propyl methylcellulose should have no significant effect on the rate of disintegration of the tablet core and subsequent drug dissolution provided that the film coat dissolves rapidly and independently of the pH of the gastrointestinal fluids. However, if hydrophobic water-insoluble film coating materials such as cellulose acetate phthalate, ethylcellulose or acrylic resins are used to coat tablet cores, the resulting film coat acts as a barrier which delays and/or reduces the rate of release of drugs from tablet cores. Thus these types of film coating materials form 'barriers' which can have a significant influence on the absorption of drugs from film-coated tablets. Whilst the formation of such 'barrier' coatings would be disadvantageous in the case of film-coated tablets intended to provide rapid rates of drug absorption, the concept of 'barrier' coating has been used (along with other techniques) to obtain more precise control over drug release than is possible with conventional uncoated tablets. In this context, film coating has been used to provide

1 limited control over the site at which a drug is released from a tablet into the gastrointestinal tract, and
2 a controlled continuous rate of drug release from a non-disintegrating (intact) tablet as it passes along the gastrointestinal tract.

In this latter case, 'barrier' coating is one of many formulation techniques which have been used to increase the duration of therapeutic action of a drug contained within a peroral dosage form. For information concerning controlled/sustained/prolonged release peroral dosage forms, the reader should refer to the reviews by Ritschel (1973) and Hon-Leung Lee and Robinson (1978).

Enteric coated tablets The use of barrier coating in order to control the site of release of an orally administered drug is well illustrated by enteric-coated tablets. An enteric coat is designed to resist gastric fluids but to disrupt or dissolve when the coated tablet enters the duodenum. Polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate and polyvinyl acetate phthalate are used as enteric coatings. These materials dissolve slowly over the gastric pH range (i.e. pH 1–3) but dissolve rapidly at the less acid pH values associated with the small intestine. Enteric coatings should preferably begin to dissolve at about pH 5 in order to ensure the availability of drugs which are absorbed primarily in the proximal region of the small intestine (Rees, 1974). Enteric coating thus provides a means of delaying the release of a drug until the dosage form reaches the small intestine. Such delayed release provides a means of protecting drugs which would otherwise be destroyed if released into gastric fluid (see earlier in this chapter). Hence enteric coating serves to improve the peroral bioavailability exhibited by such drugs from uncoated conventional tablets. Enteric coating also protects the stomach against drugs which can produce nausea or mucosal irritation if released at this site, e.g. phenylbutazone, aspirin.

In addition to the protection offered by enteric coating, the delayed release of drug also results in a significant delay in the onset of the therapeutic response of a drug. The onset of the therapeutic response is largely dependent on the residence time of the enteric-coated tablet in the stomach. Gastric emptying of such tablets is an all-or-nothing process, i.e. the tablet is either in the stomach or in the duodenum. Consequently drug is either not being released or being released. The residence time of an intact enteric-coated tablet in the stomach can vary within and between subjects from about 30 minutes to several hours (Bechgaard and Christensen, 1982). Hence there is considerable intrasubject and intersubject variation in the onset of therapeutic action exhibited by drugs administered as enteric-coated tablets.

The formulation of an enteric-coated product in the form of small individually enteric-coated granules or pellets contained in a rapidly dissolving hard gelatin capsule or a rapidly disintegrating tablet, would largely eliminate the dependency of this type of dosage form on the all-or-nothing gastric emptying process associated with the intact enteric-coated tablet. Provided that the coated granules or pellets were sufficiently small (less than 1 mm diameter), they would be able to pass the pylorus even when the sphincter was closed (Bechgaard and Christensen, 1982). Hence enteric-coated granules and pellets would exhibit a gradual but continual release from the stomach into the duodenum. This type of release would also avoid the complete dose of drug being released

into the duodenum as occurs from an enteric-coated tablet. The intestinal mucosa would thus not be exposed locally to a potentially toxic concentration of drug (Taylor, 1982).

Further information on coated tablets is given in Chapters 18 and 40.

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Preformulation

THE CONCEPT OF PREFORMULATION

1 SPECTROSCOPY

2 SOLUBILITY
Intrinsic solubility (C_o)
pK_a from solubility data
Salts
Solvents
Partition coefficient (K_w)°
Cosolvent solubility
Methodology and structure activity prediction
Choice of non-aqueous solvent (oil)
Structure-activity relationships
Dissolution
Intrinsic dissolution rate
Measurement of intrinsic dissolution rate
Common ion effect

3 MELTING POINT
Capillary melting
Hot stage microscopy
Differential scanning calorimetry and differential thermal analysis
Polymorphism
Pseudopolymorphism
True polymorphism
Crystal purity
Solubility

4 ASSAY DEVELOPMENT
U.v. spectroscopy
Molecular weight
pKa
Mixtures
Thin layer chromatography (t.l.c.)
High performance liquid chromatography (h.p.l.c.)
Normal phase h.p.l.c.
Reserve phase h.p.l.c.

5 DRUG AND PRODUCT STABILITY
Temperature
Order of reaction
Hydrolysis
The influence of pH
Solvolysis
Oxidation
Chelating agents
Photolysis
Solid-state stability
Hygroscopicity
Stability assessment

6 MICROSCOPY
Crystal morphology
Particle size analysis

7 POWDER FLOW PROPERTIES
Bulk density
Angle of repose

8 COMPRESSION PROPERTIES
Interpretation of the results from the compression scheme
Plastic material
Fragmenting material
Elastic material
Punch filming (sticking)

9 EXCIPIENT COMPATABILITY
Method
Interpretation

10 CONCLUSIONS

THE CONCEPT OF PREFORMULATION

Almost all new drugs which are active orally are marketed as tablets, capsules or both (Table 13.1). Although only a few drug compounds are eventually marketed as an injection (25% of those drugs marketed as tablets), an injection, particularly by the intravenous route, is always required during early toxicity, metabolic, bioavailability and clinical studies in order to guarantee precise drug and dose deposition. Other dosage forms may be required (Table 13.1) but these are usually drug specific and often depend to a large extent on the successful development of tablets, capsules and injections.

Prior to the development of these three major dosage forms with a new drug candidate, 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 will dictate many of the subsequent events and possible approaches in formulation development. This first learning phase is known as *preformulation*.

A suggested list of information required in preformulation is shown in Table 13.2. It is assembled in a logical order recognizing the relative importance of the data and probable existence of only limited quantities of bulk drug (mg rather than g) at this stage of its development. Investigators should also be pragmatic and only generate data which is of immediate relevance, especially if the likely dosage forms are known.

However, a knowledge of two fundamental properties is mandatory for a new compound:

1 intrinsic solubility (C_o),
2 dissociation constant (pK_a).

These will immediately determine (a) the need and (b) the possibility of making more soluble salts of the drug to eliminate solubility-related poor bioavailability, particularly from solid dosage forms.

Independent of this pharmaceutical profiling (Table 13.2), analysts will need to generate data (Table 13.3) to support the assay of existing and

Table 13.1 Frequency distribution of dosage form types manufactured in the UK (Data Sheet Compendium)

Dosage form	*Frequency (%)*
Tablets	45.8
Liquid oral	16.0
Injections	15.0
Capsules	13.0
Suppositories and pessaries	3.3
Topicals	3.0
Eye preparations	1.8
Aerosols (inhalation)	1.2
Others	0.3

Table 13.2 Preformulation drug characterization

Test	*Method/function/characterization*	*References/Bibliography*
1 Spectroscopy	Simple u.v. assay	Dalglish (1969)
2 Solubility		
aqueous	Phase solubility, purity	Mader (1954); Higuchi and Connors (1965)
pK_a	Intrinsic solubility, pH effects	
salts	Solubility control, salt formation	Albert and Serjeant (1984)
solvents	Solubility, hygroscopicity, stability	Berge, *et al.* (1977)
partition coeff K_w^o	Vehicles, extraction	Yalkowski and Roseman (1981)
dissolution	Lipophilicity, structure activity	Leo, *et al.* (1971)
	Biopharmacy	Swarbrick (1970)
3 Melting point	DSC — polymorphism, hydrates, solvates	Wendlandt (1974); Haleblian (1975), Haleblian and McCrone (1969)
4 Assay development	u.v., t.l.c., h.p.l.c.	Jaffe and Orchin (1962); Bristow (1976)
5 Stability (in solution and in solid state)	Thermal, hydrolysis, oxidation, photolysis, metal ions, pH	Mollica *et al.* (1978); Connors *et al.* (1979)
6 Microscopy	Morphology, particle size	McCrone *et al.* (1978)
7 Powder flow		
(a) bulk density	Tablet and capsule formulation	Neumann (1967)
(b) angle of repose	Tablet and capsule formulation	Neumann (1967)
8 Compression properties	Aids excipient choice	DeBoer *et al.* (1978); Jones (1981)
9 Excipient compatibility	Preliminary screening by DSC, confirmation by t.l.c.	Smith (1982)

Table 13.3 Analytical preformulation

Attribute	*Test*
Identity	Nuclear magnetic resonance (n.m.r.) Infra red spectroscopy (i.r.) Ultraviolet spectroscopy (u.v.) Thin layer chromatography (t.l.c.) 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 (u.v.) High performance liquid chromatography (h.p.l.c.)
Quality	Appearance Odour Solution colour pH of slurry (saturated solution) Melting point

new bulk material. Although their data meet a different need, it can often be used to complement and confirm pharmaceutical data. Their greater training and knowledge in analysis will assist, for example, in the identification of suitable stability-indicating assays by ultraviolet spectroscopy (u.v.) or high performance liquid chromatography (h.p.l.c.) and the screening of incompatibilities by thin layer chromatography (t.l.c.).

