intention to market. The first-choice solvent is obviously water. However, although the drug may be freely soluble, it may be unstable in aqueous solution. Chlordiazepoxide HCl is such an example. Accordingly, water-miscible solvents are used:

1. in formulations to improve solubility or stability
2. in analysis to facilitate extraction and separation (e.g. chromatography).

Oils are used in emulsions, topicals (creams and ointments), intramuscular injections and liquid-fill oral preparations (soft and hard gelatin capsules) when aqueous pH and solvent solubility and stability are unattainable Table 8.7 shows a range of solvents to fulfil these needs.

Aqueous methanol is widely used in HPLC and is the standard solvent in sample extraction during analysis and stability testing. It is often made acidic or alkaline to increase solvent power and ensure consistent ionic conditions for UV analysis. Other pharmaceutical solvents are available but are generally only required in special cases. The most acceptable non-aqueous solvents pharmaceutically are glycerol, propylene glycol and ethanol. Generally for a lipophilic drug (i.e. a partition coefficient ($\log P > 1$), solubility doubles through this series.

Where bulk is limited and the aqueous solubility is inadequate, it is better to measure the solubility in

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) $\times 10^2$	
			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

**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		

aqueous solvent mixtures rather than in a pure organic solvent. Whereas solubilities at other levels and their mixtures can be predicted, the solubility in pure solvent is often inconsistent because of cosolvent effects. Furthermore, formulations rarely use pure non-aqueous solvent, particularly injections. For example, ethanol should only be used up to 10% in an injection to prevent haemolysis and pain at the injection site, and include isotonic salts.

Partition coefficient (K_w^o)

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).

Solvent solubility

The relative polarities of solvents can be scaled using dielectric constant (ϵ), solubility parameter (δ), interfacial (γ) and hydrophilic-lipophilic balance (HLB). The best solvent in any given application is one whose polarity matches that of the solute; an ideal, fully compatible solution exists when $\delta_{\text{solvent}} = \delta_{\text{solute}}$. This can be ascertained by determining solubility maxima, using a substituent contribution approach or the dielectric requirement of the system.

The most useful scale of polarity for a solute is K_w^o (oil:water partition coefficient), as the other

approaches do not allow easy estimates for the behaviour of crystalline solids. For a wide range of drugs it is possible to relate solvent solubility and the partition coefficient ($\log K_w^o = \log P$). Yalkowsky and Roseman (1981) derived the following expression for 48 drugs in propylene glycol:

$$\log C_s = \log C_w + \int (0.89 \log P + 0.03) \quad (8.4)$$

Equation 8.4 can be applied more generally by introducing a factor ϕ to account for the relative solvent power of pharmaceutical solvents (see Table 8.8 for examples).

For a wide range of solvents Eqn 8.4 now becomes:

$$\log C_s = \log C_o + \int (\log \phi + 0.89 \log P + 0.03) \quad (8.5)$$

Methodology and structure activity prediction

Choice of non-aqueous solvent (oil) The oil:water partition (K_w^o) is a measure of the relative lipophilicity (oil-loving) nature of a compound, usually in the unionized state (HA or B), between an aqueous phase and an immiscible lipophilic solvent or oil.

Table 8.8 Solvent power (ϕ) of some pharmaceutical solvents

Solvent	Relative solvent power (ϕ)
Glycerol	0.5
Propylene glycol	1
PEG 300 or 400	1
Ethanol	2
DMA, DMF	4

Many partition solvents have been used. The largest database has been generated using *n*-octanol. The solubility parameter of octanol ($\delta = 10.24$) lies midway in the range for drugs (8–12), although some non-polar ($\delta < 7$) and polar drugs ($\delta > 13$) are encountered. This allows measurable results between equal volumes of oil and aqueous phases.

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, and then the majority of the lower aqueous phase (density of octanol = 0.8258 g mL^{-1}) is run off and centrifuged for 60 minutes at 2000 rpm. The aqueous phase is assayed before (ΣC) and after partitioning (C_w) [the aqueous concentration] to give $K_w^o = (\Sigma C - C_w)/C_w$.

If the transfer of solute to the oil phase is small, ΔC_w is small, and any analytical error increases error in the estimate of K_w^o . Indeed, to encourage greater aqueous loss ($> \Delta C_w$) a considerably more polar solvent, *n*-butanol, has been used. Where the partition coefficient is high, it is usual to reduce the ratio of the oil phase from 1:1 to 1:4 or 1:9 in order to increase the aqueous concentration (C_w) to a measurable level.

For a 1:9 oil:water ratio $K_w^o = (10 \Sigma C - C_w)/C_w$.

The partition of a polar solute between an inert non-polar hydrocarbon e.g. hexane, and water is quite different from that of hydrogen bonding solvents such as octanol. The behaviour of the weak acid phenol ($\text{p}K_a = 10$) and weak base nicotine ($\text{p}K_a = 3.1$) is worthy of note. For phenol, $K_w^{\text{octanol}} = 29.5$, whereas $K_w^{\text{hexane}} = 0.11$. The acidic solvent chloroform suppresses partition ($K_w^o = 2.239$), whereas ethyl acetate and diethyl ether are more polar. The basic behaviour of the solvents give higher K_w^o values. With solvents capable of both hydrogen donation and acceptance (octanol, nitrobenzene and oleyl alcohol), K_w^o is intermediate. For nicotine the behaviour is reversed, and the hydrogen donor (acidic) solvent chloroform partitions most strongly ($K_w^o = 77.63$), even though the neutral solvent nitrobenzene, which is marginally more lipophilic ($\log P = 1.87$ against 1.96 for chloroform), gives similar values for both phenol and nicotine. Clearly both solute and solvent characteristics are important.

In general, polar solvents are advocated to correlate biological activity with physicochemical properties. Solvents less polar than octanol, measured by water solvency, have been termed hyperdiscriminating, whereas more polar solvents such as butanols and pentanols, are hypodiscriminating. This concept refers to the discriminating power of a partitioning solvent within a homologous series. With *n*-butanol

the values of $\log P$ tend to be close, whereas with heptane and other inert hydrocarbons the differences in solute lipophilicities are exaggerated. *n*-Octanol generally gives a range consistent with other physicochemical properties when compared to drug absorption in the GI tract. Hyperdiscriminating solvents reflect more closely the transport across the blood–brain barrier, whereas hypodiscriminating solvents give values consistent with buccal absorption (Fig. 8.2). In rationalizing the effects of different partitioning solvents, a good correlation was found to exist between the solvent water content at saturation and solvent lipophilicity.

Certainly it is imperative to standardize on methodology, especially for the solvent. Where solubility constraints allow, this should be *n*-octanol, especially as the existing data bank is extensive.

Structure–activity relationships Since the pioneering work of Meyer and Overton numerous studies on correlating molecular structure and biological activity have been reported. These structure–activity relationships (SAR) can rationalize drug activity and, particularly in modern medicinal chemistry, facilitate a scientific approach to the design of more effective, elegant structural analogues.

The application of SAR depends on a sound knowledge of the physicochemical properties of each new drug candidate in a therapeutic class, and preformulation is an essential information source.

It is assumed in SAR that:

$$\log K_w^o = a \times \log k_w^{\text{octanol}} + b \quad (8.6)$$

This relationship holds for all polar and semipolar solvents, but with non-polar solvents (hexane to iso-octane) correlations are poor, and this seems to be related to water content. Given the importance of water, it is imperative that the octanol is saturated with the aqueous phase and the aqueous phase with octanol prior to any determination, otherwise the partitioning behaviour of the drug will be confounded by the mutual partitioning of the two solvents.

Although the aqueous phase is often water, it is better to measure $\log P$ under controlled pH. All drugs capable of ionization and with a measurable $\text{p}K_a$ will have intrinsic buffer capacity that affects the aqueous pH. Depending on the degree of dissociation, this will lead to an apparent K_w^o rather than the true (absolute) value, when the drug is unionized.

