Drug Development and Industrial Pharmacy, 25(8), 961–965 (1999)

COMMUNICATION

A Statistical Experimental Approach to Cosolvent Formulation of a Water-Insoluble Drug

Dennis Stephens, Luk Chiu Li,* Ed Pec, and Dan Robinson

Research and Development, Hospital Products Division, AP4, Abbott Laboratories, Abbott Park, IL 60064-3500

ABSTRACT

19-Nor-1α,25-dihydroxyvitamin D_2, an analog of vitamin D_2, is a nonpolar compound with limited solubility in water. An injectable solution was formulated using a cosolvent system consisting of water, ethanol, and propylene glycol. A statistical response surface approach was used to evaluate the effect of these three solvents on the solubility of the drug (25°C) in the ternary cosolvent system. The data generated from five selected formulations were used to develop a multiple linear regression model that quantitatively defines the solubility of the drug as a function of the cosolvent composition. Close agreement was found between the experimental data and data calculated using the model. The capability of this model to predict drug solubility in cosolvent systems with various combinations of the three solvents was also verified.

INTRODUCTION

The low water solubility of a nonpolar drug is often a major challenge to the development of an injectable solution. Various solubilization methods are available for solubility enhancement of a nonpolar drug in aqueous solution (1). Despite some concerns about tissue irritation associated with them, cosolvents are used widely to prepare injectable solutions of drugs with limited water solubility (2). Cosolvents for parenteral use are water-miscible organic solvents; the most commonly used cosolvents are ethanol, propylene glycol, glycerin, and low molecular weight polyethylene glycols (PEGs) (3). The effect of cosolvent composition on the solubility of a drug can be described by a linear relationship between the logarithm of the observed solubility of the drug and the vol-

* To whom correspondence should be addressed.

ume fraction of the cosolvents (4). The determination of such a linear relationship in a ternary cosolvent system may require the preparation and testing of a large number of samples. Furthermore, some degree of deviation from ideal additive behavior exists, causing curvature in the linear solubilization curve and affecting its prediction capability.

The use of experimental design is an alternate approach for determining drug solubility as a function of cosolvent compositions. Experimental data determined from a selected number of formulations can be used to develop a statistical model that allows the prediction of drug solubility in cosolvent systems with a composition defined in the experimental space of the design. Since there is no theoretical assumption involved, any nonideal behavior of the system will be reflected by the experimental data and taken into account by the statistical model. In this study, a statistical response surface approach, the extreme-vertices design, was used to determine the effect of cosolvent composition on the solubility of 19-Nor-1α,25-dihydroxyvitamin D_2 (19-Nor vitamin D_2 analog).

MATERIALS

The materials used were 19-Nor vitamin D_2 analog (Tetrionics, Madison, WI), lot 85-552-JE; dehydrated alcohol USP, Midwest Grain Products Company (Pekin, IL); propylene glycol USP, lot 89-053-DP (Abbott, North Chicago, IL); and water for injection USP.

METHODS

Experimental Design

The solvent composition X_i in a cosolvent system is subject to the constraint that the sum of all component proportions adds up to 1.0.

$$\sum_{I=1}^{q} X_i = 1.0 \quad (1)$$

In addition, an upper constraint b_i and a lower constraint a_i can be imposed on each solvent in the cosolvent system:

$$0 \le a_i \le X_i \le b_i \le 1.0 \quad (2)$$

The extreme-vertices design has been shown to be highly efficient for experiments with the above constraint (5). The experimental space for this design is determined uniquely by the intersection of all constraint planes. One experimental point is taken at each extreme point of vertex, one from the center of each planar face, and one at the geometric center of the entire space. A detailed algorithm has been developed for identifying the experimental point.

Table 1

Composition of Cosolvent Systems Evaluated in the Extreme-Vertices Design

Formulation No.	Ethanol (X_1)	Propylene Glycol (X_2)	Water (X_3)
1	0.00	0.50	0.50
2	0.00	0.30	0.70
3	0.30	0.00	0.70
4	0.50	0.00	0.50
5	0.20	0.20	0.60

In this study, the number of components in the cosolvent system is three, and the constraint for each component is as follows:

Water	50% to 70%
Ethanol	0% to 50%
Propylene glycol	0% to 50%

With these three experimental factors and the constraint, a total of five cosolvent systems were generated using the algorithm. Table 1 presents the composition of these systems, and Fig. 1 displays the boundary, as well as the extreme points and the geometric center of the entire experimental space.