1 SPECTROSCOPY

The first step in preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in the ultraviolet wavelengths (190–390 nm) since they are generally aromatic and/or contain double bonds. Confirmation of synthetic structure is, of course, the responsibility of the synthetic chemist. The acidic or basic nature of the molecule can be predicted from the functional groups in its structure (Perrin *et al.*, 1981). This will indicate suitable solvents to ensure solution of either the ionized or undissociated species. This is important since the ionic status of a drug can alter the shape of the u.v. spectrum by increasing absorption or changing the wavelengths (bathochromic (red) or hypsochromic (blue) shifts) at which maxima, minima or both occur.

Once the u.v. spectrum of the new drug molecule is established, it is possible to choose an analytical wavelength (often λ_{max}) that is 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_o) 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 source has passed. Equation 13.1 is the well-known Beer–Lambert law where e is the molar extinction coefficient.

$$\text{Absorbance } (A) = \log_{10} (I_o/I) = eCl \qquad (13.1)$$

However, it is usual in pharmacy to quote the *specific absorption coefficient* ($E^{1\%}_{1\,cm}$, or E^{1}_{1} for short) where the pathlength is 1 cm and the solution concentration is 1% w/v (10 mg ml^{-1}) since doses and concentrations are generally in metric units.

2 SOLUBILITY

When a preformulation programme begins, the availability of drug is always limited and the preformulation scientist may only have 50 mg. Thus, it is important that the best use of this limited bulk is made to support the continuing efforts to the synthetic chemists and the biologists pursuing activity and toxicity screens. Furthermore, because 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 (see Section 3 of this chapter and Chapter 5). Accordingly, if nothing else is measured, the solubility and pK_a must be determined. These control all future work. The solubility dictates the ease with which formulations for intravenous injection studies in animals are obtained. The pK_a allows the informed use of pH to maintain solubility and to choose salts should they be required to achieve good bioavailability from the solid state (Chapter 9) and improve stability (Chapter 7) and powder properties (Chapter 36).

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,

then potential bioabsorption problems may occur. He also found that if the intrinsic dissolution rate was greater than 1 mg cm^{-2} min^{-1} then absorption was unimpeded. However, dissolution rates of less than 0.1 mg cm^{-2} min^{-1} were likely to give dissolution rate-limited absorption. This ten-fold difference in dissolution rate translates into a lower limit for solubility of 1 mg ml^{-1} since, under sink conditions, dissolution rate and solubilities are proportional (Hamlin *et al.*, 1965).

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 (as in the case of 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 gelatin capsules (in a solution in PEG 400, glyceryl triacetate or fractionated coconut oil) or as a paste or semisolid (dissolved in oil or triglyceride) in a hard gelatin capsule may be necessary.

Intrinsic solubility (C_o)

An increase in solubility of the new drug in an acidic solution compared with its aqueous solubility suggests a weak base, and an increase in alkali, a weak acid. In both cases a dissociation constant (pK_a) will be measurable and salts should form. An increase in both acidic and alkaline solubility suggests either amphoteric or zwitterion behaviour; in this case there will be two pK_as, one acidic and one basic. No change in solubility suggests a non-ionizable, neutral molecule with no measurable pK_a. Here solubility manipulations 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). The solubility should ideally be measured at two temperatures: (a) 4 or 5 °C to ensure good physical stability and to extend short-term storage and chemical stability until more definitive data is available and (b) 37 °C to support biopharmaceutical evaluation.

However, since absolute purity is often in doubt for the first few batches of new drug, it is more accurate to determine this crucial solubility by use of a phase-solubility diagram (Fig. 13.1). 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

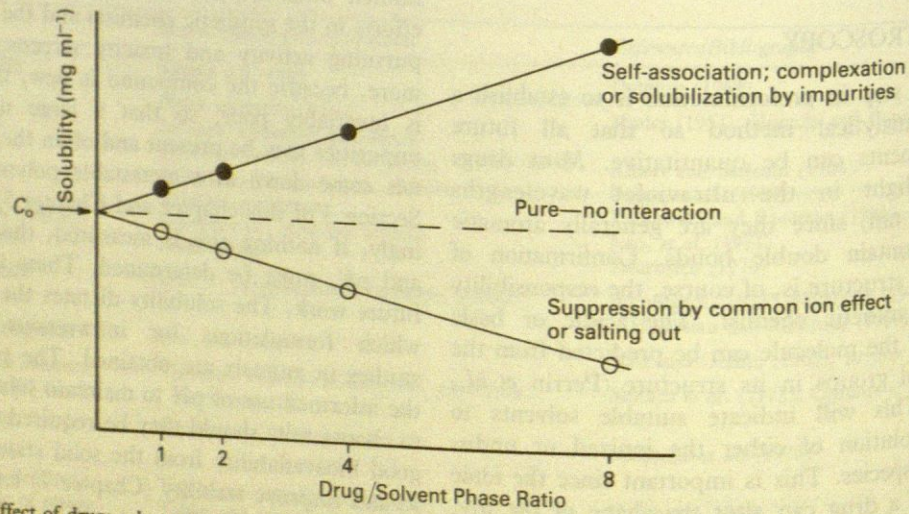

Fig. 13.1 Effect of drug: solvent ratio on solubility when the drug is impure. Assuming the compound is a base and the estimate of its solubility in 0.1 M NaOH was 1 mg ml^{-1}, four solutions of 3 ml should be set up containing 3, 6, 12 and 24 mg of drug. These give the phase ratios shown here. 3 ml is the smallest volume which can be manipulated for either centrifugation or filtration and dilution for u.v. analysis. The vials should be agitated continuously overnight and then the concentration in solution determined

Table 13.4 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
Tosylate	−1.34	0.1	Lithium	13.82	1.6
Mesylate	−1.20	2.0	Calcium	12.90	10.5
Napsylate	0.17	0.3	Magnesium	11.42	1.3
Besylate	0.70	0.3	Diethanolamine	9.65	1.0
Maleate	1.92, 6.23	3.0	Zinc	8.96	3.0
Phosphate	2.15, 7.20, 12.38	3.2	Choline	8.90	0.3
Salicylate	3.00	0.9	Aluminium	5.00	0.7
Tartrate	3.00	3.5	Others		8.8
Lactate	3.10	0.8			
Citrate	3.13, 4.76, 6.40	3.0			
Benzoate	4.20	0.5			
Succinate	4.21, 5.64	0.4			
Acetate	4.76	1.3			
Others		30.2			

* Martindale (1982), *The Extra Pharmacopoeia*, 28th edition. The Pharmaceutical Press, London.

either promotes or suppresses solubility. In the 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 a true estimate of the 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 the remaining 5% are non-ionic, amphoteric or alcohols). It is therefore appropriate to consider the Henderson–Hasselbalch equations for weak bases and acids. These have been discussed in Chapter 3 and their bioavailability consequences in Chapter 9.
For weak bases

$$pH = pK_a + \log_{10}([B] / [BH^+]) \quad (13.2)$$

and for weak acids

$$pH = pK_a + \log_{10}([A^-] / [HA]) \quad (13.3)$$

Equations (13.2) and (13.3) are used:

(a) to determine the pK_a by following changes in solubility,
(b) to allow the prediction of solubility at any pH provided that the intrinsic solubility (C_o) and pK_a are known, and
(c) 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 and there is further discussion in Chapter 3 of this book.

Salts

A major improvement in solubility can be achieved by selection of a salt. Acceptable pharmaceutical salts are shown in Table 13.4 which also includes their corresponding pK_a values (see Chapter 3 for further discussion). As an example, the consequences of changing chloridiazepoxide to various salt forms is shown in Table 13.5.

Table 13.5 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[1]
Sulphate	−3.00	2.53	Freely soluble
Besylate	0.70	2.53	Freely soluble
Maleate	1.92	3.36	57.1
Tartrate	3.00	3.90	17.9
Benzoate	4.20	4.50	6.0
Acetate[2]	4.76	4.78	4.1

[1] Maximum solubility of chlordiazepoxide hydrochloride, achieved at pH 2.89, is governed by crystal lattice energy and common ions.
[2] Chlordiazepoxide acetate may not form; pK_a too high and close to drug.

In some cases, salts prepared from strong acids or bases are freely soluble but also very hygroscopic. This can lead to instability in tablet or capsule formulations since some drug will dissolve in its own adsorbed films of moisture (the usual prerequisite for breakdown) and in the case of a weak base, a strongly acid solution may be autocatalytic. Accordingly it is often better to use a weak acid or base to form the salt provided any solubility requirements are met. A salt which is less soluble will also be generally less hygroscopic and form less acidic or basic solutions (Table 13.5). This may also be important in physiological terms. Injections should 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 since a propellant-acid reaction will corrode the canister.