Because the ionized species will have greater aqueous solubility and lower lipophilicity to HA or BOH, the measured K_w^o (apparent) will be inevitably lower. Accordingly, K_w^o (true) should be measured at >2 pH units away from the $\text{p}K_a$ ($\text{p}K_a - 2$ (acid); $\text{p}K_a + 2$ (base)) and the aqueous phase should contain a

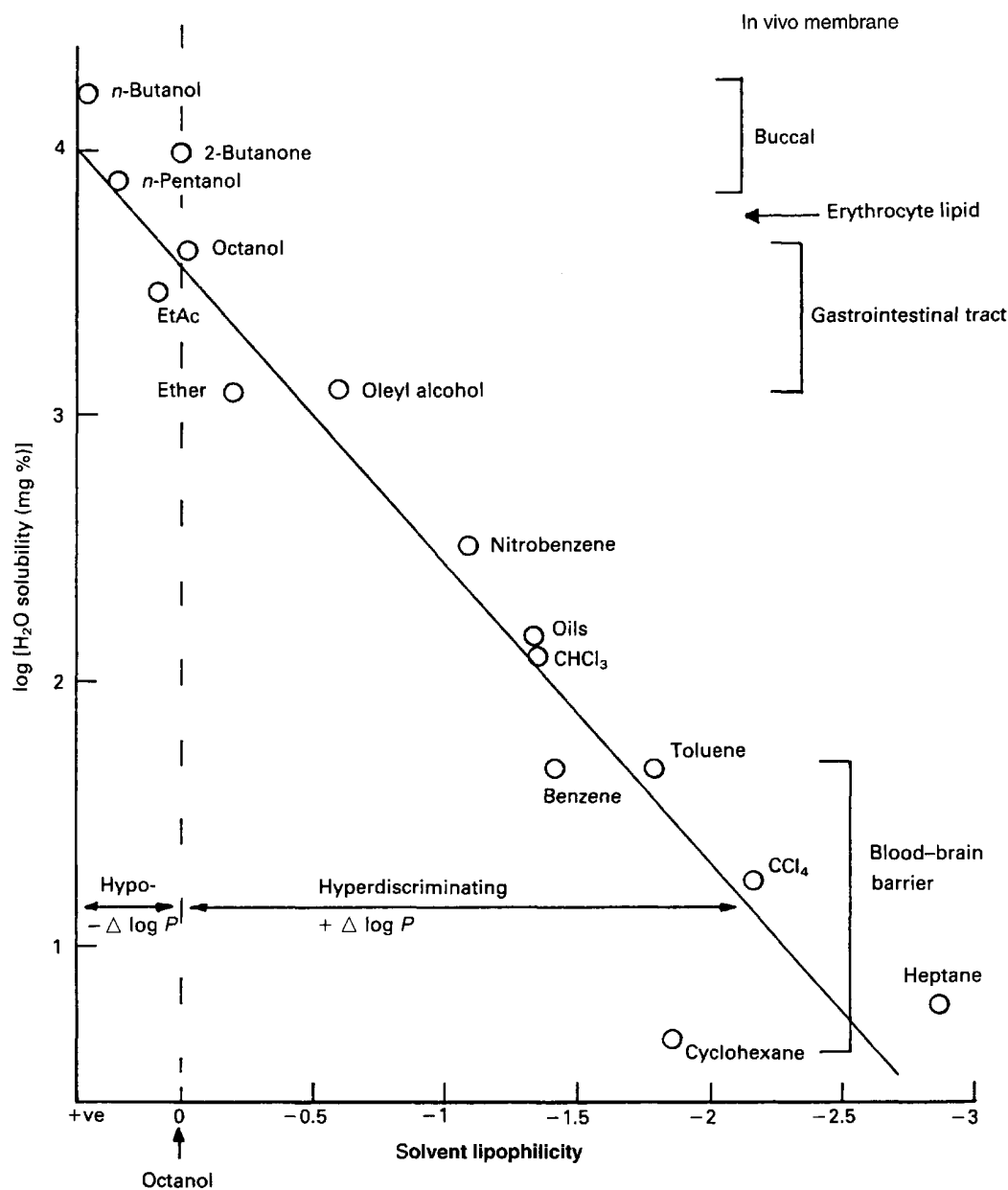


Fig. 8.2 Discriminating power of partitioning solvents as a function of their water capacity

suitable buffer. Given the importance of $\log P$ ($\log K_w^0$) in SAR, comparative data generated in a therapeutic class (R_nX , where X is the therapeutic nucleus and n is a number of substituents R) should also be determined at physiological pH 7.4.

Quantitative SAR (QSAR) is based on the premise that drug absorption is a multipartitioning process (repeated adsorption and desorption) across cellular

membranes and dependent on the lipophilicity of the drug, and the rate of penetration is proportional to the drug partition coefficient in vitro. Clearly the ionic condition in vivo will affect any correlation and, accordingly, for dissociating drugs the in vitro conditions should be similar. The widespread use of octanol in these studies and the existence of many excellent correlations in vivo is probably not

fortuitous. Octanol exhibits hydrogen bonding acceptor and donor properties typical of many biological macromolecules. The partial polarity of octanol allows the inclusion of water, which is also a feature of biological lipid membranes and leads to a more complex partitioning behaviour than a less polar, essentially anhydrous solvent.

The effect of salt formation on the measured $\log P$ is shown in Table 8.9. Generally the $\log P$ differs between 3 and 4 (K_w° from 1000 to 10 000). The lipophilicity falls by three to four orders of magnitude, which accounts for the significant increase in solubility of the salt. The physicochemical model for biological activity assumes that activity of a compound is related to the following factors associated with molecular structure:

- Electronic (charge)
- Steric (spatial size)
- Hydrophobic effects (partitioning).

Account must also be taken of structural and theoretical aspects, so that:

$$\text{Biological activity} = f[(\text{electronic}) + (\text{steric}) + (\text{hydrophobic}) + \text{structural/theoretical}] \quad (8.7)$$

The electronic parameter in Eqn. 8.7 is quantified by the sigma (σ) substituent constant of Hammett and reflects chemical reactivity in a homologous series. The substituent constant (σ) is positive for electron withdrawal (acids), whereas electron donor groups (bases) give a negative value. It can be used to predict pK_a (Perrin et al 1981).

Steric effects occur when there is a direct interaction between the substituent and the parent nucleus, and is related to substituent bulk. High positive

values of the steric effect parameter, E_s , indicate significant steric effects, with intra- and intermolecular hindrance to a reaction or finding at the active site.

The hydrophobic component is measured by the distribution between an aqueous phase and an immiscible lipid phase and parallels drug adsorption and distribution in vivo. A relationship between partition coefficients has been demonstrated within a series by quantifying differences using an additive substituent constant (π). The constant is related almost completely to the effect of a particular substituent and much less to the parent compound, and this allows the prediction of the partition coefficient, $\log P$, of a new derivative with reasonable accuracy. In addition, π can be related to biological effect as it is an additive component of the partition coefficient, and this has led to the wider application of SAR, with other modifications, notably taking into account of aromatic electron density and steric effects, to give **quantitative** SAR (i.e. QSAR).

Although all these substituents are useful, $\log P$ remains the most useful physical parameter and undoubtedly the most reliable data and correlations still come from experimentally derived partition values for the analogues in a series.

Dissolution

The dissolution rate of a drug is only important where it is the rate-limiting step in the absorption process. Kaplan (1972) suggested that provided the solubility of a drug exceeded 10 mg mL⁻¹ at pH <7, no bioavailability- or dissolution-related problems were to be expected. Below 1 mg mL⁻¹ 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

When dissolution is controlled solely by diffusion (transport control), the rate of diffusion is directly proportional to the saturated concentration of the drug in solution (i.e. solubility). Under these conditions the rate constant K_1 is defined by:

$$K_1 = 0.62 D^{2/3} \nu^{1/6} \omega^{1/2} \quad (8.8)$$

where ν is the kinematic viscosity and ω is the angular velocity of a rotating disc of drug. By maintaining the dissolution fluid viscosity and rotational speed of the sample constant, the dissolution rate

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

Free base and hydrochloride salt	$\log P$	$\Delta \log P$
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	

(dc/dt) from a constant surface area (A) will be constant and related solely to solubility. Under sink conditions ($C_s \gg C$) gives:

$$dc/dt = \frac{A}{V} K_1 C_s \quad (8.9)$$

Intrinsic dissolution rate (IDR) is given by:

$$\text{IDR} = K_1 C_s \text{ (mg cm}^2 \text{ min}^{-1}) \quad (8.10)$$

This constant rate differs from the dissolution from conventional dosage forms, which is known as total dissolution (mg mL^{-1}), where the exposed surface area (A) is uncontrolled as disintegration, deaggregation and dissolution proceed. Accordingly, the 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.

Measurement of intrinsic dissolution rate A compressed disc of material can be made by slow compression of 500 mg of drug in a 13 mm IR disc punch and die set to a high compaction pressure greater than 500 MPa (to ensure zero porosity) and a long dwell time (to improve compaction). The metal surfaces in contact should be prelubricated with, for example, stearic acid (5% w/v in chloroform). The compressed disc is fixed to the holder of the rotating basket apparatus using a low-melting paraffin wax and successively dipped so that the top and sides of the disc are coated. The lower circular face should be cleared of residual wax using a scalpel and carefully scraped to remove any stearic acid transferred from the punch face.

The coated disc is rotated at 100 rpm, 20 mm from the bottom of a 1 L flat-bottomed dissolution flask containing 1 L of fluid at 37°C. The amount of drug release is then monitored, usually by UV spectrometry, with time. The slope of the line divided by the exposed surface area gives the IDR ($\text{mg cm}^2 \text{ min}^{-1}$).

Each candidate should be measured in 0.05 M HCl (gastric) and phosphate buffer pH 7 (intestinal), and distilled water especially if sink conditions are not possible for a weak base at pH 7 or a weak acid in 0.05 M HCl. Sink conditions maintain the bulk concentration (C) at a low level otherwise the rate of dissolution is progressively reduced and the plot of concentration against time becomes non-linear. It is recommended that C should not exceed $0.1C_s$.