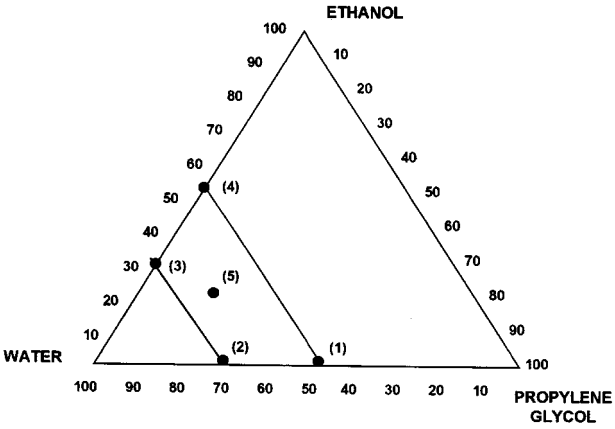

Figure 1. A graphic presentation of the design factor space and formulations evaluated in the extreme-vertices design.

The levels of each solvent component and the logarithm of drug solubility determined experimentally were subsequently fitted to a quadratic model:

$$\ln S = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6 + \eta \quad (3)$$

where S is the drug solubility, X_1 is the fraction of ethanol, X_2 is the fraction of propylene glycol, X_3 is the fraction of water, X_4 is the interaction effect between X_1 and X_2, X_5 is the interaction effect between X_1 and X_3, X_6 is the interaction effect between X_2 and X_3, β's are regression coefficients, and η is the random error.

Solubility Determination

An adequate amount of 19-Nor vitamin D_2 analog was weighed and added to 10 ml of cosolvent contained in a 10-ml stoppered glass test tube. Two samples were prepared for each cosolvent composition. The test tubes containing samples were shaken in a 25°C reciprocal shaking water bath (Precision model 25, Chicago, IL) at 100 rpm. After having been shaken for 3 days, an aliquot of sample was filtered through a 0.45-μm, 13-mm Gelman syringe filter (nylon, Acrodisc; Gelman Sciences, Ann Arbor, MI). The filtrate was further diluted a 1:1 ratio with 50% methanol. The filtrate was assayed for the content of 19-Nor vitamin D_2 analog by a high-performance liquid chromatography (HPLC) method. To make certain that a saturated solution was obtained, after the first sampling additional samples were taken 2 days subsequent to the first sample time and assayed for drug content. In addition, the composition of the cosolvents used for this experiment were also determined using HPLC.

RESULTS/DISCUSSION

Table 2 shows the results of solvent compositions and the concentration of 19-Nor vitamin D_2 in the cosolvent systems listed in Table 1. Since more than a 2% difference was shown between the experimental and the design solvent compositions (Table 1) for some of the cosolvent systems, the actual solvent composition data were used in generating the regression model. The percentage difference between the mean concentration of the 3-day samples and that for the 5-day samples (Table 2) was less than 5%. Therefore, the dissolution of the drug in the cosolvents was assumed to reach equilibrium after 5 days of shaking, and the drug concentration in the 5-day samples was taken as the solubility of the drug in the cosolvent systems.

Table 2 also shows that the solubility of 19-Nor vitamin D_2 varies from less than 1 μg/ml to over 600 μg/ml depending on the composition of the cosolvent. The increase in both organic solvent concentrations results in a marked increase in the solubility of the drug. It is apparent that the increase in solubility is more dramatic with the increase in ethanol concentration. A stepwise regression procedure in SAS® (REG procedure) was used for the development of the model (Eq. 3). After variables X_1, X_2, X_3, X_4, and X_5 (X_6 was not statistically significant) were entered, a linear model with an $R^2 = .9999$ was determined. The following equation describes the linear

Table 2

Cosolvent Composition and 19-Nor Vitamin D_2 Solubility

Formulation No.	Ethanol (X_1)	Propylene Glycol (X_2)	Water (X_3)	19-Nor Vitamin D_2 (μ/ml) A	B	Δ
1	0.000	0.506	0.494	13.22	13.78	4.3%
				14.60	15.25	
2	0.000	0.302	0.698	0.56	0.57	−3.6%
				0.62	0.56	
3	0.299	0.000	0.701	6.78	7.23	4.1%
				6.59	6.69	
4	0.498	0.000	0.502	588.82	608.18	−0.5%
				617.17	592.34	
5	0.199	0.207	0.594	15.35	16.42	3.5%
				15.97	16.01	

A = 3-day samples; B = 5-day samples; Δ = percentage difference between the means for A and B.