It is also clear from Table 13.5 that not only does the intrinsic pH of the base solution, in this example chlordiazepoxide, fall significantly from pH 8.3 if salt forms are produced but, as a consequence, the solubility increases exponentially (Eqns 13.2 and 13.3). 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. None the less it is usually better to formulate with a salt since it will control the pH of the diffusion layer (the saturated solution immediately adjacent to the dissolving surface). For example, although chlordiazepoxide base (C_s = 2 mg ml^{-1} at pH 8.3) meets the requirements for *in vivo* 'solubility' (Kaplan, 1972); commercial capsules contain chlordiazepoxide hydrochloride (C_s = 165 mg ml^{-1} at pH 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 it becomes more soluble and its dissolution rate increases as it moves 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 the parent drug. Sodium and potassium salts of weak acids dissolve much more rapidly than the parent acid and some comparative data are shown in Table 13.6. 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 the pH of gastric fluid (which is usually approximately pH 1.5) because of their buffering action. The pH approximates to a saturated unbuffered aqueous solution (calculated pH in Table 13.6) and the dissolution rate is governed by this pH and not the bulk media 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. Since solubility is exponentially dependent on pH (Eqns 13.2 and 13.3) there is a significant increase in dissolution rate over the free acid. 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 media. With weak bases, their salts dissolve rapidly in the stomach but there is no absorption since the drug is ionized and absorption is delayed until the intestine. There, any undissolved drug, as salt, rapidly dissolves since 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 13.5. The maleate

Table 13.6 Dissolution rates of weak acids and their sodium salts

Drug	*pKa*	*pH (at C_S)*	*Dissolution rate ($mg\ cm^{-2}\ min^{-1}$) × 10^2*	
			Dissolution media	
			0.1M HCl (pH 1.5)	*phosphate (pH 6.8)*
Salicylic acid	3.0	2.40	1.7	27
Sodium salicylate		8.78	1870	2500
Benzoic acid	4.2	2.88	2.1	14
Sodium benzoate		9.35	980	1770
Sulphathiazole	7.3	4.97	<0.1	0.5
Sodium sulphathiazole		10.75	550	810

Dissolution rate data from Nelson (1958).

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 many fold, independently of its position in the gastrointestinal tract.

Miller and Holland (1960) stated that different salts of a drug rarely change its pharmacology, only its physical properties. Wagner (1961) qualified this statement to acknowledge that salts do effect the intensity of the response. 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 in hygroscopicity and stability influence formulation.

Consequently each new drug candidate must be examined extensively to choose the most suitable salt for formulation and because each potential salt will behave differently, each requires separate preformulation screening.

Solvents

As mentioned in the introduction, it is generally necessary to anticipate the formulation of an injection even if there is no intention of actually marketing such a product. The first choice for a solvent is obviously water. However, although the drug may be freely soluble, some are unstable in aqueous solution. Accordingly water-miscible solvents must be used (a) as cosolvents in formulations to improve solubility or stability and (b) in analysis to facilitate extraction and separation (e.g. in 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 cosolvent solubility and stability are unattainable. Table 13.7 shows a range of solvents to fulfil these needs. Aqueous methanol is widely used in h.p.l.c. 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 u.v. analysis. Other pharmaceutical solvents are available (see Spiegel and Noseworthy, 1963) 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. one with a partition coefficient (log P) greater than 1), solubility doubles through this series.

Where bulk is limited and when the aqueous solubility is inadequate, it is useful to measure the solubility in aqueous cosolvent 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. Furthermore, formulations rarely demand 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 (Cadwallader, 1978).

The reader will find more details on the properties of solutions in Chapter 3 and on the formulation of solutions in Chapter 14.

Partition coefficient (K_w^o)

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

(a) Solubility: both aqueous and in mixed solvents.

Table 13.7 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 1.07)			Dissolution (gastric), basic extraction
0.1 M NaOH (pH 13.1)			Acidic extraction
Buffer (pH 7)			Dissolution (intestinal)
Ethanol	24	12.7	Formulation, extraction
Propylene glycol	32	12.6	Formulation
Glycerol	43	16.5	Formulation
PEG 300 or 400	35		Formulation

Solvents are considered further in the chapter on the formulation of solutions (Chapter 14).

(b) Drug absorption *in vivo*: applied to a homologous drug series for structure activity relationships (SAR).
(c) Partition chromatography: choice of column (h.p.l.c.) or plate (t.l.c.) and choice of mobile phase (eluant), see Section 4.

The measurement of K_w^o and its use in cosolvent solubility and structure activity relationships are pertinent here, while application in aqueous solubility prediction is discussed under melting point (Section 3) and in chromatography in Section 4.

Cosolvent solubility

The relative polarities of solvents have been scaled using dielectric constant (ϵ), solubility parameter (δ), interfacial tension (γ) and hydrophilic–lipophilic balance (HLB), the latter normally being applied to non-ionic surfactants in emulsion technology. The best solvent in any given situation is one whose polarity matches that of the solute; an ideal, fully compatible solution exists when $\delta_{solvent} = \delta_{solute}$. This can be ascertained by determining solubility maxima, using a substituent contribution approach (Fedors, 1974). An alternative measure is to evaluate the dielectic requirement of the system (Paruta & others, 1965).

However the most practically useful scale of polarity or lipophilicity for a solute is its K_w^o oil: water partition coefficient, since the other approaches do not allow easy estimates for the behaviour of crystalline solids (solutes).

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

$$\log C_s = \log C_w + f(0.89 \log P + 0.03) \quad (13.4)$$

Equation 13.4 can be applied more generally by introducing a factor ϕ to account for the relative solvent power of pharmaceutical solvents found in practice (Table 13.8), and predicted by comparison of interfacial tension against a liquid hydrocarbon, tetradecane (Yalkowsky *et al.*, 1975).
Equation 13.4 now becomes, for a wide range of solvents:

Table 13.8 Solvent power (ϕ) of some pharmaceutical solvents

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

$$\log C_s = \log C_o + f(\log \phi + 0.89 \log P + 0.03) \quad (13.5)$$

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. Many partition solvents have been used (Leo *et al.*, 1971), but the largest data base has been generated using *n*-octanol. This is, aside from any scientific argument, the major justification to continue its use in preformulation. The solubility parameter of octanol ($\delta = 10.24$) lies midway in the range for the majority of drugs (δ = between 8 and 12) although some non-polar ($\delta < 7$) and polar drugs ($\delta > 13$) are encountered. This allows more easily measurable results than in inert solvents (e.g. hydrocarbons) since it is convenient to partition between equal volumes of oil and aqueous phases.

A typical technique is the *shake flask method* whereby 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 (C_w, aqueous solubility) partitioning to give $K_w^o = (\Sigma C - C_w)/C_w$).

Clearly 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, heptane etc., is quite different to hydrogen bonding solvents like octanol (Hansch and Dunn, 1972). The behaviour of the weak acid phenol ($pK_a = 10$) and weak base nicotine ($pK_a = 3.1$) is worthy of note. For phenol, $K_w^{octanol} = 29.5$ whereas $K_w^{hexane} = 0.11$. The acidic solvent, chloroform, suppresses partition ($K_w^o = 2.239$) whereas although ethyl acetate and diethyl ether are more polar, the basic behaviour of the solvents give the highest K_w^o. With solvents capable of both hydrogen donation and acceptable (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 ($K_w^o = 77.625$), 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 solute and solvent characteristics are important.

In general, polar solvents are advocated to correlate biological activity with physicochemical properties (Hansch and Dunn, 1972). Solvents less polar than octanol, measured by water solvency, have been termed hyperdiscriminating by Rekker (1977) while those more polar, e.g. butanols and pentanols, as 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 too close while 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 g.i. tract. Hyperdiscriminating solvents reflect more closely the transport across the blood–brain barrier, while hypodiscriminating solvents give values consistent with buccal absorption (Fig. 13.2).

Based on the assertion by Leo *et al.* (1971) in rationalizing the effects of different partitioning solvents, a good correlation exists between the solvent water content at saturation (log [H_2O] mg/100 ml) and solvent lipophilicity. This relationship also indicates the lipophilicity of biological membranes and the relative discrimination power (Rekker, 1977) of the partitioning solvents.

Certainly within a laboratory it is imperative to standardize on methodology, especially the solvent. Where solubility constraints allow, this should invariably be *n*-octanol especially since the existing data bank is extensive (Hansch and Leo, 1979).

Structure-activity relationships Since the pioneering work of Meyer (1899) and Overton (1901) numerous studies on correlating molecular structure and biological activity have been reported (Tute, 1971). 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 therefore preformulation is a particularly useful information source.

It is assumed in SAR that (Collander, 1951):

$$\log K_w^o = a \times \log K_w^{octanol} + b \qquad (13.6)$$

This relationship holds for for all polar and semi-polar solvents. However, correlations are poor with non-polar solvents (hexane, heptane, cyclohexane, carbon tetachloride and iso-octane) and again this seems to be related to water content. Given the obvious 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 complicated by the mutual partitioning of the two solvents.

