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CHEMOMETRIC MODELLING OF DISSOLUTION RATES OF GRISEOFULVIN FROM SOLID DISPERSIONS WITH POLYMERS

Daniela Bonelli[1], Sergio Clementi[1], Cynthia Ebert[2], Mara Lovrecich[3] and Fulvio Rubessa[3]

[1]Department of Chemistry, University of Perugia, Italy

[2]Institute of Pharmaceutical Chemistry, University of Trieste

[3]Institute of Pharmaceutical Technology, University of Trieste, Italy

ABSTRACT

The quantitative relationship between the release rate of griseofulvin and the chemical and physical properties of a series of polymers, used for the preparations of solid dispersions, was investigated by the application of multiple regression analysis (MRA), partial least square analysis (PLS) and a new non linear chemometric procedure called CARSO (Computer Aided Response Surface Optimization).

It was confirmed that the degree of crystallinity of griseofulvin and the wettability of the powder samples are important in the dissolution mechanism and in the prediction of

dissolution profiles of griseofulvin from these solid dispersions.

INTRODUCTION

The dissolution rate of poorly water-soluble drugs may be enhanced by their prior dispersion in a water-soluble carrier (1). Griseofulvin, a slightly soluble antifungal antibiotic, is incompletely and irregularly absorbed after oral administration because of its slow dissolution rate in the gastrointestinal tract (2-4). Its dissolution rate is increased when the drug is dispersed in polyvinylpyrrolidone (5-7), polyethylene glycol (8-12) and other carriers (13-18). However the dissolution profiles of griseofulvin from such systems have not been fully analyzed by mathematical models. Only Takai et al. (19) determined a series of factors affecting dissolution of griseofulvin in various water soluble polymers by the application of multiple regression analysis (MRA).

Scope of this paper is the establishment of an appropriate quantitative relationship between the release rate of griseofulvin and the chemical and physical properties of the polymers used for the solid dispersions. The mathematical expression would make possible to point out which characteristics of the polymer are required to enhance the drug release rate and to predict the response for unmeasured polymers.

The data set used for this chemometric investigation is

taken partly from literature (19) and partly from a previous work of some of us (20) (Table 1).

DATA ANALYTIC METHODS

Multiple regression analysis (MRA) is commonly used in chemistry to predict response variables from a set of causal variables (equation 1).

$$y_k = b_o + \Sigma\, b_i\, x_{ki} + e_{ki} \qquad \text{(eq. 1)}$$

Unfortunately, the regression coefficients b_i are interpreted as the influence of the i-th variable x on the dependent variable y. This straightforward interpretation is not correct if the variables are not scaled. Moreover there are at least three weak points in using multiple regression analysis in this area (21-23). First, the number of objects should be at least three times greater than the number of variables, otherwise the risk for spurious correlations is large. Second, MRA is based on the causal assumption that each variable is precise and relevant to the problem: in other words, the model dimensionality is fixed a priori. Finally, the regression coefficients become unreliable if there are significant correlations between the descriptor variables (multicollinearity).

Principal components analysis (PCA), which has the same mathematical form as MRA, is aimed at finding out the simplest mathematical model able to describe satisfactorily the data set

TABLE 1 - Physico-chemical properties of the polymers.

	Polymer	y	x_1	x_2 (°)	x_3 (cP)	x_4	x_5 (mg/ml)	x_6 (mg/ml)
1	Gum arabic	1.17	0.745	16.5	0.049	4.90	70.6	4.11
2	Sodium alginate	1.61	0.673	30.0	2.33	7.33	74.8	1.58
3	Carrageenan	2.74	0.589	29.7	2.60	9.00	72.9	1.26
4	Locust bean gum	2.17	0.714	18.0	1.81	6.67	76.2	1.84
5	Guar gum	0.965	0.621	17.0	3.29	6.40	79.5	2.13
6	Gum tragacanth	2.65	0.684	20.0	2.15	5.13	77.9	1.76
7	Pectin	2.32	0.764	22.8	0.94	3.77	91.6	2.79
8	CMC-Na	2.26	0.781	19.3	1.32	6.79	103	1.78
9	MC-I	4.80	0.537	13.3	0.37	6.58	109	2.02
10	MC-II	4.16	0.625	13.5	1.30	5.23	107	3.11
11	MC-III	6.54	0.464	13.0	1.63	5.42	107	4.08
12	Dextran T-40	1.94	0.740	15.8	0.09	7.34	61.2	5.72
13	Dextran T-70	1.22	0.900	12.5	0.07	7.72	63.3	3.61
14	HPC-SL	13.20	0.616	10.5	0.14	5.66	103	2.61
15	HPC-L	15.30	0.735	9.0	0.27	6.87	107	1.05
16	HPC-M	15.40	0.644	16.5	0.55	4.01	103	1.23
17	HPC-H	14.80	0.647	21.0	2.15	5.93	106	0.492
18	Polyvinyl alcohol	7.20	0.316	14.0	0.15	6.35	114	1.68
19	PVP K-15	4.89	0.810	10.0	0.08	5.13	82.6	15.90
20	PVP K-30	5.22	0.590	15.5	0.09	4.56	106	4.35
21	PVP K-90	8.89	0.462	22.0	0.36	6.07	111	2.64
22	PEG-4000	3.54	1.090	10.3	0.08	6.19	66.9	25.70
23	PEG-6000	4.55	0.778	8.5	0.05	5.43	62.8	11.50
24	PVM/MA 67000	2.23	0.128	45.1	0.87	3.40	110.05	22.05
25	PVM/MA 20000	8.18	0.091	49.0	0.12	3.21	98.01	4.83
26	GANTREZ ES 225	0.28	0.366	55.0	0.19	4.63	77.29	23.50
27	GAAN 5%	1.125	0.095	56.3	1.70	5.08	82.89	26.85