By comparing the IDR of a salt in water with that obtained in acid and alkali, or the free base with its salts in the same medium, a measure of the salt's ability to control its immediate microenvironment will emerge.

The equation derived from the Henderson-Hasselbalch equation:

$$\text{IDR} = k' [C_o(1 + \text{antilog } [pK_a - \text{pH}])] \quad (8.11)$$

shows that the rate of dissolution of a drug candidate is clearly a function of its intrinsic solution (C_o), its dissociation constant (pK_a), and the pH of either the bulk dissolution medium or the microenvironment created by the dissolving salt. Using the measured rate of the free base at known bulk pH, expected rates in other media, using the experimental salts, can be calculated and compared with experimental values.

The importance of improvements in the IDR due to microenvironmental pH control lies in the improvement in vivo of a salt over the parent drug. Where no increase is found there is likely to be no advantage in using that particular salt. Improvements are obviously more likely if the salt former is strong. For a weak base, the hydrochloride ($pK_a = -6.10$) offers the best advantage, but in some instances this may prove disappointing because of Cl^- ions. Thus the measurement of IDR can be useful diagnostically.

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 (Table 8.10). Counter-ions other than Cl^- , such

Table 8.10 Examples of weakly basic drugs which have decreased solubility in acidic and Cl^- solutions

Chlortetracycline
Demethylchlortetracycline
Methacycline
Demeclocycline
Phenazopyridine
Cyproheptadine
Bromhexine
Triamterine

as nitrate, sulphate and phosphate, have also been implicated. They are usually inorganic, because of their small size.

To identify a common ion interaction the IDR of the hydrochloride (or inorganic) salt should be compared between:

- water and water containing 1.2% w/v NaCl, and
- 0.05 M HCl and 0.9% w/v NaCl in 0.05 M HCl.

Both saline media contain 0.2M Cl^- , which is typically encountered in fluids in vivo.

A common ion effect with Cl^- will result in a significantly reduced IDR in the presence of sodium chloride. Other salt forms are then indicated, e.g. tosylate, mesylate etc., but the parent molecule will still remain sensitive to Cl^- and solubilities will be suppressed in the presence of saline, although not to the same extent as Cl^- is not involved in the dissolving microenvironment. Any improvement with the new salt can be assessed by again measuring the IDR with and without saline. As some compounds are sensitive to other counter-ions, e.g. nitrate, sulphate and phosphate can be demonstrated by including the appropriate sodium salt in the dissolution medium. Phase solubility studies have indicated that basic amine drugs are more soluble in organic acids than inorganic. Where a hydrochloride salt exhibits sub-optimal solubility then the next logical choice is probably a salt of toluene sulphonc acid (tosylate: $\text{p}K_a = -1.34$). Mesylate, napsylate, besylate and maleate salts offer progressively more weaker acidic alternatives.

With low-solubility amine drugs, the salts of polyhydroxy acids, e.g. lactate, often give the greatest aqueous solubility because of their accessible hydroxy groupings.

MELTING POINT

Techniques

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

1. Capillary melting
2. Hot stage microscopy
3. Differential scanning calorimetry or thermal analysis.

Capillary melting

Capillary melting (the observation of melting in a capillary tube in a heated metal block) gives infor-

mation about the melting range but it is difficult to assign an accurate melting point.

Hot stage microscopy

This is the visual observation of melting under a microscope equipped with a heated and lagged sample stage. The heating rate is controllable and up to three transitions can be registered. It is more precise as the phase transitions (first melt, 50% melt and completion) can be registered on a recorder as the melting proceeds, and because of the high magnification the values are more accurate.

Differential scanning calorimetry and thermal analysis

Neither of the previous methods is as versatile as either differential thermal analysis (DTA) or differential scanning calorimetry (DSC). An additional advantage is that the sample size required is only 2–5 mg.

DTA measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate. DSC is similar to DTA, except that the instrument 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 no physical or chemical change occurs within the sample then there is neither a temperature change nor input energy to maintain an isotherm. However, when phase changes occur then latent heat suppresses a temperature change and the isothermal energy required registers as an electrical signal generated by thermocouples. Crystalline transitions, fusion, evaporation and sublimation are obvious changes in state which can be quantified (Fig. 8.3).

The major concern in preformulation is polymorphism, and the measurement of melting point and other phase changes is the primary diagnostic tool. Confirmation by IR spectroscopy and X-ray diffraction is usually required.

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

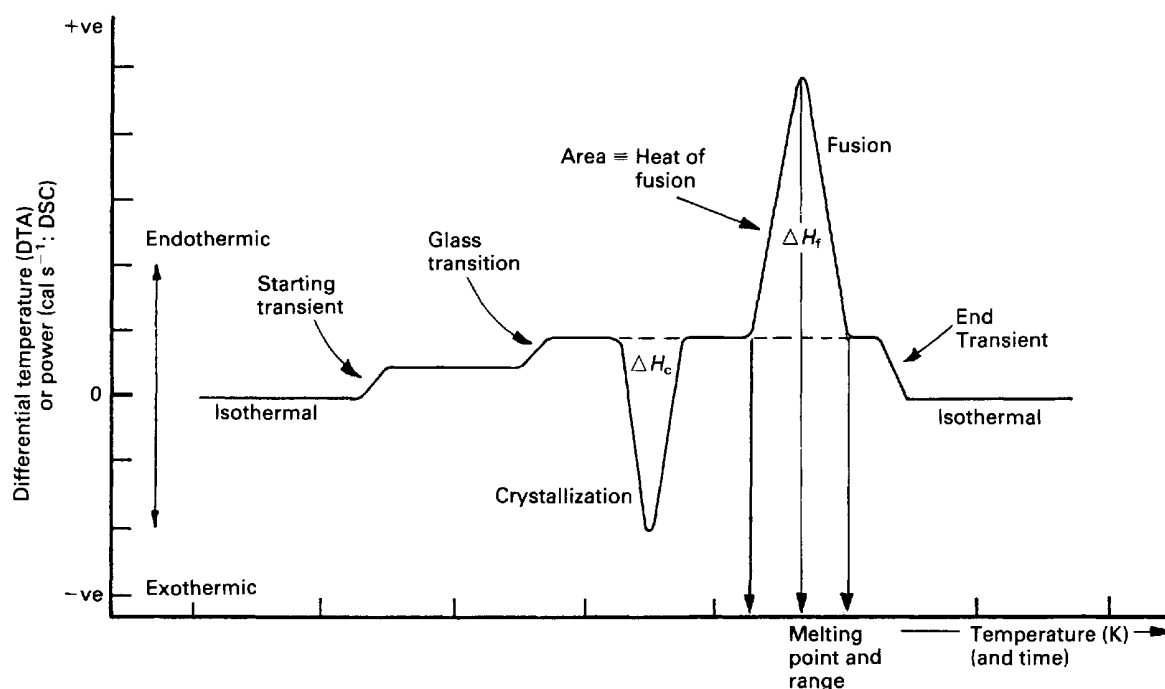


Fig. 8.3 Schematic differential scanning calorimeter thermogram.

properties so that they behave as distinct chemical entities. 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. The importance of polymorphism is illustrated by the biopharmaceutical data for fluprednisolone (Fig. 8.4).

It is convention to number the polymorphs in order of stability at room temperature, starting with form I using Roman numerals. Form I usually has the highest melting point and the lowest solubility; in suspension formulation it is essential to use the least soluble polymorph because of Ostwald ripening.

Accordingly, 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)

Prior to this, 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. Trace levels of solvent are usual in early batches of new drug candidates (residues from the final crystallization). 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.

The distinction between these false forms and true polymorphs can be ascertained by observing the melting behaviour of the compound dispersed in silicone oil using hot-stage microscopy.

Pseudopolymorphs will evolve a gas (steam or solvent vapour), causing the oil to bubble. True

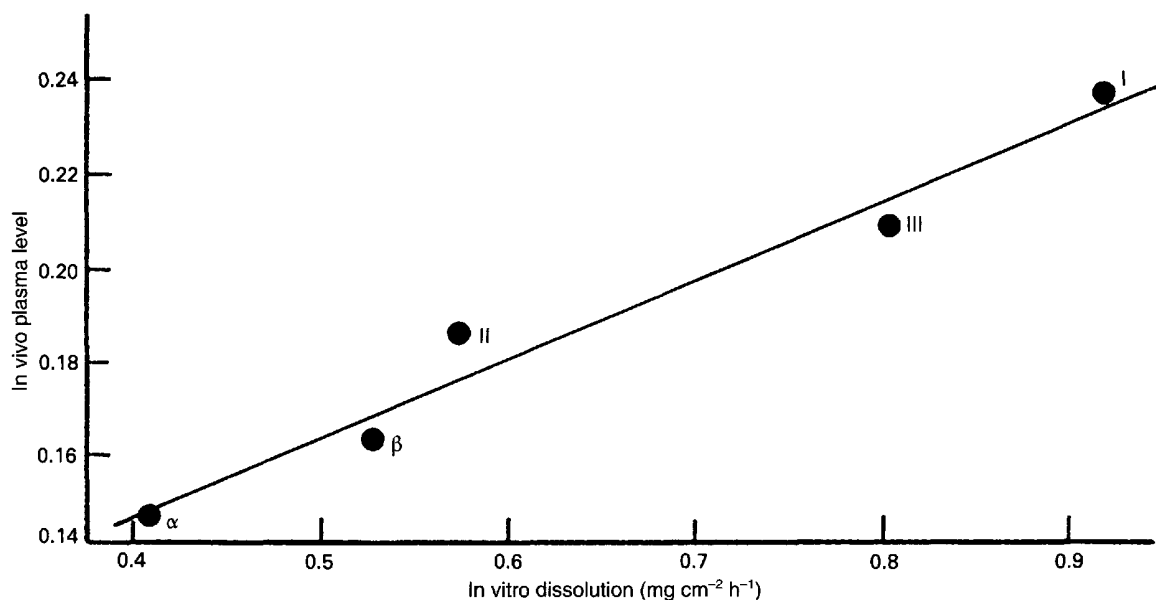


Fig. 8.4 The relationship between in vitro and in vivo release from fluprednisolone implants.

polymorphs merely melt, forming a second globular phase. The temperature at which the solvent volatilizes will be close to the boiling point of the solvent.