While the aqueous phase is often simply water, it is better to measure log P under controlled pH using aqueous buffers. All drugs capable of ionization and with a measurable pK_a, whether weak acids or bases will have intrinsic buffer capacity affecting 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

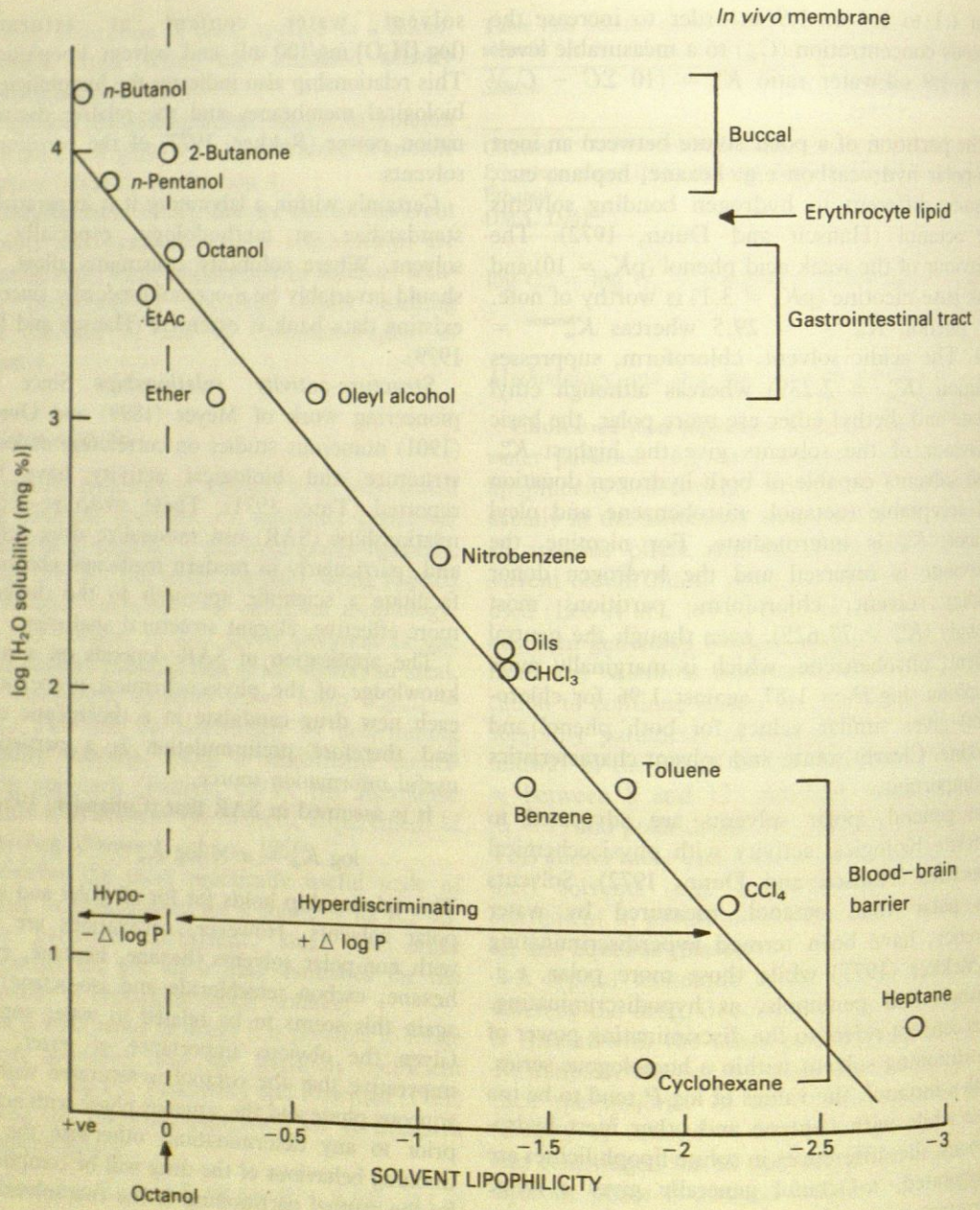

Fig. 13.2 Discriminating power of partitioning solvents as a function of their water capacity

drug is unionized. Since the ionized species will have greater aqueous solubility and lower lipophilicity to HA or BOH then 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 pK_a (pK_a − 2 (acid); pK_a + 2 (base)) and the aqueous phase should contain a suitable buffer. Given the importance of log P (log K_w^o) in SAR, comparative data generated in a therapeutic class (R_n.X, where X is the therapeutic nucleus and n is a number of substituents' R) should also be determined at a physiological pH of 7.4.

Quantitative SAR (QSAR) is based on the

premise that drug absorption is a multi-partitioning 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 (Hansch & Dunn, 1972) and the existence of many excellent correlations *in vivo* is probably not entirely fortuitous. Octanol exhibits hydrogen bonding acceptor and donor properties typical of many biological macromolecules. Furthermore the partial polarity of octanol allows the inclusion of water, which is also a feature of biological lipid membranes. This 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 13.9. Generally the log P differs from between 3 and 4 (i.e. K_w^o ranges from 1000 to 10 000), and 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 these different factors associated with molecular structure:

(a) electronic (charge)
(b) steric (spatial size)
(c) hydrophobic effects (partitioning).

Table 13.9 The effect of salt formation on the log P of some weakly basic drugs

Free base and hydrochloride salt	*log P*	*Δ 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	
Propranolol	3.18	3.63
Propranolol HCl	−0.45	
Phenylpropanolamine	1.83	2.92
Phenylpropanolamine HCl	−1.09	

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

$$\text{Biological Activity} = f[(\text{electronic}) + (\text{steric}) + (\text{hydrophobic}) + (\text{structural/theoretical})] \quad (13.7)$$

The electronic parameter above is quantified by the sigma (σ) substituent constant of Hammelt (1940) and reflects chemical reactivity in a homologous series. The substituent constant (σ) is positive for electron withdrawal (acids), while 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 also 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 binding at the active site.

The hydropholic component is measured by the partition or distribution behaviour of a compound between an aqueous phase and an immiscible lipid phase and parallels drug adsorption and distribution *in vivo*. Hansch and Fujita (1964) demonstrated a general relationship between the partition coefficient within a series by quantifying differences using an additive substituent constant (π). This constant is related almost completely to the effect of 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. Additionally π can be related to biological effect since it is an additive component of the partition coefficient and has led to the wider application of SAR, which by other modifications, notably taking into account aromatic electron density and steric effects, to give *quantitative* SAR (i.e. QSAR) (see Davis and Higuchi, 1970 for application of QSAR equations).

While 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 of 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 that the solubility of a drug exceeded 10 mg ml^{-1} at pH 7 then no bioavailability or dissolution related problems were to be expected. Below 1 mg ml^{-1}, such problems were quite possible and salt formation (see Section 2, Salts) could improve absorption and solubility by controlling the pH of the microenvironment independently of the drug and dosage forms position within the g.i. tract.

The equations controlling the rate of dissolution of solids are described in Chapter 5 and the biopharmaceutical consequences discussed in Chapter 9. The Nernst (1904) modification to the Noyes–Whitney (1897) equation can be applied generally to the dissolution of solids (see Chapter 5).

Intrinsic dissolution rate

When dissolution is solely controlled 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 (Levich, 1962):

$$K_1 = 0.62\, D^{2/3}\, \nu^{1/6}\, \omega^{1/2} \qquad (13.8)$$

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

$$dc/dt = \frac{A}{V}\, K_1\, C_s \qquad (13.9)$$

and the intrinsic dissolution rate (IDR) is given by

$$\text{IDR} = K_1\, C_s \text{ (mg cm}^2 \text{ min}^{-1}\text{)} \qquad (13.10)$$

This constant rate differs from the dissolution from conventional dosage forms, which is known as total dissolution (mg min^{-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 effects, e.g. pH, ionic strength and counter ions.

Measurement of intrinsic dissolution rate At the preformulation stage a compressed disc of the material can be made by slow compression of 200 mg of drug in a 13 mm i.r. disc punch and die set to a high compaction pressure greater than 350 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 using a 5% w/v solution in chloroform. The compressed disc is fixed to the holder of the rotating basket apparatus BP 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-litre flat bottomed dissolution flask containing 1 litre of fluid at 37 °C. The amount of drug release is then monitored, usually by u.v. spectrometry, with time. The slope of the line divided by the exposed surface area gives the IDR, for example, in mg cm^2 min^{-1}.

Each candidate should be measured in 0.05 M HCl (gastric : pH 1) 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 0.1 C_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 (see Chapter 3)

$$\text{IDR} = k' \left(C_o(1 + \text{antilog}\,(pK_a - \text{pH}))\right) \qquad (13.11)$$

shows that the rate of dissolution of a drug

candidate is clearly a function of its intrinsic solubility (C_o), its dissociation constant (pK_a) and either the pH of the bulk dissolution medium or 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 likely improvement in *in vivo* performance 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 this may prove, in some instances, disappointing. Thus measurement of IDR can be useful diagnostically.

Common ion effect

A common interaction with solvent, which is often overlooked, is the common ion effect. The addition of a common ion often reduces the solubility of a slightly soluble electrolyte (Long & McDevitt, 1952). This 'salting out' results from the removal of water molecules as solvent due 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, e.g. diazepam.

Hydrochloride salts often exhibit suboptimal solubility in gastric juice due to the abundance of Cl^- ions. A number of examples from the pharmaceutical literature are shown in Table 13.10 for acidic hydrochloride solutions. Other counter ions, other than Cl^-, such as nitrate, sulphate and phosphate, have also been implicated.

To identify a common ion interaction, the IDR of the hydrochloride salt should be compared between:

(a) water and water containing 1.2% w/v NaCl,
(b) 0.05 M HCl and 0.9% w/v NaCl in 0.05 M HCl.