Polymers: CMC-Na, carboxymethylcellulose sodium; MC-I, methylcellulose (13-18cP); MC-II, methylcellulose (350-

550cP); MC-III, methyl cellulose (4000cP); HPC, hydroxypropylcellulose; PVP, polyvinylpyrrolidone; PEG, polyethylenglycol; Gantrez Es 225, ethyl half ester of PVM/MA 67000; GAAN 5%, ester of PVM/MA 67000 with nonylphenoxypoly(ethylenoxyethanol).

y = amount of griseofulvin (mg/ml) dissolved after 6 minutes

x_1 = apparent degree of crystallinity of griseofulvin in sample powder

x_2 = wetting of samples by water

x_3 = logarithm of viscosity of 1% polymer solution

x_4 = pH of 1% polymer solution

x_5 = solubilizing effect of polymer on griseofulvin

x_6 = apparent dissolution rate of polymer

(equation 2). However, PCA is not aimed at finding out any cause-effect relationship. This latter problem can be solved by the PLS method (Partial Least Squares analysis in latent variables) which does not require any preliminary assumption on the relevance of individual variables, since it relies on PCA. In the latent variable analysis the objective is to find out possible relationships between one or more dependent variables and a number of potentially explanatory variables. The question is whether it is possible to describe the elements of the Y vector as a simple function of the elements of the X matrix (24).

In the past this problem was handled by computing a PC model for the X matrix followed by the establishment of any

linear relationship between these principal components (latent variables) and the y. Instead of this two-steps procedure, called principal components regression (PCR), it is possible to perform the analysis in a single stage, accomplishing the two steps simultaneously, by using the appropriate PLS algorithm.

When the dependent variable is just one, the PLS method extracts the principal components of the descriptors block (equation 2) under the constraint to maximize the relationship with the dependent variable values (equation 3). The algorithm is iterative for each dimension as in PCA (24).

$$x_{ki} = x_i + \Sigma\, b_{ai}\, t_{ka} + e_{ki} \qquad \text{(eq. 2)}$$

$$y_k = y + \Sigma\, d_a\, t_{ka} + h_{ka} \qquad \text{(eq. 3)}$$

The method is included in the SIMCA/MACUP package and has already been used successfully in recent years (23-25). In a recent comparative study we showed that PLS seems to be the appropriate statistical method capable to overcome the pitfalls of multiple regression analysis (22).

In PLS, different from MRA, the ratio between variables and objects is not important; the relevance of individual variables results from the analysis and their correlations are used just to find out the numerical solution. The results obtained by the PLS method permit to detect unambiguously which causal variables are relevant to the response. In addition, PLS is capable to classify samples in different categories in cases where classification is relevant and possible.

A unique model, permitting both interpretation and prediction, is also possible according to a new, non linear, chemometric procedure called CARSO (Computer Aided Response Surface Optimization) (26).

This procedure, developed for determining response surfaces by PLS modelling in order to make possible its use also with non-designed experimental data can be briefly summarized as follows:

1) the X matrix is coded and expanded to include squares and cross products terms;

2) PLS is used to model this expanded matrix;

3) the PLS loadings are transformed into polynomial coefficients for each of the terms; the polynomial equation now describes mathematically the response hypersurface and can be used for its characterization;

4) the maximum value assumed by the response within the experimental domain is found by means of canonical or Lagrange analysis;

5) the ranges, within which the response is higher than a certain value, are determined by means of analytical or graphical tools.