True polymorphism

After the study of pseudopolymorphism (see also Chapter 9 for further discussion on polymorphism), the evaluation of true polymorphism can proceed unconfounded. Most polymorphs are obtained by solvent manipulation. Others can be produced without the presence of solvent by thermal techniques, notably sublimation and recrystallization from the melt. Supercooling of the melt is particularly useful in discovering unstable modifications.

The initial difficulty is to measure the melting point of the metastable form, and here heating rate is critical. Too-rapid heating will obscure the endotherm, whereas too slow a heating rate may allow transition or encourage decomposition. Often, therefore, comparison at two rates, e.g. 2 and 20°C min⁻¹, is necessary.

The difference in melting point (ΔT_m) between polymorphs is a measure of the metastable polymorph stability. Where $\Delta T_m < 1^\circ\text{C}$ then neither is significantly more stable and either may be obtained upon conventional crystallization. If ΔT_m is 25–50°C then the lower melting species will be difficult to crystallize and will rapidly revert. The closer the two melting points ($\Delta T_m \rightarrow 1\text{--}25^\circ\text{C}$) then the unstable form(s) can be obtained easily before a solid–solid

transformation occurs. This can be suppressed by using small samples, as individual crystals of even highly unstable forms can be melted.

If it appears that polymorphism is occurring or likely, then a cooperative study with the bulk chemists should determine the most stable form (chemical and physical). Differences in solubility and melting point must also be assessed and then a decision made to determine which form to progress through to the next stage of formulation. Small differences in stability but higher solubility of a relatively metastable form may lead to a preferential choice of a polymorph other than form I, but this is unlikely and is not encouraged by regulatory authorities.

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.

Such studies are particularly important because the scarcity of available drug powder often precludes accurate solubility determinations.

Melting point and solubility are related via the latent heat of fusion, which is the amount of heat generated during melting or fusion. A crystal with weak bonds has a low melting point and low heat of fusion. Conversely, a strong crystal lattice leads to a high melting point and a high heat of fusion. Because solubility also requires the disruption of crystal structure to allow molecular dispersion in the solvent, it is also influenced by intermolecular forces.

Polymorphs differ in melting point and solubility. The existence of different crystal arrangements for the same compound inevitably leads to differences in crystal lattice energy, as intermolecular distances will

be different in the alternative forms. This effect is shown in Figure 8.5 for riboflavin.

ASSAY DEVELOPMENT

The assumption that the drug is stable may not be valid as drugs are notoriously unstable, particularly as hydrolysis is often the predominant cause. In order to follow drug stability, in both solution and solid phase, it is mandatory to have suitable stability-indicating assays. In some cases UV spectroscopy can be used, but in general chromatography is required to separate the drug from its degradation products and any excipients. Thin-layer

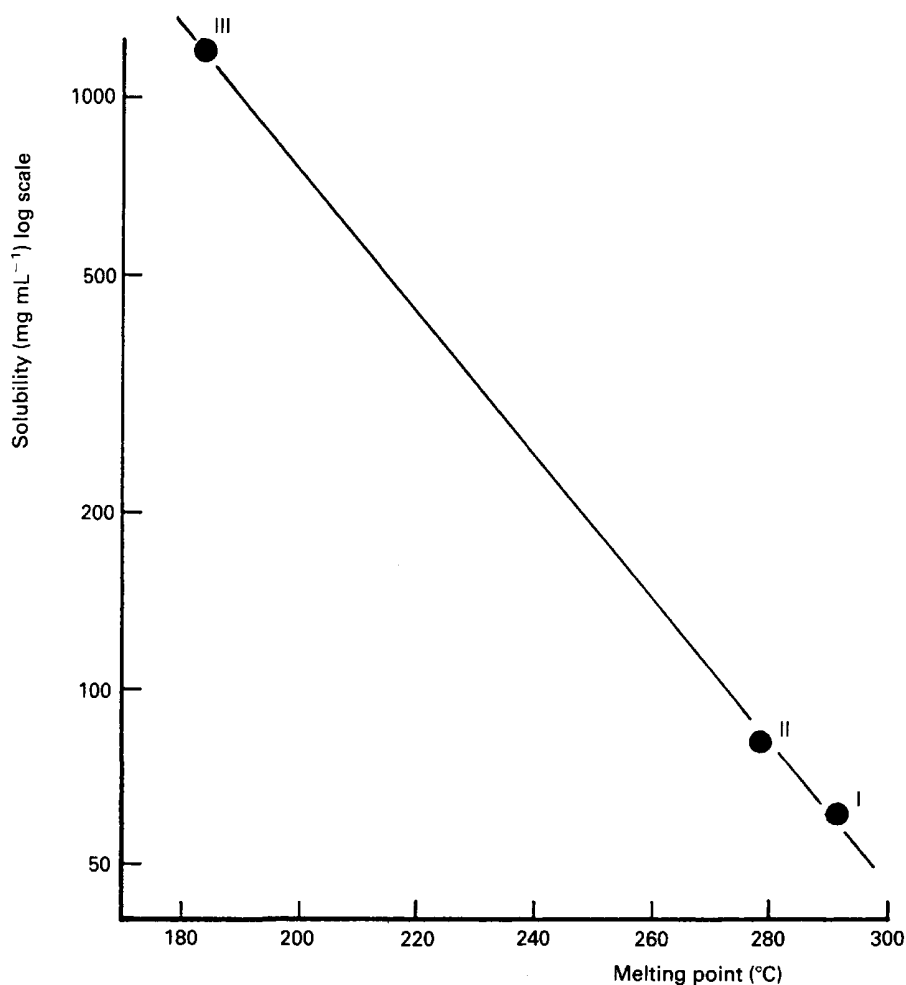


Fig. 8.5 The relationship between melting point and solubility for three polymorphs of riboflavin.

chromatography (TLC) is widely used in a semi-quantitative mode to estimate impurity levels, to establish the number of impurities, and to collect samples from the plate for subsequent HPLC (high-performance (pressure) liquid chromatography). HPLC is now acknowledged as the most versatile and powerful technique in pharmaceutical analysis and is the method of choice in preformulation stability assessment.

UV spectroscopy

The principles of UV spectroscopy were enumerated earlier and will serve to quantify many of the subsequent physical constants and solubilities above. TLC, and particularly HPLC, has largely superseded UV spectroscopy as a basic analytical tool in stability assessment. However, certain UV techniques are worthy of discussion:

- Solubility
- Molecular weight
- pK_a
- Assay (potency)
- Mixtures:
 - resolving compound products
 - stability: hydrolysis, oxidation (coloured products).

Molecular weight

To a first approximation the molar extinction coefficient (ϵ) of a chromophore (absorbing molecular group) is unaffected by distant substituent groups in a molecule. Therefore, if ϵ of the chromophore is known from another related compound in the series, the molecular weight of the new derivative can be calculated from the absorbance of a solution of known concentration, as $\text{mol. wt.} = 10 \epsilon / E$.

pK_a

pK_a measurement by spectroscopy is indicated when solubility is too low, or when the pK_a is particularly low (<2) or high (>11) for determination by potentiometry. The method depends on determining the ratio of molecular species (neutral molecular at $\text{pH} < pK_a - 2$ (acid), $\text{pH} > pK_a + 2$ (base)) to the ionized species in a series of seven buffers ($\text{pH} = \pm 1$ of pK_a). An analytical wavelength (λ) is chosen where the greatest difference in absorbance exists between the molecular species and the pure ionized moiety at two pH units from the pK_a .