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

Table 13.10 Examples of weakly basic drugs which have decreased solubility in acidic (HCl) solution

Chlortetracycline
Demethylchlortetracycline
Methacycline
Demeclocycline
Papaverine
Trihexyphenidyl
Isoxsuprine
Phenazopyridine
Cyproheptadine
Bromhexine
Triamterene

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. sulphate, tosylate, mesylate etc., but the parent molecule may well still remain sensitive to Cl^- and solubilities will be suppressed in the presence of saline although not to the same extent since 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. Since some compounds are sensitive to other counter ions, e.g. nitrate, sulphate and phosphate, this can be demonstrated by including the appropriate sodium salt in the dissolution medium. The phase solubility studies of Dittert *et al.* (1964) indicated that basic amine drugs were more soluble in organic acids than inorganic. Where a hydrochloride salt exhibits suboptimal solubility then the next logical choice is probably a salt of toluene sulphonic acid (tosylate: $pK_a - 1.34$). Mesylate, napsylate, besylate and maleate salts offer progressively more weaker acidic alternatives (Table 13.4). With low solubility amine drugs the salts of polyhydroxy acids, e.g. lactate, often give the greatest aqueous solubility due to their accessible hydroxy groupings (Senior, 1973; Agharkar *et al.*, 1976).

3 MELTING POINT

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

(a) capillary melting
(b) hot stage microscopy
(c) differential scanning calorimetry thermal analysis.

Capillary melting

Capillary melting (the observation of melting in a capillary tube in contact with a heated metal block) gives information 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 since the phase transitions (first melt, 50% melt and completion) can be registered on a recorder as the melting proceeds and, by virtue of high magnification, the values are more accurate.

Differential scanning calorimetry and differential 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 is occurring within the sample then there is neither a temperature change nor the need to input energy to maintain an isotherm. However, when phase changes occur then latent heat suppresses the temperature increase (or fall) and the change in temperature or isothermal energy required registers on a recorder as a result of an electrical signal generated by thermocouples. Crystalline transitions, fusion, evaporation and sublimation are obvious changes in state which can be quantified (Fig. 13.3).

The major concern in performulation is polymorphism and the measurement of melting point and other phase changes are the primary diag-

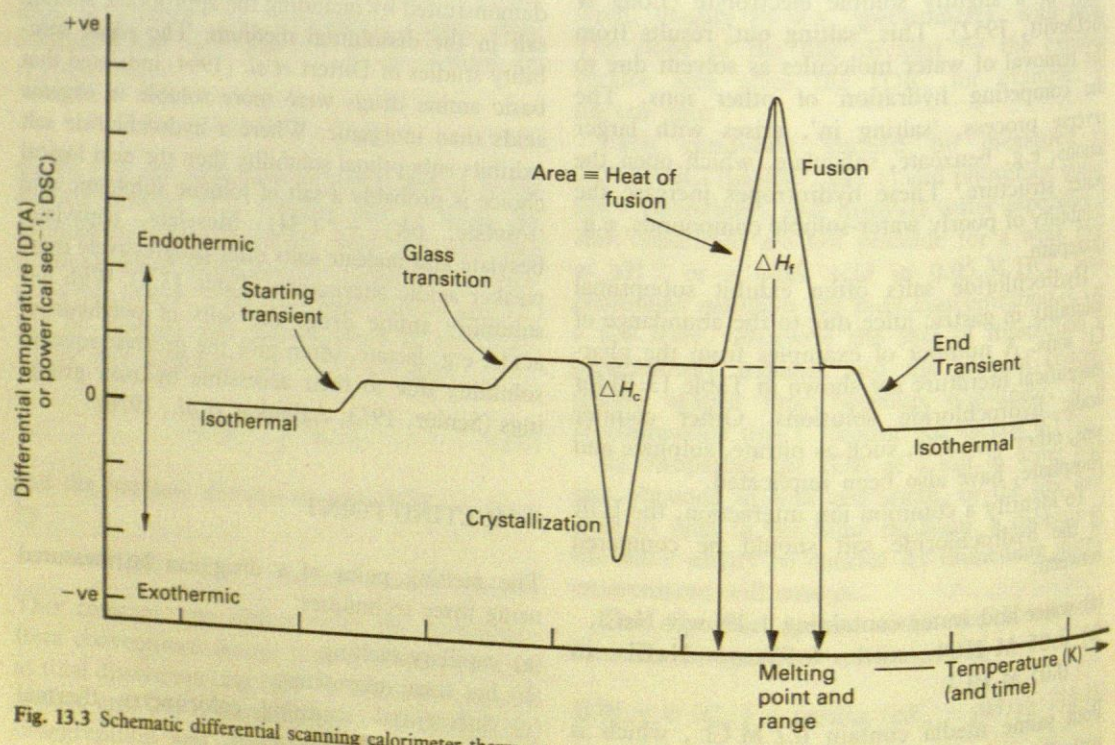

Fig. 13.3 Schematic differential scanning calorimeter thermogram

nostic tool. Confirmation by ion spectroscopy and X-ray diffraction are common.

Polymorphism

A polymorph is a solid material with at least two different molecular arrangements each of which gives a distinct crystal species. These differences disappear in the liquid or vapour state. Of concern are their relative stabilities and solubility. The lowest melting species is generally stable and other polymorphs are metastable and convert to the stable form. There are also large differences in their physical 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 (Kuhnert-Brandstatter, 1965).

The steroid, progesterone, has as many as five polymorphs, while the sulphonamide sulphabenzamide has four polymorphs and three solvates. The importance of polymorphism is illustrated by the biopharmaceutical data for fluprednisolone (Fig. 13.4).

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 lowest solubility; in suspension formulation it is essential to use the least soluble polymorph because of Ostwald ripening (Pearson & Varney, 1969).

Accordingly, in preformulation, the following should be investigated.

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

Pseudopolymorphism

Before this study begins, the presence of false polymorphs, or pseudopolymorphs, should be identified since most polymorphs can be obtained by changing the recrystallizing solvent. Typical

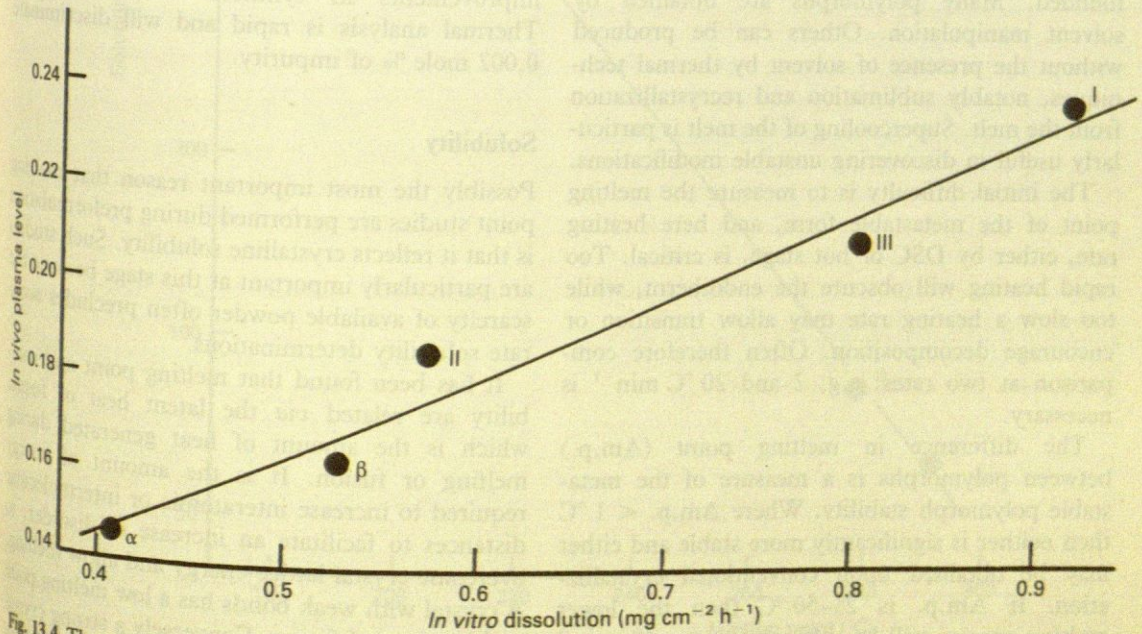

Fig. 13.4 The relationship between *in vitro* and *in vivo* release from fluprednisolone implants. (From the data of Haleblian and Biles, 1967)

solvents inducing polymorphic change are: water, methanol, ethanol, acetone and chloroform, *n*-propanol, isopropyl alcohol, *n*-butanol, *n*-pentanol, toluene and benzene. The presence of trace levels of solvent (either water or organic) is usual in early batches of new drug candidates, as residues from the precipitation process used in the final crystallization. These can become molecular additions to the crystal and change its habit. These hydrates (water) and solvates (e.g. methanolate, ethanolate) have been confused with true polymorphism and led to the term pseudopolymorphism. The distinction between these false forms and true polymorphs can be obtained 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 bubbling of the oil. True 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 and can be used for identification.

True polymorphism

After the study of pseudomorphism, the evaluation of true polymorphism can proceed unconfounded. Many 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, either by DSC or hot stage, is critical. Too rapid heating will obscure the endotherm, while 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 (Δm.p.) between polymorphs is a measure of the metastable polymorph stability. Where Δm.p. < 1 °C then neither is significantly more stable and either may be obtained upon conventional crystallization. If Δm.p. is 25–50 °C then the lower melting species will be difficult to crystallize and will revert rapidly. The closer the two melting points (Δm.p. between 1 and 25 °C), then the unstable forms(s) can be obtained easily before a solid–solid transformation occurs. This can be suppressed by using small samples since individual crystals of even highly unstable forms can be melted.