A key step in the procedure is the selection of the "best" maximum within the experimental domain. Canonical analysis is useful only if the response surface is "bell shaped" (all canonical eigenvalues are negative), and the absolute maximum

lies internal to the domain. The Lagrange analysis, instead, is constrained to seek for the values assumed by the response at the extreme points located at the border (faces, edges, etc.) of the domain. Since the number of extreme points increases drammatically on increasing the number of causal variables (the dimensionality of the problem), it is appropriate to restrict the choice of x variables to the mininum possible number.

RESULTS AND DISCUSSION

LINEAR MODELLING BY MRA AND PLS

Our approach starts from refitting, by linear modelling, the release and physico-chemical data already reported on the first 23 polymers (19). The literature data included, besides those listed in Table 1, four more release measurements, taken after 2, 4, 8 and 10 minutes, an indicator variable (the solubility in methanol of the polymer) and two more physical variables: the angle of repose of sample powder and the thickness of gel formed on the sample disk surface.

The statistical tools used in the quoted study was MRA and the first step in our approach was to check the goodness of the regression models reported there for y = log C after 6 minutes. Since those regression equations did not contain all original variables, but did contain some squared terms, we supposed that the selection of the relevant terms was made by stepwise regression. However, if one wants to consider all those nine

variables both in their linear and squared terms there are 19 parameters to be calculated by means of 23 points. Because of the groupings of the points, there is a further decrease in the degrees of freedom so that no solution is possible for the multiple regression analysis of the matrix containing all linear and squared terms.

Obviously, when we use only the terms included in the equations reported in the quoted reference the method works (the number of parameters to calculate is about a half) giving exactly the same regression coefficients. Nevertheless, there is no indication on why only those particular terms were selected (the A.A. reported they used a program written on their own), so that we supposed they carried out a sort of "trial and error" computation, choosing at the end, for each y, the equations with the best correlation coefficients.

This discussion shows: a) how subjective the choice of the "best" equation is in multiple regression, and b) the inappropriate use of indicator variable of the type 1/0, which does not meet the continuity conditions required in multivariate statistics but appeared to be the most relevant factor in determining the release rate. Consequently, we decided to run PLS analysis which is aimed at giving straightforward interpretation on the relevance of variables. Since there is no need, in principle, for the squared terms we used only the linear terms. Furthermore, because this model is aimed

at predicting the release rates for our four new polymers, polymethylvinylether/maleic anhydride (PVM/MA) and its half esters, we did not use the indicator variable nor the other two physical measurements, which were not available for our PVM/MA polymers (19).

Since the PLS modelling permits the simultaneous use of a number of dependent variables, we carried out a preliminary two-components PC model, explaining 65% of the variance, just to check whether the five y's (amount of griseofulvin released in various times) had almost exactly the same information content. This was confirmed by the loadings plot reported in Figure 1. On the contrary, Figure 2, the scores plot, indicates the dramatic differences between three groups of polymers: the HPCs, the PVM/MAs and the other ones.

Because of the high degree of correlation between the y variables, modelling each of them would give pratically the same results in terms of dependence of the release rate upon the physical properties of the polymers. Hence, we selected the release rate after 6 minutes as the most appropriate and stable y-variable for further investigation.

Our subsequent step was therefore to establish the PLS model between log C and the polymer properties for the first 23 points as reported in Table 1. One single latent variable explains almost 50% of the y-variance and the main factor responsible for the release rate is solubility of the polymer