Thin-layer chromatography

All chromatographic procedures emanate from the Russian botanist Tswett (1906), who separated plant pigments by pipetting solutions on to the top of packed glass tubes. Tswett's work led to the development of column chromatography and, under pressure, to HPLC. Other workers used paper as a support, and before the advent of HPLC paper chromatography was used for simplicity and speed. TLC arose from a need to satisfactorily separate lipids, which paper techniques could not achieve, but it was soon realized that the technique was also considerably more flexible. Paper chromatography is limited by the cellulose support, whereas the thin layer of material on a glass plate can be prepared from a slurry of a wide variety of different chemical types, e.g. silica gel, celite, alumina, cellulose (analogous to paper chromatography) and chemically modified celluloses; and more recently with the advent of reversed-phase chromatography, C_2 , C_8 and C_{18} silanized and diphenyl silica.

Modern TLC was established by Stahl (1956) and separations were found to be considerably shorter than on paper, spots were more compact, resolution better, and submicrogram samples could be separated and recovered if necessary (by scraping away the spot using a fine spatula), re-extracted and injected on to HPLC.

TLC is now generally regarded as a reliable and sensitive qualitative technique for the separation of complex mixtures in stability samples. In a typical analysis, extracted samples are spotted 20 mm from the bottom of a square glass plate, 200×200 mm, coated with a dry slurry of silica ($250 \mu\text{m}$ thick) and placed in a closed tank containing a 10 mm layer of eluting solvent, which has produced a saturated vapour phase. The sample is developed (separated) by the capillary movement of the solvent up the plate and is therefore similar to HPLC. It is a thin flat column (stationary phase) with solvent (mobile phase) pumped by capillary flux, and much of the theory (Snyder 1968) is the same. Consequently, TLC and HPLC are complementary. TLC will quantify the number of components (as they can be seen) and estimate their concentration by reference to standards run concurrently, whereas HPLC can quantify their level, confident that all have been separated. The developing solvent for TLC (particularly HPTLC (high-performance TLC) and reverse phase) is also a useful guide to identify the mobile phase for HPLC.

High-performance liquid chromatography

High-performance (pressure) liquid chromatography (HPLC) is essentially column chromatography

performed by eluting under pressure. By pumping the eluting solvent (mobile phase) under a pressure of up to 40 MPa (6000 psi) and a flow rate of up to 3 mL min⁻¹, the column can be much smaller and use much smaller particle size packing material (stationary phase). This results in shorter retention times (solute time on column), high sensitivity (typically 1 ng), the need for only a small sample volume (0–50 µL) and yet high selectivity (separation power) for the resolution of complex mixtures.

HPLC methods can be divided into two distinct modes.

Normal-phase HPLC

Normal phase HPLC is performed by eluting a silica-packed column, which is hydrophilic, with a non-polar mobile phase. The mobile phase is usually hexane, to which is added one or more of the following, in increasing order of polarity: chloroform (CHCl₃), tetrahydrofuran (THF), acetonitrile (ACN), isopropyl alcohol (IPA) or methanol (MeOH). Separation is achieved by partition with differential adsorption and desorption of both the solute and solvents during passage down the column. Polar solutes are retained, but more lipophilic molecules are not. By increasing the polarity of the mobile phase (e.g. by adding MeOH or IPA), polar solutes are eluted more quickly, whereas non-polar solutes are better retained and their order of retention is changed. Decreasing solvent polarity increases polar solute retention and facilitates the elution of lipophilic molecules.

In general, normal-phase HPLC is used for moderately polar solutes (freely soluble in methanol). Non-polar hydrocarbon-soluble solutes are difficult to retain and very polar and water-soluble solutes are difficult to elute sufficiently.

Reverse-phase HPLC

When the solute is eluted by a polar (largely aqueous) mobile phase over a hydrophobic stationary phase, the chromatography is known as reverse phase. Solute behaviour is the reverse of that described for normal phase HPLC, which uses a hydrophilic silica stationary phase. Separation between the stationary phase and the mobile phase is solvophobic, analogous to partitioning.

Hydrophobicity of the stationary phase is achieved by bonding a coating on to the silica support. The most common bonded phases are alkyl silanes of C₁₈ (octadecylsilane, ODS), C₈ (octylsilane, OS), and C₁ (trimethylsilane). The predominantly aqueous mobile

phase usually contains methanol, ACN and/or THF to modify solvent polarity by matching the lipophilicity of the solutes in order to facilitate good chromatography. Ionization control can be achieved in the range pH 2–8. The inclusion of 1–2% acetic acid or diethylamine is used to suppress the ionization of weak acids and bases respectively (*ion-suppression chromatography* is used to increase lipophilicity and improve the retention of polar solutes).

In general polar solutes have short retention times on reverse phase, whereas non-polar compounds are retained. Increasing the mobile phase polarity (by increasing the water concentration) shortens retention for polar solutes while retaining fewer polar compounds. Decreasing solvent polarity (by decreasing water concentration) helps retain polar compounds, but more lipophilic solutes are eluted more rapidly. Non-aqueous reverse phase (NARP HPLC, where THF or methylene chloride replaces water in the mobile phase) is used to separate lipophilic solutes.

The great flexibility of choice in mobile phase (by using solvents ranging from water to hexane), the increasing number of available stationary phases (particularly bonded phases) and the inherent sensitivity of HPLC produces a powerful analytical technique. It is the method of choice in preformulation stability studies.

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. Typical stress conditions are shown in Table 8.11.

Drug degradation occurs by four main processes:

- Hydrolysis
- Oxidation
- Photolysis
- Trace metal catalysis.

Hydrolysis and oxidation are the most common pathways, and in general light (*c*) and metal ions catalyse a subsequent oxidative process.

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 MgBr₂, KNO₃, NaBr, NaCl and KNO₃ respectively.
^c At pH of maximum stability in simple aqueous solution.

Temperature

Thermal effects are superimposed on all four chemical processes. Typically a 10°C increase in temperature can produce a 2–5-fold increase in decay. Often the increase in reaction rate with temperature follows an Arrhenius-type relationship: a plot of the log of the rate of reaction against the reciprocal of absolute temperature yields a straight line. The reaction rate can then be calculated at any temperature and allows a prediction of shelf-life at room temperature by extrapolation. This assumption forms the basis of accelerated stability tests. However, the mechanism or pathway of the chemical breakdown often changes with temperature. This will be indicated by a discontinuity or ‘knee joint’ in the Arrhenius plot. This is not easily detected and would inevitably lead to erroneous conclusions, based on elevated temperature data, to predict shelf-lives at room temperature or under refrigeration. Reactions often change at about 50°C, and this is a sensible ceiling.

Order of reaction

The time course of degradation depends on the number of reactants, whose concentration influences the rate. It is often more convenient to express reaction rates in terms of time. The most common is the **half-life**, the time at which the concentration has halved ($t_{1/2}$ or t_{50}). The shelf-life of a product can be likewise expressed as t_{95} (i.e. the time for 5% loss) etc.

In the absence of a definitive value for the activation energy (E_a), which can be obtained from the slope of the Arrhenius plot, it is prudent to assume a low value (e.g. 10 kcal mol⁻¹), as this will lead to higher reaction rates and any prediction of shelf-life will be conservative. Values for a wide range of drug

degradation reactions are 10–100 kcal mol⁻¹, but are usually in the range 15–60 kcal mol⁻¹ with a mean of 19.8. Most occur by first-order kinetics (logarithmic) but some are zero order, e.g. aspirin in aqueous suspension, and a few are second order, e.g. chlorbutol hydrolysis.

Hydrolysis

The most likely cause of drug instability is hydrolysis. Water plays a dominant role and in many cases it is implicated passively as a solvent vector between two reacting species in solution. The solution is often saturated, so that studies in dilute solution can be completely misleading (see Solid-state stability, later in this chapter).

Hydrolytic reactions involve nucleophilic attack of labile bonds, e.g. lactam > ester > amide > imide, by water on the drug in solution, and are first order. When this attack is by a solvent other than water it is known as **solvolysis**.

A number of conditions catalyse the breakdown:

- The presence of OH⁻
- The presence of H₃O⁺
- The presence of divalent metal ions
- Ionic hydrolysis (protolysis) is quicker than molecular
- Heat
- Light
- Solution polarity and ionic strength
- High drug concentrations.

The influence of pH

The degradation of most drugs is catalysed by extremes of pH, i.e. high [H₃O⁺] and [OH⁻], and many drugs are most stable between pH 4 and 8.



Where maximum stability dictates wider values, it is important for injections that there is low buffer capacity to prevent unnecessary challenge to the homeostatic pH (7.4) of blood.

Weakly acidic and basic drugs are most soluble when ionized, and it is then that instability is most likely as they are charged. This leads to a problem, as many potent drugs are extremely poorly soluble and pH ionization is the most obvious method to obtain a solution. In some cases, therefore, the inclusion of a water-miscible solvent in the formulation will increase stability by:

1. Suppressing ionization
2. Reducing the extreme of pH required to achieve solubility
3. Reducing water activity by reducing the polarity of the solvent, e.g. 20% propylene glycol in chlordiazepoxide HCl injection.

Reactions in aqueous solution are usually catalysed by pH, and this is monitored by measuring degradation rates (usually pseudo first order) against pH, keeping temperature, ionic strength and solvent concentration constant. Suitable buffers include acetate, citrate, lactate, phosphate and ascorbate (an intrinsic antioxidant).

