PHARMACEUTICAL PREFORMULATION:
The Physicochemical Properties of Drug Substances

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Solubility

When a preformulation programme begins, the availability of bulk is always limited and the scientist may only have 50 mg. Thus, it is imperative that the best use of the limited bulk is made, to support the continuing efforts of 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 number of impurities may be present and often the first seeding comes down as a metastable polymorph (Chapter 3). Accordingly if nothing else is measured, the solubility and pK_a must be determined since these largely control all future work. The solubility dictates the ease with which formulations for gavage and intravenous injection studies in animals are obtained. The pK_a allows the informed use of pH to manipulate solubility and choose salts, should they be required to achieve good bioavailability from the solid state, and to improve stability (Chapter 5) and powder properties (Chapter 6).

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 adsorption problems may occur. He also found that if the intrinsic dissolution rate (IDR, section 2.7) was greater than 1 mg cm^{-2} min^{-1} then adsorption was unimpeded, while less than 0.1 mg cm^{-2} min^{-1} gave dissolution rate-limited adsorption. This ten-fold difference in dissolution rate translates to a lower limit for solubility of 1 mg ml^{-1} since under sink conditions, dissolution rate and solubility 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 is to be formulated as a tablet or capsule. In the range 1–10 mg ml^{-1}, serious consideration should be given to salt preparation. These guidelines are shown graphically in Fig. 2.1. Where the solubility of the drug cannot be manipulated in this way (a neutral molecule: glycoside, steroid, alcohol or where the pK_a is less than 3 for a base or greater than 10 for an acid), then liquid filling (a solution in PEG 400, glyceryl triacetate or fractionated coconut oil) in a soft gelatin capsule, or as a paste or semisolid (dissolved in oil or triglyceride) in a hard gelatin capsule may be necessary.

2.1 INTRINSIC SOLUBILITY (C_o)

First examine the chemical structure, or determine the solubility in 0.1 N HCl, 0.1 N NaOH and water by UV. An increase in acid over aqueous solubility suggests a weak