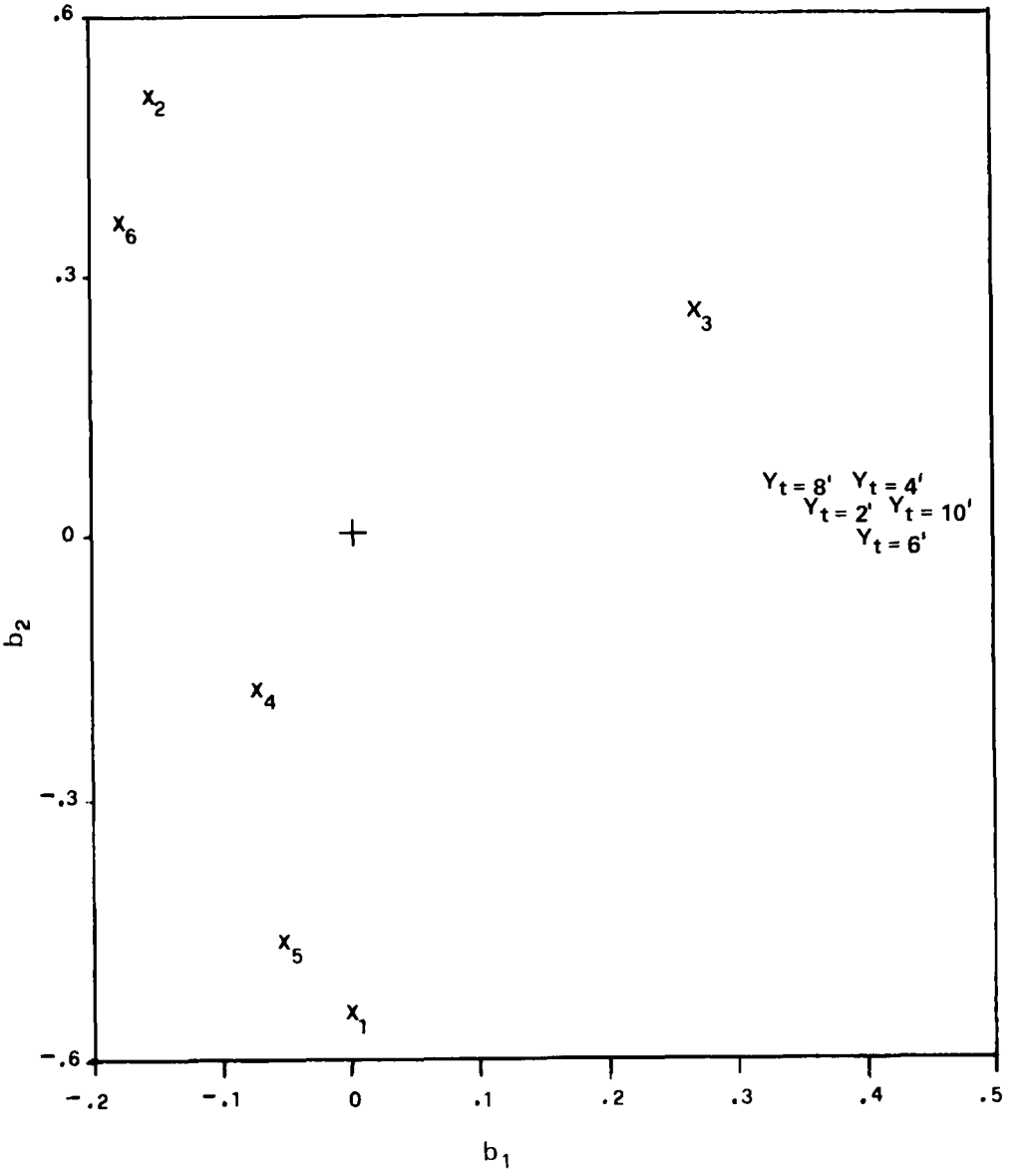

FIGURE 1

Loading plot indicating the relative information content of the variables.