Solvolysis

Where the reacting solvent is not water, then breakdown is termed solvolysis. Furthermore, the definition can be extended to include any change in solvent polarity (usually measured as dielectric constant) as a result of increased ionic strength. Phenobarbitone is considerably more stable in preparations containing water-miscible solvents, whereas aspirin, which undergoes extensive hydrolysis, is degraded further by aqueous solvents. Both effects are directly related to the dielectric constant (polarity) of the solvent. In general, if a compound produces degradation products which are more polar then the addition of a less polar solvent will stabilize the formulation. If the degradation products are less polar, then the vehicle should be more polar to improve stability. With the hydrolysis of neutral non-polar drugs, e.g. steroids, the transition state will be non-polar with no net charge. In this case solvents will not affect the rate of decomposition and can be used with impunity to increase solubility.

Oxidation

Oxidation is controlled by the environment, i.e. light, trace metals, oxygen and oxidizing agents. Reduction

is a complimentary reaction (redox) and there is a mutual exchange of electrons. Oxidation is a loss of electrons and an oxidizing agent must be able to take electrons. In organic chemistry, oxidation is synonymous with dehydrogenation (the loss of hydrogen) and this is the mode of action of polyhydroxyphenol antioxidants, e.g. hydroquinone. However, most antioxidants function by providing electrons or labile H^+ , which will be accepted by any free radical to terminate the chain reaction. A prerequisite for effective antioxidant activity in any particular preparation is that the antioxidant is more readily oxidized than the drug.

Chelating agents

Chelating agents are complexes, unlike simple ligands, e.g. ferrocyanide ($Fe(CN)_6^{4-}$), which form complex salts by a single bond provided by a lone electron pair. Chelating agents are capable of forming more than one bond. For example, ethylene diamine is bidentate (two links), tripyridyl is tridentate (three) and ethylene diamine tetra-acetic acid (EDTA) is hexadentate (six), which makes it particularly effective as a pharmaceutical chelating agent.

Photolysis

Oxidation, and to some extent hydrolysis, is often catalysed by light. The energy associated with this radiation increases as wavelength decreases, so that the energy of UV visible is greater than that of IR and is independent of temperature (Table 8.12).

When molecules are exposed to electromagnetic radiation they absorb light (photons) at characteristic wavelengths which causes an increase in energy, which can:

- cause decomposition
- be retained or transferred
- be converted to heat
- result in light emission at a new wavelength (fluorescence, phosphorescence).

Table 8.12 Relationship between wavelength and associated energy of various forms of light

Type of radiation	Wavelength (nm)	Energy (kcal mol ⁻¹)
UV	50–400	287–72
Visible	400–750	72–36
IR	750–10 000	36–1

Natural sunlight lies in the wavelength range 290–780 nm, of which only the higher energy (UV) range (290–320 nm) causes photodegradation of drugs, and sunburn. Fluorescent lighting tubes emit visible light and potentially deleterious UV radiation in the range 320–380 nm, whereas conventional tungsten filament light bulbs are safe, emitting radiations > 390 nm.

Thus photolysis is prevented by suitable packaging: low actinic amber glass bottles, cardboard outers and aluminium foil overwraps and blisters. Clear flint glass absorbs around 80% in the 290–320 nm range, whereas amber glass absorbs more than 95%. Plastic containers, by comparison, absorb only 50%.

Solid-state stability

Many of the processes of composition apply generally, particularly when the drug is in solution. However, certain important distinctions arise with the stability of drugs in the solid state, e.g. in tablets and capsules. There is limited information in the pharmaceutical literature, owing largely to the complexities of formulated systems and the difficulties in obtaining quantitative data. This paucity of data must not be interpreted to mean that this area is unimportant, especially given the popularity of tablets and capsules.

In all solid dose formulations there will be some free moisture (contributed by excipients as well as the drug), and certainly in tablets a significant percentage, typically 2% w/w, is required to facilitate good compression. This free water acts as a vector for chemical reactions between drug and excipients, and the adsorbed moisture films are saturated with drug compared to the dilute solutions encountered in injectables. The ionic equilibria are quite different and comparison is meaningless. They should not be extrapolated glibly to the solid state.

Hygroscopicity

A substance that absorbs sufficient moisture from the atmosphere to dissolve itself is deliquescent. A substance that loses water to form a lower hydrate or becomes anhydrous is termed efflorescent. These are extreme cases, and most pharmaceutical compounds are usually either impassive to the water available in the surrounding atmosphere or lose or gain water from the atmosphere, depending on the relative humidity (RH). Materials unaffected by RH are termed non-hygroscopic, whereas those in dynamic equilibrium with water in the atmosphere are hygro-

scopic. Ambient RH (0% poles and desert, 55% temperate and 87% tropics) can vary widely and continually depending on the weather and air temperature, and these cyclic changes lead to constant variations in the moisture content of unprotected bulk drug and excipients. The constant sinusoidal change in day and night temperatures is the major influence. For this reason pharmaceutical air conditioning is usually set below 50% RH, and very hygroscopic products, e.g. effervescent, which are particularly moisture sensitive, are stored and made below 40% RH. Tablets and capsules must be hydrophilic to facilitate wetting and the process of deaggregation and drug dissolution. As a paradox they must have limited hygroscopicity to ensure good chemical and physical stability under all reasonable climatic conditions. Good packaging will accommodate moisture challenge, e.g. glass bottles, foil blisters and desiccant. However, preformulation studies on the drug and potential excipient combinations should provide the basis for more robust formulations and a wider, more flexible and cheaper choice of pack, while still reducing significantly any hydrolytic instability due to absorbed free moisture. Pharmaceutical bulk, i.e. drug salts, should be chosen as being non-hygroscopic. As a working limit this should be <0.5% H₂O at <95% RH.

Stability assessment

The testing protocols used in preformulation to ascertain the stability of formulated products must be performed in solution and in the solid state since the same drug (salt) will be used in both an injection and a capsule, for example. These protocols are discussed briefly in Chapter 7, and a suggested scheme for preformulation samples has been shown in Table 8.11.

MICROSCOPY

The microscope has two major applications in pharmaceutical preformulation:

1. Basic crystallography, to determine crystal morphology (structure and habit), polymorphism and solvates
2. Particle size analysis.

Most pharmaceutical powders have crystals in the range 0.5–300 μm . However, the distributions are often smaller, typically 0.5–50 μm , to ensure good



blend homogeneity and rapid dissolution. These are the major reasons for particle size control.

A lamp-illuminated mono-objective microscope fitted with polarizing filters above and below the stage is more than adequate. For most preformulation work a 10 × eyepiece and a 10 × objective are ideal, although occasionally, with micronized powders and when following solid–solid and liquid–liquid transitions in polymorphism, 10 × 20 may be required.

Crystal morphology

Crystals are characterized by repetition of atoms or molecules in a regular three-dimensional structure, which is absent in glasses and some polymers. There are six crystal systems (cubic, tetragonal, orthorhombic, monoclinic, triclinic and hexagonal) which have different internal structures and spatial arrangements. Although not changing their internal structure, which occurs with polymorphism, crystals can adopt different external structures. This is known as crystal habit, of which five types are recognized:

- Tabular: moderate expansion of two parallel faces
- Platy: plates
- Prismatic: columns
- Acicular: needle-like
- Bladed: flat acicular.

These occur in all six crystal systems.

Conditions during crystallization will contribute to changes in crystal habit and may be encountered in early batches of a new drug substance until the synthetic route has been optimized. Crystal habit can be modified by:

1. Excessive supersaturation, which tends to transform a prism or isodiametric (granular) crystals to a needle shape.
2. Cooling rate and agitation, which changes habit as it changes the degree of supersaturation. Naphthalene gives thin plates (platy) if rapidly recrystallized in cold ethanol or methanol, whereas slow evaporation yields prisms.
3. The crystallizing solvent affects habit by preferential absorption on to certain faces, inhibiting their growth. Resorcinol produces needles from benzene and squat prisms from butyl acetate.
4. The addition of cosolvents or other solutes and ions which change habit by poisoning crystal growth in one or more directions. Sodium chloride is usually cubic, but urea produces an octahedral habit.

Particle size analysis

Small particles are particularly important in low-dose high-potency drug candidates, as large particle populations are necessary to ensure adequate blend homogeneity (coefficient of variation <1–2%), and for any drug whose aqueous solubility is poor (<1 mg mL⁻¹), as dissolution rate is directly proportional to surface area (inversely proportional to particle size).

There are numerous methods of particle sizing. Sieving is usually unsuitable during preformulation owing to the lack of bulk material. The simplest (but unfortunately the most tedious) method for small quantities is the microscope. The Coulter Counter (a conductivity method based on electrolyte displacement as the sample is drawn through a small hole) and laser light scattering are widely used for routine bulk analysis and research.