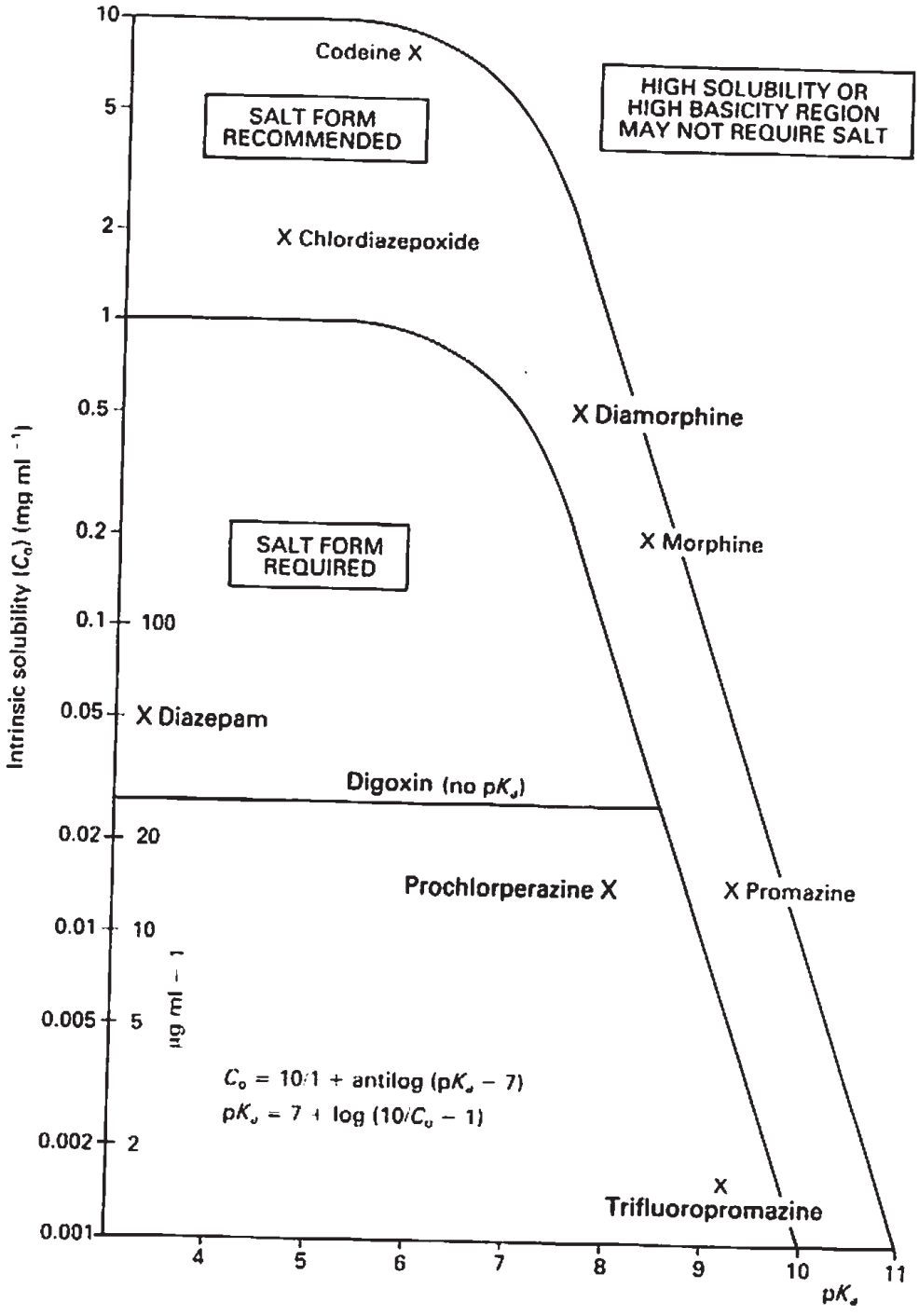

Fig. 2.1 — Relationship between drug pK_a and solubility. Solubility > 10 mg ml^{-1} at < pH 7 (Kaplan, 1972) is required to ensure good bioavailability.

base, and in alkali, a weak acid. In both cases, a dissociation constant (pK_a) will be measurable and salts should form. An increase in both acid and alkali solubility suggests either amphoteric or zwitterionic behaviour and there will be at least 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 manipulation will require either solvents or complexation.

When the purity of the drug sample can be assured, then the value obtained in acid for a weak acid or alkali for a weak base can be assumed to be the intrinsic solubility (C_o), i.e. the unionized form. However, since absolute purity is often in doubt on the first few synthetic batches, it is more accurate to determine this crucial solubility from a phase–solubility diagram (Fig. 2.2). The solubility should ideally be measured at two temperatures:

(1) 4°C: to ensure good physical stability and extended short-term storage and chemical stability until more definitive data are available. The density of water is maximum at 4°C and this imposes the greatest challenge to saturated aqueous solubility.
(2) 37°C: to support biopharmaceutical evaluation, since this is body temperature.

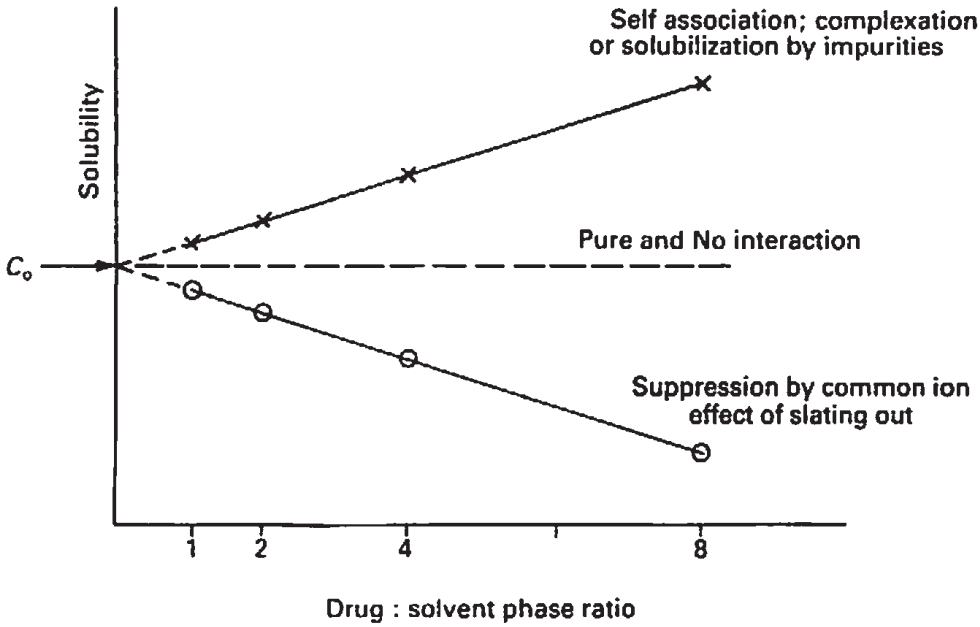

Fig. 2.2 — Effect of drug : solvent ratio on solubility when the drug is impure.

Assuming the compound is a base and the estimate in 0.1 N NaOH gave 1 mg ml^{-1}, then four solutions of 3 ml should be set up containing 3, 6, 12 and 24 mg of drug respectively. These give the phase ratios shown in Fig. 2.1. Three millilitres is the smallest volume which can be manipulated, by either centrifugation or filtration, followed by dilution for UV analysis. The vials containing the samples should be agitated continuously for 16 hours (overnight) and then the concentration in solution determined. The data should be plotted according to Fig. 2.1 and the line extrapolated to zero phase ratio, where the 'solubility' will be independent of solvent level

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