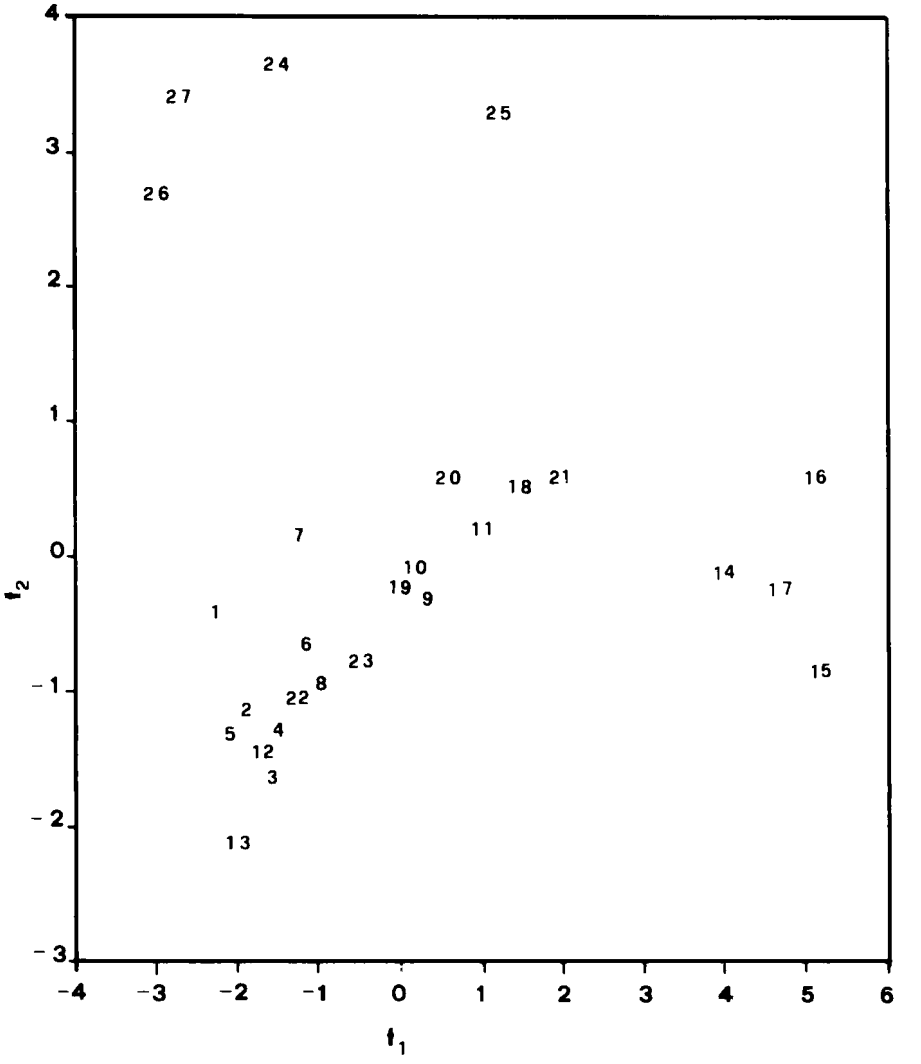

FIGURE 2

Scores plot indicating the difference between the groups of the polymers.

in methanol. The release rates showed a fairly good standard deviation of the predictions (0.23) within the model. However, the predictions for the release rates of the PVM/MAs are useless (negative), as it could be expected owing to the great dishomogeneity of the data set.

RESPONSE SURFACE MODELLING

The dishomogeneity of the polymers in the properties space renders inappropriate the linear modelling of their release rates. The final step of our approach was, therefore, the response surface modelling by the CARSO procedure.

The selection of the variables to be used for the procedure was made on the basis of their information content (Figure 1) and taking into account the possibility of controlling them for further developments of new polymers.

According to these criteria, and since the procedure requires a low number of variables, we decided to use only variables x_1 (apparent degree of cristallinity of griseofulvin in sample powder), x_2 (wetting of samples by water), x_3 (logarithm of the viscosity of polymer solution) and x_4 (pH of polymer solution).

The hypothesis set forth (19) that we wanted to verify was the importance of increasing wetting and decreasing cristallinity for enhancing the dissolution rate of griseofulvin. The PLS model of the expanded matrix required

TABLE 2

Coefficients of the polynomial equation describing the response surface, obtained by CARSO.

$b_0 = 5.40$	$b_1 = -2.02$	$b_2 = -1.67$
$b_3 = -1.09$	$b_4 = -0.68$	$b_{11} = -1.24$
$b_{22} = 1.70$	$b_{33} = -2.33$	$b_{44} = -1.04$
$b_{12} = 4.20$	$b_{13} = 3.01$	$b_{14} = 1.55$
$b_{23} = 1.54$	$b_{24} = 0.63$	$b_{34} = -1.71$

four latent variables and, after collapsing the loadings into polynomial coefficients (Table 2), gave a response surface which exhibited a saddle (minimax).

The costrained extreme points within the experimental domain had therefore to be searched for by the Lagrange analysis. The best maximum ($y > 16$), is found for the following coordinates:

$x_1 = x_2 = x_4 = -1, \quad x_3 = -0.85.$

For this point of the surface the analytical solutions giving the limits for each variable show that x_1 (degree of cristallinity) should be lower than 0.11, x_2 (wetting) should be lower than 9.0, while x_3 (logarithm of viscosity) should be included between -0.35 and 0.70 and x_4 (pH) should be included between 2.5 and 5.8.

CONCLUSIONS

The most important factors influencing the release rate of the griseofulvin are indeed the degree of crystallinity of the drug and the wettability of the powder samples which should be kept to their lowest numerical values, corresponding to decreasing cristallinity and increasing wetting.

The ranges of values required for viscosity and pH are, on the contrary, much larger. Consequently, these polymer properties are less critical to increase the dissolution rate of griseofulvin.

Interestingly, none of the polymers studied so far has, simultaneously, both the required characteristics, since the PVM/MAs have higher values of x_2 and the HPCs higher values of x_1. New polymers possessing both required limit values should exhibit, according to the model developed by CARSO, greater dissolution rates.

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