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Short Communication

The use of co-solvents in parenteral formulation of low-solubility drugs

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Intravenous dosing of a drug by bolus injection may require administration at a concentration in excess of the drug's intrinsic aqueous solubility. For some drugs, for example those without an ionization centre or very weak bases, it may be impossible or impractical to enhance drug solubility by manipulation of the pH of the vehicle. The formulator then has to employ vehicles containing non-aqueous co-solvents (Yalkowsky and Roseman, 1981).

Co-solvents in i.v. formulations can lead to problems of toxicity, reduced blood compatibility and injection difficulty because of increased vehicle viscosity. The vehicle should contain a minimum amount and low concentration of the co-solvent to reduce these effects, and in particular, to prevent haemolysis $< 10\%$ ethanol (Cadwallader, 1978), $< 32\%$ propylene glycol (Cadwallader et al., 1964) or $< 40\%$ PEG 400 (Smith and Cadwallader, 1967) in isotonic saline are generally required.

To significantly enhance the solubility of semi-polar drugs high concentrations of non-aqueous co-solvents may be required (Gould et al., 1984). Consequently the concentration and/or the amount of co-solvent required in the product to maintain the total required dose may be in excess of the level acceptable for i.v. bolus injection. The formulator then usually recommends that the drug concentration is decreased, to reduce the co-solvent requirement, and the injection is then given by i.v. infusion.

This communication demonstates the utility of formulating a highly concentrated injection, requiring dilution immediately prior to administration. Specifically, it maintains the solution phase of the drug over a wide range of possible storage

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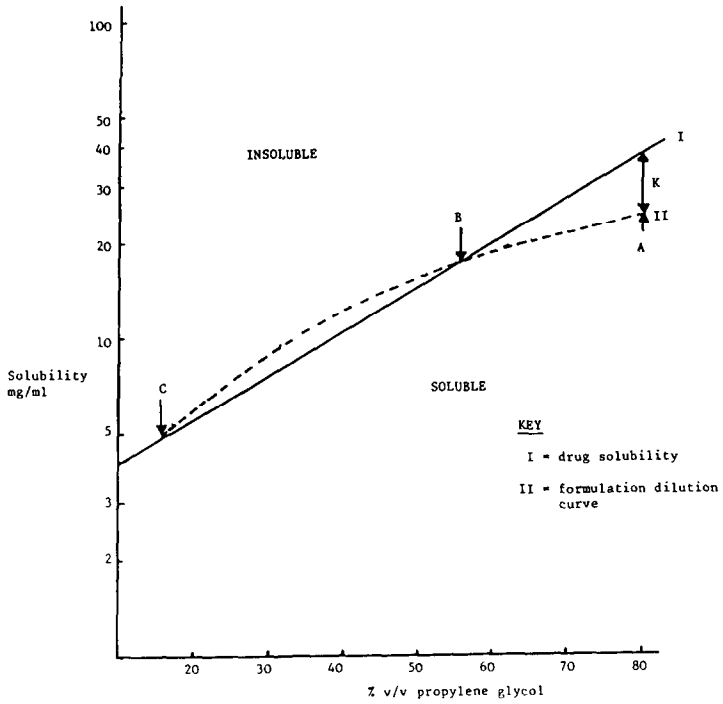

Fig. 1. Drug solubility at 4°C as a function of co-solvent content and the dilution of a 25 mg/ml drug concentration solution in 80% v/v propylene glycol.

conditions while still allowing dilution to acceptable levels of co-solvent to provide the bolus dose under controlled temperature conditions. The approach depends on the graphical comparison of the exponential relationship between drug solubility and co-solvent fraction (Fig. 1) and the linear relationship between drug and co-solvent fraction as a concentrated solution of the drug is diluted (Yalkowsky and Valvani, 1977).

A specific example we cite for this approach is for a very weakly basic semi-polar experimental compound (intrinsic solubility 3 mg/ml at 4°C), where a 50 mg dose i.v. bolus of the drug was required in an injection volume not exceeding 10 ml, i.e. a minimum of a 5 mg/ml solution at 4°C. This temperature was selected so that the dosage form could reliably withstand transportation and warehousing. To allow a further margin of safety we considered it advisable to ensure that the drug concentration was at least 20% below the saturation solubility (C_s), i.e. 6 mg/ml at 4°C in the selected vehicle.