If it appears that polymorphism is occurring, or is likely to occur, in the samples supplied for preformulation work then a cooperative study with the bulk chemists should determine the most stable form (chemically and physically). Differences in solubility and melting point must also be assessed and then a decision can be 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.

Crystal purity

Thermal analysis has been widely used as a method of purity determination (Grady *et al.*, 1973) and the USP includes an appendix describing the method. This is particularly pertinent at the preformulation stage since 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

Possibly the most important reason that melting point studies are performed during preformulation is that it reflects crystalline solubility. Such studies are particularly important at this stage because the scarcity of available powder often precludes accurate solubility determinations.

It has been found that melting point and solubility are related *via* the latent heat of fusion which is the amount of heat generated during melting or fusion. It is the amount of energy required to increase interatomic or intermolecular distances to facilitate an increase in disorder, to overcome crystal lattice energy and allow melting. 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. Since 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 since intermolecular distances will be different in the alternative forms. This effect is shown for riboflavine in Fig. 13.5.

The differences outlined above have led to differences *in vivo* in the blood level curves of some polymorphs. Some examples of this and the resulting biopharmaceutical consequences are discussed in Chapter 9 and the reader is referred to this for further information.

4 ASSAY DEVELOPMENT

In Section 1 of this chapter a simple u.v. assay was described which enabled the quantitative determination of drug in solution and could be used to generate the solubility data described in Section 2. However, the assumption that the drug is stable enough to survive these manipulations may not always be valid since drugs are notoriously unstable, particularly as hydrolysis is often the predominant cause (see Section 5). In order to

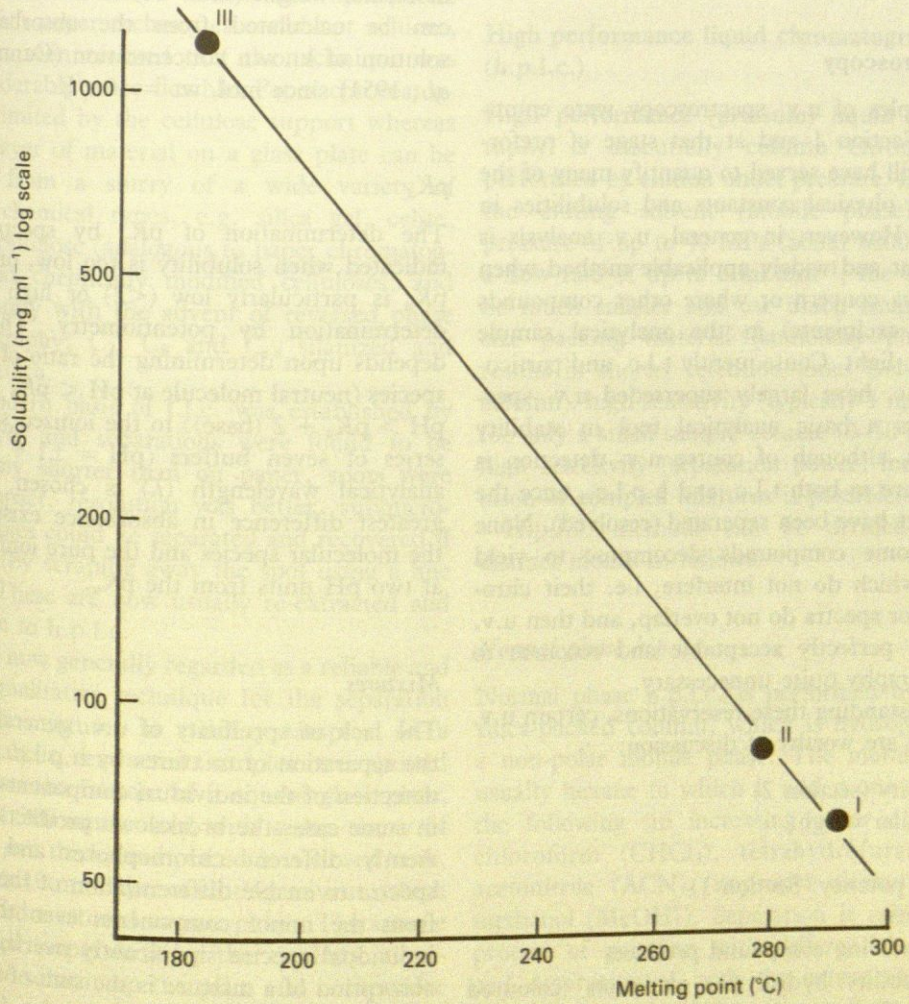

Fig. 13.5 The relationship between melting point and solubility for three polymorphs of riboflavine

follow drug stability, both in solution and in solid phase, it is necessary to have suitable stability indicating assays. In some cases u.v. spectroscopy can be used, but in general chromatography is required to separate the drug from its degradation products and interfering excipients. Thin layer chromatography (t.l.c.) is widely used in a semi-quantitative mode to estimate impurity levels, to establish the number of impurities and for collecting samples from the plate for subsequent injection into the column of h.p.l.c. (high performance (pressure) liquid chromatography) equipment. H.p.l.c. is now acknowledged as the most versatile and powerful technique in pharmaceutical analysis; it is the method of choice in preformulation stability assessment (Section 5).

U.v. spectroscopy

The principles of u.v. spectroscopy were enumerated in Section 1 and at that stage of preformulation will have served to quantify many of the subsequent physical constants and solubilities in Section 2. However, in general, u.v. analysis is not a potent and widely applicable method when stability is a concern or where other compounds (drugs or excipients) in the analytical sample absorb u.v. light. Consequently t.l.c. and particularly h.p.l.c. have largely superseded u.v. spectroscopy as a basic analytical tool in stability assessment, although of course u.v. detection is still a feature in both t.l.c. and h.p.l.c., once the components have been separated (resolved). None the less some compounds decompose to yield products which do not interfere, i.e. their chromophores or spectra do not overlap, and then u.v. analysis is perfectly acceptable and recourse to chromatography quite unnecessary.

Notwithstanding these reservations, certain u.v. techniques are worthy of discussion:

(a) solubility (section 2)
(b) molecular weight
(c) pK_a
(d) assay (potency: Section 1)
(e) mixtures
  (i) resolving compound products
  (ii) stability: hydrolysis, oxidation (coloured products).

First it is important to recognize the attributes of an acceptable assay and the dependence on adequate instrumentation, cells and solvents. This is dealt with in detail in analytical texts and will not be repeated here.

Molecular weight

To a first approximation, the molar extinction coefficient (e) of a chromophore (absorbing molecular group) is unaffected by distant substituent groups in the molecule, especially if they do not absorb in the vicinity of the main chromophore. If, therefore, e of a chromophore is known from another related compound in the series, the molecular weight (mol. wt) of the new derivative can be calculated from the absorbance of a solution of known concentration (Cunningham *et al.*, 1951) since mol. wt $= 10\ e/E$.

pK_a

The determination of pK_a 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 upon determining the ratio of molecular species (neutral molecule at pH $< pK_a - 2$ (acid), pH $> pK_a + 2$ (base)) to the ionized species in a series of seven buffers (pH $= \pm 1 + pK_a$). The 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.

Mixtures

The lack of specificity of u.v. generally requires the separation of mixtures by h.p.l.c. before u.v. detection of the individual components. However, in some cases the breakdown products have sufficiently different chromophores and absorption spectra to enable differentiation of the main peak from the minor components even though their individual spectra significantly overlap, since the absorption of a mixture is the sum of the separate absorptions of the components.

Thin layer chromatography (t.l.c.)

All chromatographic procedures emanate from the work of the Russian botanist Tswett (1906) who separated plant pigments by pipetting solutions on to the top of glass tubes packed with alumina, silica, chalk and sucrose and eluting them with various solvents. This interest in colours led to the term chromatography. The term has been retained and is now applied to all chemical quantitative separations. Tswett's work led to the development of column chromatography and then, under pressure by pumping the eluant, to h.p.l.c. Other workers used paper as a support, and before the advent of h.p.l.c., paper chromatography was more important due to its simplicity and speed. T.l.c. 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.

The modern basis of t.l.c. was established by Stahl (1956) and separations were found to be considerably shorter than on paper, spots were more compact, resolution was better, submicrogram samples could be separated and recovered if necessary (by scraping away the spot using a fine spatula). These are now usually re-extracted and injected on to h.p.l.c.

T.l.c. 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 mm × 200 mm coated with a dry slurry of silica (250 μm thick) and placed in a closed tank, containing a 10 mm layer of eluting solvent, which has produced a satured vapour phase. The sample is developed (separated) by the capillary movement of the solvent up the plate and is therefore similar to h.p.l.c. except it is a thin flat column (stationary phase) with solvent (mobile phase) pumped by capillary flux and much of the theory (see Snyder, 1968; Bristow, 1976) is the same. Consequently t.l.c. and h.p.l.c. are complimentary. T.l.c. will quantify the number of components (since they can be seen) and estimate their concentration by reference to standards run concurrently, when h.p.l.c. can quantify their level, confident that all have been separated. The developing solvent for t.l.c. (particularly h.p.t.l.c. (high performance t.l.c.) and reverse phase) is also a useful guide to identify the mobile phase for h.p.l.c.