POWDER FLOW PROPERTIES

Of primary importance when handling a drug powder is flow. When limited amounts of drug are available this can be evaluated by measurements of bulk density and angle of repose. These are extremely useful derived parameters to assess the impact of changes in drug powder properties as new batches become available. Changes in particle size and shape are generally very apparent; an increase in crystal size or a more uniform shape will lead to a smaller angle of repose and a smaller Carr's index.

Bulk density

A simple test has been developed to evaluate the flowability of a powder by comparing the poured (fluff) density (ρ_{Bmin}) and tapped density (ρ_{Bmax}) of a powder and the rate at which it packed down. A useful empirical guide is given by Carr's compressibility index ('Compressibility' is a misnomer, as compression is not involved):

$$\text{Carr's index (\%)} = \frac{\text{Tapped} - \text{Poured density}}{\text{Tapped density}} \times 100 \quad (8.12)$$

This is a simple index that can be determined on small quantities of powder and may be interpreted as in Table 8.13.

A similar index has been defined by Hausner (1967):

$$\text{Hausner ratio} = \frac{\text{Tapped density} (\rho_{Bmax})}{\text{Poured density} (\rho_{Bmin})} \times 100 \quad (8.13)$$

Table 8.13 Carr's index as an indication of powder flow	
Carr's index (%)	Type of flow
5–15	Excellent
12–16	Good
18–21	Fair to passable ^a
23–35	Poor ^a
33–38	Very poor
>40	Extremely poor
^a May be improved by glidant, e.g. 0.2% Aerosil.	

Values less than 1.25 indicate good flow (= 20% Carr), whereas greater than 1.25 indicates poor flow (= 33% Carr). Between 1.25 and 1.5, added glidant normally improves flow.

Carr's index is a one-point determination and does not always reflect the ease or speed with which the powder consolidates. Indeed, some materials have a high index (suggesting poor flow) but may consolidate rapidly. Rapid consolidation is essential for uniform filling on tablet machines, when the powder flows at ρ_{Bmin} into the die and consolidates, approaching ρ_{Bmax} at compression. An empirical linear relationship exists between the change in bulk density and the log number of taps in a jolting volumeter. Non-linearity occurs up to two taps and after 30 taps when the bed consolidates more slowly. The slope is a measure of the speed of consolidation and is useful for assessing powders or blends with similar Carr's indices and the benefit of glidants.

Angle of repose

A static heap of powder, with only gravity acting upon it, will tend to form a conical mound. One limitation exists: the angle to the horizontal cannot exceed a certain value, and this is known as the angle of repose (θ). If any particle temporarily lies outside this limiting angle, it will slide down the adjacent surface under the influence of gravity until the gravitational pull is balanced by the friction caused by interparticulate forces. Accordingly, there is an empirical relationship between θ and the ability of the powder to flow. However, the exact value for angle of repose does depend on the method of measurement. The angles of repose given in Table 8.14 may be used as a guide to flow.

A simple relationship between angle of repose, Carr's index and the expected powder flow is shown in Figure 8.6. When only small quantities of powder are available, an alternative is to determine the 'angle of spatula' by picking up a quantity of powder on a

Table 8.14 Angle of repose as an indication of powder flow properties	
Angle of repose (degrees)	Type of flow
<20	Excellent
20–30	Good
30–34	Passable ^a
>40	Very poor
^a May be improved by a glidant, e.g. 0.2% Aerosil.	

spatula and estimating the angle of the triangular section of the powder heap viewed from the end of the spatula. This is obviously crude but is useful during preformulation, when only small quantities of drug are available.

COMPRESSION PROPERTIES

The compression properties of most drug powders are extremely poor and necessitate the addition of compression aids. When the dose is less than 50 mg, tablets can usually be prepared by direct compression with the addition of modern direct compression bases. At higher doses the preferred method would be wet massing.

Nonetheless, information on the compression properties of the pure drug is extremely useful. Although it is true that the tableted material should be plastic, i.e. capable of permanent deformation, it should also exhibit a degree of brittleness (fragmentation). Thus if the drug dose is high and it behaves plastically, the chosen excipients should fragment, e.g. lactose, calcium phosphate. If the drug is brittle or elastic, the excipients should be plastic, i.e. microcrystalline cellulose, or plastic binders should be used in wet massing. Obviously, as the dose is reduced this becomes less important as the diluent vehicle dominates compressibility.

The compression properties (elasticity, plasticity, fragmentation and punch filming propensity) for small quantities of a new drug candidate can be established by the sequence outlined in Table 8.15. An interpretation of the results follows.

Plastic material

When materials are ductile they deform by changing shape (plastic flow). As there is no fracture, no new surfaces are generated during compression and a

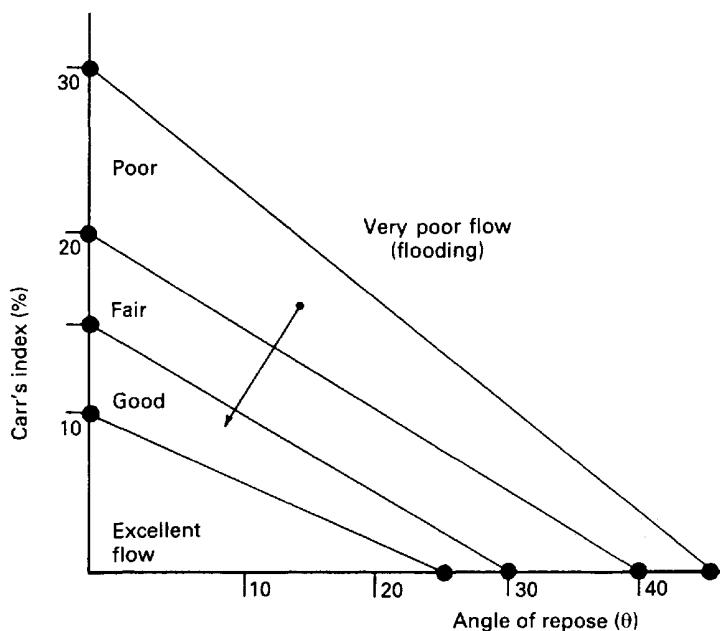


Fig. 8.6 Relationship between angle of repose, Carr's index of a powder and its flow characteristics.

Table 8.15 Scheme for the evaluation of drug compression properties

Sample code	500 mg drug + 1% magnesium stearate		
	A	B	C
Blend in a tumbler mixer for	5 min	5 min	30 min
Compress 13 mm diam. compacts in a IR hydraulic press at	75 MPa	75 MPa	75 MPa
for a dwell time of	2 s	30 s	2 s
Store tablets in a sealed container at room temperature to allow equilibration	24 h	24 h	24 h
Perform crushing strength on tablets and record load	A N	B N	C N

more intimate mix of magnesium stearate (as in sample C, Table 8.15) leads to poorer bonding. Because these materials bond after viscoelastic deformation, and because this is time dependent, increasing the dwell time at compression (B) will increase bonding strength. Thus, a material exhibiting crushing strengths in order $B > A > C$ would probably have plastic tendencies.

Fragmentation

If a material is predominantly fragmenting, neither lubricant mixing time (C) nor dwell time (B) should affect tablet strength. Thus materials which show crushing strengths which are independent of the

method of manufacture outlined in Table 8.15 are likely to exhibit fragmenting properties during compression, with a high friability.

Elastic material

Some materials, e.g. paracetamol, are elastic and there is very little permanent change (either plastic flow or fragmentation) caused by compression: the material rebounds (recovers elastically) when the compression load is released. If bonding is weak the compact will self-destruct and the top will detach (capping), or the whole cylinder cracks into horizontal layers (lamination). An elastic body will give as follows:

A will cap or laminate.

B will probably maintain integrity but will be very weak.

C will cap or laminate.

Elastic materials require a particularly plastic tabletting matrix or wet massing to induce plasticity.

Punch filming (sticking)

Finally, the surface of the top and bottom punches should be examined for drug adhesion. The punches can be dipped into a suitable extraction solvent, e.g. MeOH, and the drug level determined. This will probably be higher for *A* and *B* (Table 8.15), as magnesium stearate is an effective antiadherent and 30 minutes' mixing (*C*) should produce a monolayer and suppress adhesion more effectively.

Sticky materials can be improved by a change in salt form; by using high excipient ratios; by using abrasive inorganic excipients; by wet massing; and/or by the addition of up to 2% magnesium stearate.

Table 8.16 Suggested primary candidates as excipients for tablet and capsule formulations

Excipient	Function ^a
Lactose monohydrate	F
Dicalcium phosphate dihydrate	F
Dicalcium phosphate anhydrous	F
Microcrystalline cellulose	F
Maize starch	D
Modified starch	D
Polyvinylpyrrolidone	B
Sodium starch glycolate	D
Sodium croscarmellose	D
Magnesium stearate	L
Stearic acid	L
Colloidal silica	G

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

EXCIPIENT COMPATIBILITY

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

Thermal analysis can be used to investigate and predict any physicochemical interactions between components in a formulation and can therefore be applied to the selection of suitable chemically compatible excipients. Primary excipients recommended for initial screening for tablet and capsule formulations are shown in Table 8.16.