Table 3

Experimental and Predicted 19-Nor Vitamin D_2 Solubility in Cosolvent Systems Evaluated in the Extreme-Vertices Design

Formulation	Experimental Solubility[a] (μg/ml)	Predicted Solubility (μg/ml)
1	14.51	14.49
2	0.57	0.57
3	6.96	6.95
4	600.26	600.00
5	16.22	16.22

[a] Average of two samples.

model with its significant variables and their regression coefficients (parameter estimates):

$$\ln S = 16.21\,X_1 + 10.52\,X_2 - 5.37\,X_3 - 2.14\,X_4 + 4.07\,X_5 \quad (4)$$

Table 3 shows the experimental and predicted data for cosolvent compositions listed in Table 2. The close agreement between the experimental data used for model development and the predicted data further demonstrates the accuracy of the model.

To verify the predicting capability of this model, three cosolvent systems were prepared with the solvent compositions shown in Table 4. The experimental drug solubility and the predicted values generated using Eq. 4 are also presented in Table 4. The percentage difference between the experimental and predicted solubility data for 19-Nor vitamin D_2 analog in these three cosolvent systems was found to vary from +14.9% to 16.8%, depending on the composition of the cosolvent. In spite of the discrepancies between the predicted and experimental data, the model (Eq. 4) can be used to estimate the solubility of 19-Nor vitamin D_2 in cosolvents consisting of water, ethanol, and propylene glycol with their proportions defined by the constraint of the design.

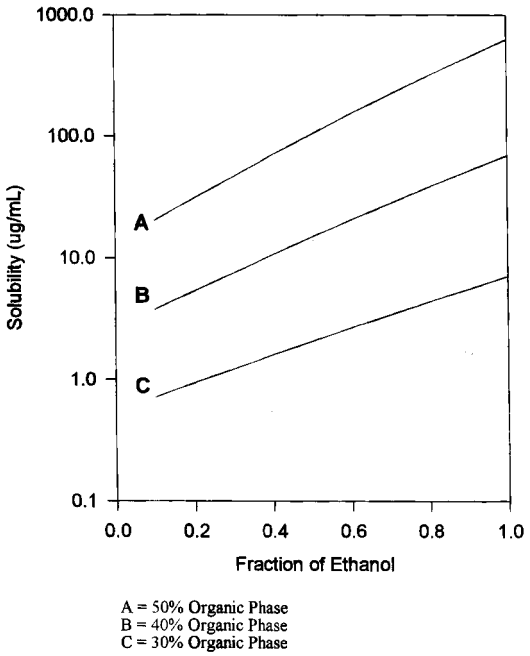

Figure 2. Solubility of vitamin D_2 analog in cosolvents.

Figure 2 depicts the effect of the fraction of ethanol in the organic phase at three different organic-phase (ethanol and propylene glycol) levels in the cosolvent systems on the solubility of 19-Nor vitamin D_2 analog. At a fixed organic-phase level, the increase in the fraction of ethanol results in an exponential increase in drug solubility, as indicated by the positive slope of the solubility curves. The increasing slope of the solubility curves as a function of total organic-phase level leads to the conclu-

Table 4

Experimental and Predicted 19-Nor Vitamin D_2 Analog Solubility in Three Cosolvent Systems

Formulation No.	Cosolvent Composition[a]			Experimental[b] (μ/ml)	Predicted (μ/ml)	Difference (%)
	Ethanol	PG[c]	Water			
6	0.100	0.257	0.643	2.88	3.31	+14.9
7	0.201	0.308	0.491	72.90	81.10	+11.2
8	0.347	0.102	0.551	119.37	99.37	−16.8

[a] Experimental data.
[b] Average of two samples.
[C] Propylene glycol.

sion that the enhancing effect of ethanol is more significant at a higher total organic-phase level. The solubility curves in Fig. 2 can provide valuable information for the design of a cosolvent system for 19-Nor vitamin D_2 analog.

REFERENCES

1. S. Sweetana and M. J. Akers, J. Pharm. Sci. Technol., 50(5), 330 (1996).
2. J. T. Rubino, Cosolvents and cosolvency, in *Encyclopedia of Pharmaceutical Technology*, Vol. 3 (J. Swarbrick and J. C. Boylan, Eds.), Marcel Dekker, New York, 1990.
3. S. Nema, R. J. Washkuhn, and R. J. Brendel, J. Pharm. Sci. Technol., 51(4), 166 (1997).
4. J. T. Rubino, J. Blanchard, and S. H. Yalkowsky, J. Pharm. Sci. Technol., 38(6), 215 (1984).
5. V. L. Anderson and R. A. McLean, *Design of Experiments, a Realistic Approach*, Marcel Dekker, New York, 1974.