For further details of t.l.c. and h.p.l.c. the reader is referred to analytical texts.

High performance liquid chromatography (h.p.l.c.)

High performance (pressure) liquid chromatography is essentially column chromatography performed by elution under pressure. By pumping the eluting solvent (mobile phase) under a pressure of up to 40 MPa (about 6000 p.s.i.) 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 in 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 is possible.

H.p.l.c. methods can be divided into two distinct modes as follows.

Normal phase h.p.l.c.

Normal phase h.p.l.c. 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 ($CHCl_3$), tetrahydrofuran (THF), acetonitrile (ACN), isopropyl alcohol (IPA) or methanol (MeOH)). Separation is achieved by a process of partition with differential adsorption and desorption of both the solute and solvents during passage down the column. Polar solutes are

retained whereas 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 while non-polar solutes are better retained; their order of retention may also change. Decreasing solvent polarity increases polar solute retention and facilitates the elution of lipophilic molecules.

In general, normal phase h.p.l.c. is used for moderately polar solutes, for example, those freely soluble in methanol. Non-polar hydrocarbon-soluble solutes are difficult to retain and very polar, water-soluble solutes are difficult to elute sufficiently.

Reverse phase h.p.l.c.

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 h.p.l.c. and uses a hydrophilic silica stationary phase. Separation between the stationary phase and mobile phase is solvophobic, analogous to partition behaviour (see section 2 of this chapter).

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 C_{18} (octadecylsilane, ODS), C_8 (octylsilane, OS) and C_1 (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 by using pH buffers (phosphate and acetate) 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. This is known as *ion-suppression chromatography*. This technique is used to increase lipophilicity and improve retention of polar solutes.

In general polar solutes have short retention times on reverse phase h.p.l.c. while non-polar compounds are retained. Increasing the mobile phase polarity (by increasing the water concentration) shortens retention for polar solutes while retaining less polar compounds. Decreasing solvent polarity (by decreasing water concentration) helps retain polar compounds while more lipophilic solutes are eluted more rapidly.

Non-aqueous reverse phase (NARP) h.p.l.c., 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 h.p.l.c. produces a powerful analytical technique. Accordingly it is the method of choice in preformulation stability studies.

Further details may be found in the literature of h.p.l.c. equipment manufacturers, in the books of Bristow (1976), Pryde and Gilbert (1979) and Hamilton and Sewell (1977) and in standard analytical chemistry texts.

5 DRUG AND PRODUCT STABILITY

Wherever possible, commercial pharmaceutical products should have a shelf life of 5 years. The potency should not fall below 90% at 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 13.11.

Drug degradation occurs by four main processes:

(a) hydrolysis
(b) oxidation
(c) photolysis
(d) 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 13.11 Stress conditions used in preformulation stability assessment

Test	*Conditions*
Solid	
Heat (°C)	4, 20, 30, 37, 37/75% RH, 50 and 75
Moisture uptake	30, 45, 60, 75 and 90% RH at RT[1, 2]
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[3]	U.v. (254 and 366 nm) and visible (south facing window) at RT
Oxidation[3]	Sparging with oxygen at RT; u.v. may accelerate breakdown

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

Temperature

Thermal effects are superimposed on all four chemical processes. Clearly a greater available free energy leads to a more rapid reaction and typically a 10 °C increase in temperature produces a 2–5-fold increase in decay.

Often the increase in reaction rate with temperature follows an Arrhenius-type relationship (see Chapter 7). As long as the Arrhenius relationship holds and a plot of the log of the rate of reaction against the reciprocal of absolute temperature yields a straight line, the reaction rate can be calculated at any temperature. In turn this allows a prediction of shelf life at room temperature by extrapolation. This assumption forms the basis of many accelerated stability tests. However, the mechanism or pathway of the chemical breakdown often changes with temperature. This may be indicated by a discontinuity of 'knee joint' in the Arrhenius plot but often this is not easily detected and this would inevitably lead to erroneous conclusions, based on elevated temperature data, to predict shelf lives at room temperature or under refrigeration.

Order of reaction

The time course of degradation depends on the number of reactants whose concentration influences the rate and the orders of reaction and the mathematical relationships relating decomposition to time are described in Chapter 7.

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 ($t_{\frac{1}{2}}$ or t_{50}). The shelf life of a product can be likewise expressed as t_{90} (i.e. the time for a 10% loss).

In the absence of a definitive value for the activation energy (E_a), which may normally be obtained from the slope of the Arrhenius plot, it is prudent to assume a low value (e.g. 10 kcal mol^{-1}), since this will lead to higher reaction rates and any prediction of shelf life will be conservative. Values for a wide range of reactions are 10–100 kcal mol^{-1}, but are usually in the range 15–60 kcal mol^{-1} with a mean of 19.8 (Kennon, 1964).

Most breakdowns are first order in nature but some are zero order, e.g. aspirin in aqueous suspension, whilst a few are second order, e.g. chlorbutol hydrolysis.

Hydrolysis

The most likely cause of drug instability is hydrolysis. Obviously water plays a dominant role but in many cases it is implicated passively, particularly in solid dosage forms. Here it acts 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, below).

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:

(a) presence of OH^-
(b) presence of H_3O^+
(c) presence of divalent metal ions
(d) ionic hydrolysis (protolysis) is quicker than molecular
(e) heat
(f) light
(g) solution polarity and ionic strength
(h) high drug concentrations.

The influence of pH

The degradation of most drugs is catalysed by extremes of pH, i.e. high $[H_3O^+]$ 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 the buffer has a low capacity to prevent unnecessary challenge to the homoeostatic pH 7.4 of blood.

Weakly acidic and basic drugs are most soluble when ionized and it is then that instability is most likely since the species are charged. This leads to a potential problem since 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 (a) suppressing ionization, (b) reducing the extreme of pH required to achieve solubility, (c) contributing itself to solubility, e.g. 20% propylene glycol in chlordiazepoxide injection and (d) reducing the water activity by reducing the polarity of the solvent.

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 (the latter having intrinsic antioxidant activity).

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, which is equivalent to an increased solvent polarity. For example, 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 than itself 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 and with no net charge. In this case solvents will not affect the rate of decomposition and can be used with impunity to increase solubility.

Finally, although solvolytic breakdown may be significant, the advantages of cosolvent solubility, as in the case of chloramphenicol, may be more attractive provided the intrinsic stability is good.

Oxidation

Whereas in hydrolysis, water (or solvent), pH and temperature are the major factors involved, oxidation is largely controlled by the environment: light, trace metals, oxygen and oxidizing agents. Reduction is a complimentary reaction (Red-Ox) 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. 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, which unlike simple ligands, e.g. ferrocyanide $(Fe(CN)_6^{4-})$, which form complex salts by a single bond provided by a lone electron pair, are capable of forming more than one bond. For example, ethylene diamine is bidentate (two links), tripyridyl is tridentate (3) and ethylene diamine tetraacetic acid (EDTA) is hexadentate (6) which means this is particularly effective as a pharmaceutical chelating agent.

Photolysis

Oxidation, and to some extent hydrolysis, is often catalysed by light. The energy associated with the

radiation increases as its wavelength decreases, so that the energy of u.v. > visible > i.r., and is independent of temperature (see Table 13.12).

Table 13.12 Relationship between wavelength and associated energy of various forms of light

Type of radiation	*Wavelength (nm)*	*Energy (kcal mol^{-1})*
U.v.	50–400	287–72
Visible	400–750	72–36
I.r.	750–10 000	36– 1

When molecules are exposed to electromagnetic radiation they absorb light (photons) at characteristic wavelengths which causes an increase in the energy state of the compound. This energy can:

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

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

Thus photolysis is prevented by suitable packing: 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 half this amount of radiation. For further details see Chapter 44.

Solid-state stability

Many of the processes of decomposition mentioned in the preceding paragraphs of this chapter 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 tables and capsules. There is limited information in the pharmaceutical literature largely due to the complexities of formulated systems and the difficulties in obtaining quantitative data. This scarcity of data must not be interpreted to mean that this area is unimportant, especially given the popularity of tablets and capsules.

In all solid dosage formulations there will be some free moisture (contributed by various additives or excipients, as well as the drug) and, certainly in tablets, a significant percentage, typically 25% w/w, is required to facilitate good compression. This free water has the ability to act as a vector for chemical reactions between drugs and excipients as saturated solutions.

Because of the differences observed in the behaviour of drugs in the solid state or in contact with limited amounts of water, such as adsorbed moisture films, when compared with their reaction in solution, studies in dilute solution can often be quite meaningless and should not be extrapolated glibly to the solid state.

Hygroscopicity

A substance which absorbs sufficient moisture from the atmosphere to dissolve itself is deliquescent. A substance which loses water to form a lower hydrate or becomes anhydrous is termed efflorescent. These are extreme cases and usually most pharmaceutical compounds either are impassive to the water available in the surrounding atmosphere or either lose or gain water from the atmosphere depending on the relative humidity (RH). Materials unaffected by RH are termed non-hygroscopic while those in dynamic equilibrium with water in the atmosphere are hygroscopic. Ambient RH 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. For this reason pharmaceutical air conditioning is usually set below 50% RH and very hygroscopic products, which are particularly moisture sensitive, are stored below 40% RH.

Formulated solid products, such as 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 choice of pack, while still reducing significantly any hydrolytic instability due to absorbed free moisture.