Method

The preformulation screening of drug–excipient interactions requires 5 mg of drug, in a 50% mixture with the excipient, to maximize the likelihood of observing an interaction. Mixtures should be examined under nitrogen to eliminate oxidative and pyrolytic effects at a standard heating rate (2, 5 or 10°C min⁻¹) on the DSC apparatus, over a temperature range which will encompass any thermal changes due to both the drug and excipient.

The melting range and any other transitions of the drug will be known from earlier investigations into purity, polymorphism and solvates. For all

potential excipients (Table 8.16) it is sensible to retain representative thermograms in a reference file for comparison.

Interpretation

A scheme for interpreting DSC data from individual components and their mixtures is shown in Figure 8.7. Basically, the thermal properties of a physical mixture are the sum of the individual components, and this thermogram can be compared with those of the drug and the excipient alone. An interaction on DSC will show as changes in melting point, peak shape and area and/or the appearance of a transition. However, there is invariably some change in transition temperature and peak shape and area by virtue of mixing two components, and this is not due to any detrimental interaction. In general, provided that no new thermal events occur, no interaction can be assigned. Chemical interactions are indicated by the appearance of new peaks, or where there is gross broadening or elongation of an exo- or endothermic change. Second-order transitions produce changes in the baseline. Such observations may be indicative of the production of eutectic or solid solution-type melts. The excipient is then probably chemically reactive and incompatible with the drug, and should be avoided. Where an interaction is suspected but the thermal changes are small, the incompatibility should be confirmed by TLC.

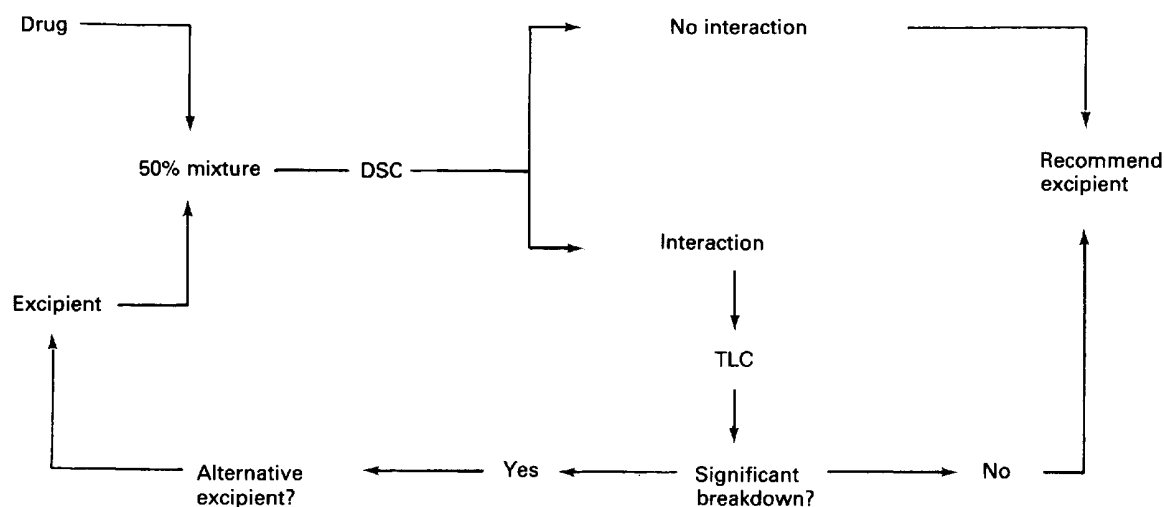


Fig. 8.7 Scheme to identify chemically compatible excipients using DSC with confirmatory TLC.

The advantages of DSC over more traditional, routine compatibility screens, typically TLC, is that no long-term storage of the mixture is required prior to evaluation, nor is any inappropriate thermal stress (other than the DSC itself, which had drug and excipient controls) required to accelerate the interactions. This, in itself, may be misleading if the mode of breakdown changes with temperature and elevated temperatures fail to reflect the degradation path occurring under normal (room temperature) storage.

Where confirmation is required by TLC, samples (50:50 mixtures of drug and excipient) should be sealed in small neutral glass test tubes and stored for either 7 days at 50°C or 14 days at 37°C.

It is important to view the results of such incompatibility testing with caution. For example, magnesium stearate is notoriously incompatible with a wide range of compounds when tested, yet because it is only used at low levels – typically 0.5–1% – such apparent incompatibility rarely produces a problem in practice in long-term storage and use.

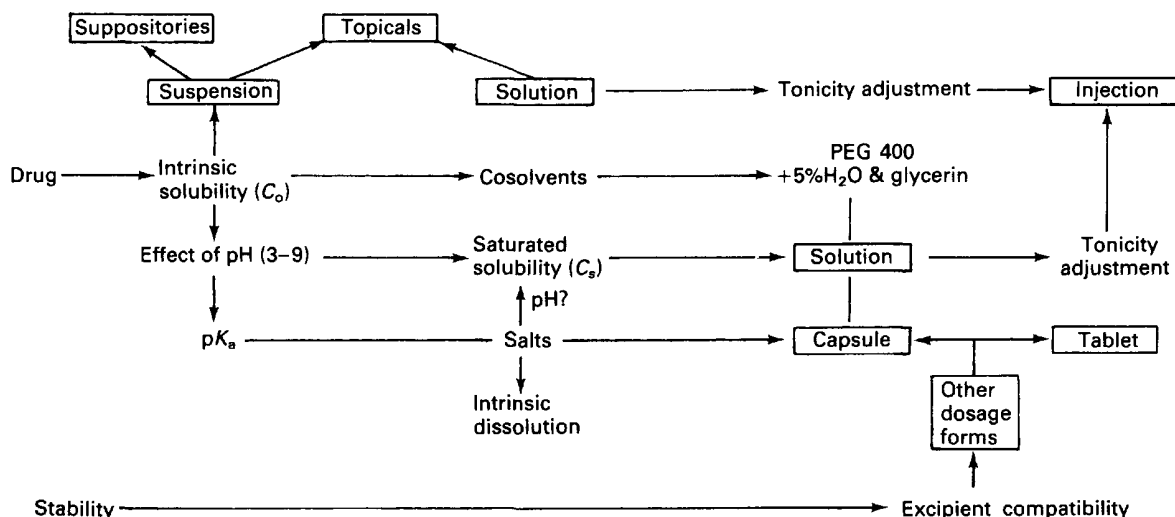


Fig. 8.8 A generic development pathway: the relationship between preformulation and formulation in dosage form development. The formulation stages are shown in boxes and the preformulation stages are unboxed.

CONCLUSIONS

Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage form technology (Fig. 8.8). The need for adequate drug solubility cannot be overemphasized. The availability of good solubility data should allow the selection of the most appropriate salt for development. Stability studies in solution will indicate the feasibility of parenteral or other liquid dosage forms, and can identify methods of stabilization. In parallel, solid-state stability by DSC, TLC and HPLC, and in the presence of tablet and capsule excipients, will indicate the most acceptable vehicles for solid dosage forms.

By comparing the physicochemical properties of each drug candidate within a therapeutic group (using C_s , pK_a , melting point, K_w) the preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response, and advise the bulk chemist about the selection and production of the best salt with appropriate particle size and morphology for subsequent processing.

REFERENCES

- Albert, A.A. and Serjeant, E.P. (1984) *Ionization Constants of Acids and Bases*. Wiley, New York.
Kaplan, S.A. (1972) *Drug Metab. Rev.*, **1**, 15–32.
Meyer, H. (1899) *Arch. Exp. Pathol. Pharmacol.*, **42**, 109
Perrin, D.D. Dempsey, B. and Serjeant, E.P. (1981) *pK_a Predictions for Organic Acids and Bases*. Chapman & Hall, London.
Yalkowski, S.H. and Roseman, T.J. (1981) *Techniques of Solubilization of Drugs*, ed. S.H. Yalkowski, Marcel Dekker, New York, Chapter 3.

BIBLIOGRAPHY

- Albert, A.A. and Serjeant, E.P. (1984) *Ionization Constants of Acids and Bases*, Wiley, New York
Davies, S.S. and Higuchi, T. (1970) *J. Pharm. Sci.*, **59**, 1376.
Hamilton, R.J. and Sewell, P.A. (1977) *Introduction to High Performance Liquid Chromatography*. Chapman & Hall, London.
Jones, T.M. (1981) *Int. J. Pharm. Tech. Prod. Mfr.*, **2**, 17.
Kennon, L. (1964) *J. Pharm. Sci.*, **53**, 815–818.
Pryde, A. and Gilbert M.T. (1979) *Applications of High Performance Liquid Chromatography*. Chapman & Hall, London.
Smith, A. (1982) *Anal. Proc.*, **19**, 559.
Yalkowski, S.H., Amidon, G.L., Zografi, G. and Flynn, G.L. (1975) *J. Pharm. Sci.*, **64**, 48.
Yalkowski, S.H. and Roseman, T.J. (1981) *Techniques of Solubilization of Drugs*, Chapter 3, ed. S.H. Yalkowski, Marcel Dekker, New York.