OPTIMISATION OF THE DEVELOPMENT OF PARENTERAL FORMULATIONS USING MULTIPLE LINEAR REGRESSION : SOLUBILITY OF DRUG CANDIDATES IN CO-SOLVENT SYSTEMS

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The development of many dosage forms is essentially an optimisation process but frequently an acceptable rather than optimum solution to the formulation goal is achieved. However mathematical and evolutionary optimisation techniques exist which can be adapted to assist formulation studies (Schwartz 1973; Shek et al 1980).

Recently we have been developing parenteral formulations using a non-aqueous co-solvent approach. In order to achieve the required concentration and co-solvent levels suitable for toxicity studies an optimisation method using a multiple linear regression solubility model was employed. We report the details of this mathematical method for one particular drug candidate.

Equilibrium solubilities (C_s) were measured at room temperature in three aqueous co-solvent systems: propylene glycol (PG), polyethylene glycol 300 (PEG 300) and dimethylacetamide (DMA) at levels of 10, 15, 20, 30% w/v. A mathematical model fitting the solubility data to the co-solvent levels (independent variables) was derived using multiple linear regression analysis (BMDP statistical package). Prior to the analysis all independent variables were shown to be non-correlated at the 10% level of significance, and the number of experiments conducted sufficient to avoid undue risk of chance correlations (Topliss & Costello 1972). The model derived was defined by the equation:

$$C_s = [0.24 \pm 0.04]\ \%\ PG + [1.00 \pm 0.04]\ \%\ DMA + [0.27 \pm 0.04]\ \%\ PEG\ 300 - 0.33 \text{ mg/ml}$$

$n = 13 \qquad r = 0.9954 \qquad r^2 = 0.9909 \qquad P < 0.01$

where all coefficients are significant at the 95% confidence level and over 99% of the variation in the solubility data is accounted for by the regression model. Figure 1 shows a plot of the calculated vs. observed solubilities for the 13 observations used to derive the model (training set). The agreement is excellent over the whole of the solubility range. The equation can be used to calculate solubilities, within the defined region, for any new formulation of interest. This was tested by further determining the solubility of the drug in the co-solvent systems (Predictor set) and once again (Figure 1) the agreement between the predicted and measured solubilities is excellent.

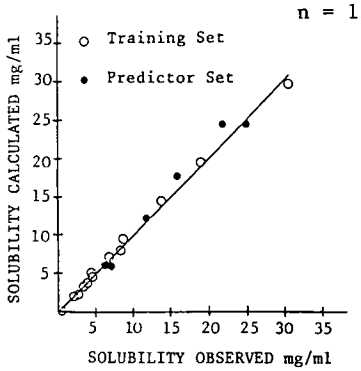

Figure 1

Solubility calculated (predicted) vs. solubility observed.

The method is powerful for assisting the development of co-solvent parenteral formulations particularly when solvent synergism occurs. It allows optimisation of the formulation within the competing constraints of the pharmaceutical system.

Schwartz, J.B., Flamboltz, J.R., Press, R.H. (1973) J.Pharm.Sci. 62: 1165
Shek, E., Ghani, M., Jones, J.E. (1980) Ibid 69: 135
Topliss, J., Costello, R. (1972) J.Med.Chem. 18: 1006

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