Stability assessment

The testing protocols used to ascertain the stability of formulated products must be performed both in solution and in the solid state since the same drug may be manufactured both as an injection and a capsule, for example. These protocols have been discussed briefly in Chapter 7 and a suggested scheme is shown in Table 13.11.

6 MICROSCOPY

The microscope has two major applications in pharmaceutical preformulation:

(a) basic crystallography, to determine crystal morphology (structure and habit), polymorphism and solvates and
(b) 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. Accordingly a lamp illuminated mono-objective microscope fitted with polarizing filters above and below the stage is more than adequate to study these materials. 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 the constituent atoms or molecules in a regular three-dimensional structure which is absent in glasses and some polymers. These are six crystal systems (cubic, tetragonal, orthorhombic, monoclinic, triclinic and hexagonal — see a standard chemistry text) which have different internal structures and spatial arrangement of molecules or atoms. While not changing the internal structure, which occurs with polymorphism, crystals can adopt different external structures. This is known as crystal habit of which five types are recognized:

(a) tabular: moderate expansion of two parallel faces;
(b) platy: excessive plate-like development;
(c) prismatic: columnar form;
(d) acicular: needle-like prism;
(e) bladed: flattened acicular.

These can occur in all six crystal systems.

Conditions during crystallization of the drug will contribute to changes in crystal habit and may well be encountered in early batches of a new drug substance during preformulation until the synthetic route has been optimized. The following examples show ways in which crystal habit can be modified.

(a) Excessive supersaturation tends to transform a prism or isodiametric (granular) crystals to a needle shape.
(b) Cooling rate and agitation is effective in changing habit since it changes the degree of supersaturation. Naphthalene gives thin plates (platy) if rapidly recrystallized in cold ethanol or methanol whereas slow evaporation yields prisms.
(c) 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.
(d) The addition of cosolvents or other solutes and ions may change habit by poisoning crystal growth in one or more directions. Sodium chloride is usually cubic but urea causes an octahedral habit.

Particle size analysis

The particle size of a drug has fundamental effects on two important concerns in solid dosage form formulation:

(a) dose uniformity
(b) dissolution rate.

Small particles are particularly important in low dose, high potency drug candidates since large particle populations are necessary to assure adequate blend homogeneity (coefficient of variation less than 2%), and also for any drug whose aqueous solubility is poor (<1 mg ml^{-1}), since dissolution rate is directly proportional to surface area (i.e. to particle size^{-1}). Cohesion, adhesion and powder flow are also dependent (see Chapter 36).

There are numerous methods of particle sizing. Sieving is usually unsuitable during preformulation due 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 (see Chapter 33 for details).

7 POWDER FLOW PROPERTIES

Of primary importance to the formulator when handling a drug powder is an assessment of its flow properties. Various methods of assessing powder flow are discussed fully in Chapter 36; however, when limited amounts of drug are available these can be evaluated simply by measurements of bulk density and angle of repose of the powder. 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 smaller Carr's index (see below and Chapter 36).

Bulk density

Neumann (1967) and Carr (1965) developed a simple test to evaluate flowability of a powder by comparing the poured (fluff) density ($\rho_{B\,min}$) and tapped density ($\rho_{B\,max}$) of a powder and the rate at which it packed down. A useful empirical guide is given by the Carr's compressibility index. Here 'compressibility' is a misnomer since compression is not involved.

Carr's index (%)

$$= \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100 \qquad (13.12)$$

It is a simple index that can be determined on small quantities of powder and may be interpreted as in Table 13.13.

Table 13.13 Carr's index as an indication of powder flow properties

Carr's Index (%)	*Type of flow*
5–15	Excellent
12–16	Good
18–21	Fair to passable*
23–35	Poor*
33–38	Very poor
>40	Extremely poor

* May be improved by the addition of glidant, e.g. 0.2% Aerosil.

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

$$\text{Hausner ratio} = \frac{\text{Tapped density } (\rho_{B\,max})}{\text{Poured density } (\rho_{B\,min})} \qquad (13.13)$$

Values less than 1.25 indicate good flow (= 20% Carr), while 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 consolidation of the powder occurs. Indeed some materials have a high index (suggesting poor flow) but they may consolidate rapidly. Rapid consolidation is essential for uniform filling on tablet machines when the powder flows at $\rho_{B\,min}$ into the die and consolidates, to approach $\rho_{B\,max}$, prior to compression. An empirical linear relationship exists between the per cent change in bulk density and the log number of taps in a jolting volumeter (see Chapter 36). 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, or the beneficial effects of glidants.

Angle of repose

A static heap of powder, when only gravity acts 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 can depend on the method of measurement (see Chapter 36).

The values of angle of repose given in Table 13.14 may be used as a guide to the type of flow to expect. A simple graphical relationship between angle of respose, Carr's index and the expected powder flow is shown in Fig. 13.6. 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 the spatula and estimating the angle of the triangular section of the powder heap viewed from the end of the spatula. This is obviously a somewhat crude determination but is useful during preformulation when only small quantities of drug are available.

Table 13.14 Angle of repose as an indication of powder flow properties

Angle of repose (degrees)	*Type of flow*
<25	Excellent
25–30	Good
30–40	Passable*
>40	Very poor

* May be improved by the addition of glidant, e.g. 0.2% Aerosil.

8 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 but at higher doses the preferred method would be wet massing (see Chapters 37 and 39).

None the less information on the compression properties of the pure drug is extremely useful. While it is true that the tableted material should

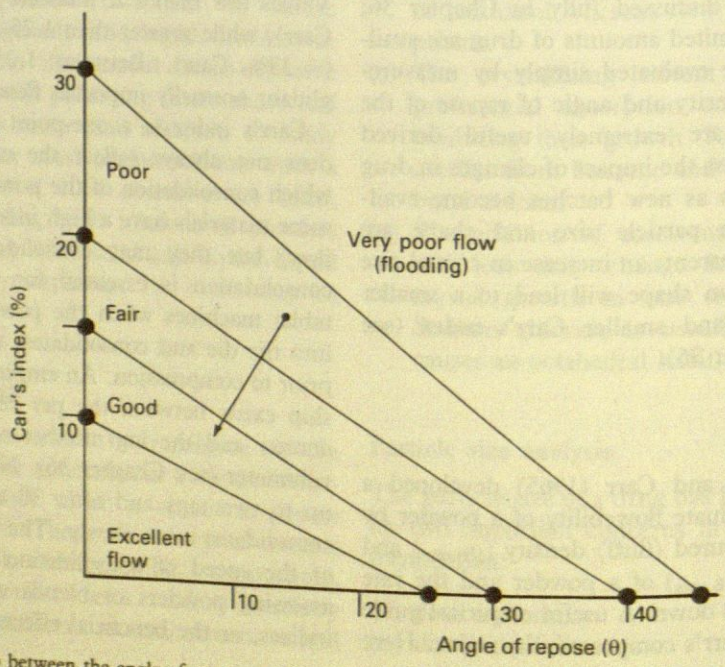

Fig. 13.6 Relationship between the angle of repose and Carr's index of a powder and its flow characteristics

be plastic, i.e. capable of permanent deformation, it should also exhibit a degree of brittleness (fragmentation). Accordingly 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, e.g. microcrystalline cellulose, or plastic binders could be used in wet massing. Obviously, as the dose is reduced, this becomes less important as the diluent vehicle dominates compressibility. This is discussed more fully in Chapter 39.

The compression properties (elasticity, plasticity, fragmentability and punch filming propensity) for small quantities of a new drug candidate can be established by the sequence outlined in Table 13.15.

Table 13.15 Scheme for the evaluation of drug compression properties.

	500 mg drug + 1% magnesium stearate		
Sample code	*A*	*B*	*C*
Blend in a tumbler mixer for	5 min	5 min	30 min
Compress 13 mm diameter compacts in a 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

Interpretation of the results from the compression scheme

Plastic material When materials are ductile they deform by changing shape (plastic flow). Since there is no fracture, no new surfaces are generated during compression and a more intimate mix of magnesium stearate (as in sample C in Table 13.15) leads to poorer bonding (DeBoer *et al.* 1978). Since these materials bond after viscoelastic deformation, and this is time-dependent, increasing the dwell time at compression (B in Table 13.15) will increase bonding strength. Thus, a material exhibiting tablet crushing strengths in the order B > A > C would probably have plastic tendencies.

Fragmenting material If a material is predominantly fragmenting, neither lubricant mixing time (C in Table 13.15) nor dwell time (B) should affect tablet strength. Thus materials which show tablet crushing strengths which are independent of the scheme of manufacture outlined in Table 13.15 are likely to exhibit fragmenting properties during compression, with a high friability.

Elastic material Some materials, paracetamol is an example, are elastic and there is very little permanent change (either plastic flow or fragmentation) caused by compression; the material rebounds (elastically recovers) 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 respond as follows to the preparation methods outlined in Table 13.15.

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 tableting matrix or wet massing to induce plasticity (see Chapters 37 and 39 for further details).

Punch filming (sticking) Finally, the surface of the top and bottom punches should be examined for adhesion of drug. The punches can be dipped into a suitable extraction solvent and the drug level determined. This will probably be higher for A and B (Table 13.15) since magnesium stearate is an effective anti-adherent 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.

9 EXCIPIENT COMPATIBILITY

The successful formulation of a stable and effective solid dosage form depends on the careful