A linear relationship was observed between the logarithm of the measured saturation solubility and fraction co-solvent in mixtures of propylene glycol (PG) and water or saline (% v/v) at 4°C (Fig. 1). A vehicle containing 25% v/v PG in saline would satisfy the formulation objective of 6 mg/ml at 4°C. However, this level of PG with the drug was found to cause slight damage to human red blood cells in an in vitro screen.

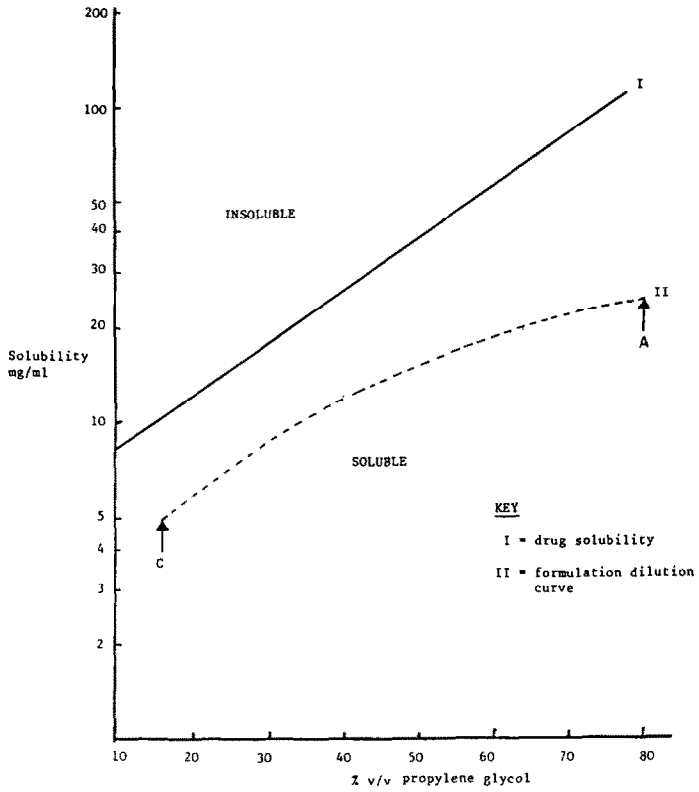

Fig. 2. Drug solubility at room temperature as a function of co-solvent content, and the effect of diluting a drug solution.

Fig. 1 shows the same drug solubility at 4°C where the solubility vs fraction co-solvent line defines the divide between regions of drug insolubility and solubility. A 25 mg/ml drug concentrate was then proposed, in 80% v/v PG, which required a dilution of 1 : 5 to achieve the bolus concentration and an acceptable level (16% v/v) of PG. Dilution of this concentrated solution is also shown in Fig. 1. Prior to dilution (A), the solution is well below the saturation solubility by a factor K ($0.2C_s$) and is therefore physically stable at this temperature. On dilution at 4°C, the formulation would remain in the soluble region until point B where further dilution would render it super-saturated. On continuation to a 1 : 5 dilution (point C) where the drug concentration is now 5 mg/ml, in a vehicle containing 16% v/v PG, the solution is physically unstable since it is saturated at this temperature. If we now consider dilution of the same system at room temperature (Fig. 2) then at all dilutions (A–C) the formulation remains in the soluble region. Thus, a concentrate containing 25 mg/ml in 80% PG is physically stable at 4°C storage, and has the potential, as long as it is diluted at temperatures *above* 4°C (i.e. at room temperature), to yield a physically stable solution of 5 mg/ml with 16% co-solvent. This

formulation, once diluted, proved to be blood compatible and non-irritant on injection.

In conclusion, the concentrate for dilution approach has proved an elegant solution to a common i.v. formulation problem. It produces a physically stable formulation which results in the administration of low levels of co-solvent to the patient, thus reducing or eliminating the effects of co-solvent toxicity and erythrocyte damage. Furthermore, such co-solvent concentrate systems also have the potential to overcome chemical instability problems.

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