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RESEARCH PAPER

A Formulation Development Strategy for Multivariate Kinetic Responses

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ABSTRACT

The purpose of this paper was to evaluate a multivariate strategy for handling time-dependent kinetic data during formulation development. Dissolution profiles were evaluated by the Weibull equation, multiple linear regression (MLR), principal component analysis (PCA), alone and in combination. In addition a soft independent modeling of class analogy (SIMCA) was performed. Employing a typical kinetic model for solid formulations (here Weibull) showed difficulties with the model adaptation, resulting in increased model standard deviation and thereby failure in identifying significant variables. In general, the selection of a kinetic model is crucial for finding the significant formulation variables. Describing the dissolution profile based on MLR models of individual time points described the dissolution rates as a function of formulation variables with good precision. Establishing prediction models made it easy to evaluate effects on the entire dissolution profile. The use of PCA/MLR (PCR) reduced the influence of noise from single measurements in a kinetic profile, since they develop statistical parameters representing the profile without being dependent on a physicochemically-modeled profile. The use of PCA reduced the eight time-point variables to two latent variables (principal components), simplifying the classification of formulations and new samples as well as avoiding unwanted effects of model non-linearities between the factors and responses (model error). The group membership of new samples was demonstrated by SIMCA.

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Key Words: *Dissolution profiles; MLR; Multivariate analysis; PCA; PCR; SIMCA*

INTRODUCTION

The development of a pharmaceutical product generates a considerable amount of scientific data during formulation, process, and analytical characterization studies. This multivariate information should be treated as such (i.e., multivariate) not only during formulation development, but also in the quality control and troubleshooting at a future commercial production site. This philosophy should be highlighted, planned, and integrated into the process during the development phase, resulting in analytical data generation, collection and interpretation providing information about the significance of the investigated formulation parameters.

Time-dependent kinetic data are especially challenging to interpret, as they are of multivariate nature, partly inherent covariate, and often nonlinear. In principle such data may be evaluated by three different approaches:

1. fitting of a more or less physicochemically-based model and correlating the resulting parameters to the independent *X*-variables (e.g., Michaelis–Menten, Weibull);
2. treating each time signal as an independent response neglecting the dependency (e.g., multiple least-squares regression);
3. instead of physicochemical parameters, developing statistical parameters representing the kinetic profile (e.g., principal component-related methods).

In this study, data generated during an initial formulation study was subjected to the proposed multivariate procedures. The response was one of the most common quality control criteria, the dissolution rate. Since the rate of release of active substance is often found to directly determine the biological response, it is crucial that the statistical procedures take into account the entire profile, not, as is commonly done, by selecting a more or less arbitrary single time point.

For mathematical modeling we use and discuss tools such as multiple linear regression (MLR), partial least-squares regression (PLS) (1), and the Weibull equation (2). To avoid possible non-linearities between the investigated factors and responses we apply principal component analysis (PCA) [introduced by Pearson (3) and Hotelling (4) and further described by Wold et al. (5)] and soft independent modeling of class analogy (SIMCA) (6). The aim is to discuss the applicability of these approaches, the challenges they present, and demonstrate their properties on a suitable time-dependent kinetic dataset.

It should be noted that in addition to the principal component-based methods discussed in this paper, other multivariate methods capable of handling time-dependent kinetic data exist, e.g., artificial neural networks (7).

MATERIALS AND METHODS

Dataset

A dataset generated during our research concerning drug delivery systems for colon delivery was chosen as a candidate for our study. The dataset given in Table 1 consists of the results from a three-way full factorial design with two levels designed to evaluate the suitability of formulations for neutron activation. The release characteristics of the formulations were employed as response. Further details about the experimental design may be found in Ref. 8. All factors were coded during our evaluation employing 1 for the lower level and 2 for the higher level. In order to demonstrate the effect of formulations showing deviating dissolution due to unknown (i.e., unmodeled) factors, seven additional samples labeled NEW were added at a later stage, see Table 1. The affecting factor on this occasion was actually heat, since elevated temperatures are observed during neutron irradiation.

Calculations

The Weibull model without lag time (2) was fitted to all release profiles:

$$M = \mu\{1 - \exp[-(t/T_d)^\beta]\}$$

where M is the amount released at time t, μ is the total amount released at infinite time, T_d is a rate constant, and β is a shape factor related to the physical release mechanism. Curve fitting was performed

Table 1

The Formulation Variables (A = Type of Suppository Base, B = Addition of Samarium Oxide, C = Neutron Irradiation), Dissolution Values, and Weibull Parameters

Sample No.	A	B	C	5 min	15 min	30 min	60 min	90 min	120 min	180 min	300 min	μ	T_d	β	RSD[a]
11	1	1	1	4.5	11.4	16.3	19.1	20.2	20.9	21.5	21.8	21.3	21.1	0.9	3.1
12	1	1	1	4.5	12.0	16.2	19.4	21.4	22.3	23.3	24.4	23.8	27.7	0.8	4.3
13	1	1	1	2.9	10.0	15.3	18.2	19.5	20.0	21.1	21.7	20.7	24.4	1.0	5.1
14	1	1	1	4.8	12.6	18.1	22.0	23.7	24.4	25.8	26.6	25.8	26.1	0.8	3.6
15	1	1	1	4.6	12.8	19.1	23.5	24.7	25.2	26.2	26.7	25.9	23.3	1.0	2.9
16	1	1	1	5.9	12.4	15.7	19.5	21.3	22.1	22.4	23.1	22.9	23.7	0.7	2.2
21	2	1	1	2.6	6.8	12.7	24.7	36.0	43.5	53.6	62.4	65.4	111.7	1.1	1.8
22	2	1	1	2.9	7.2	13.1	25.3	33.4	38.1	43.6	58.9	70.9	165.4	0.9	6.4
23	2	1	1	2.7	6.3	14.4	27.3	36.2	42.2	49.6	58.9	60.9	102.3	1.1	3.1
24	2	1	1	3.7	8.7	15.7	28.5	38.1	46.6	54.6	65.3	70.3	115.2	1.0	2.1
25	2	1	1	4.2	8.9	14.4	26.1	36.3	45.4	56.6	80.9	175.2	539.7	0.8	3.1
26	2	1	1	2.8	7.2	13.9	25.1	35.1	41.5	48.2	68.4	99.0	257.3	0.9	6.1
31	1	2	1	5.2	12.6	17.7	19.7	20.0	20.2	20.3	20.3	20.2	15.3	1.1	0.9
32	1	2	1	5.3	11.5	13.8	14.4	14.5	14.5	14.6	14.6	14.5	10.0	1.1	0.8
33	1	2	1	4.6	10.4	13.1	16.2	16.7	16.7	16.8	16.9	16.8	17.1	0.9	2.0
34	1	2	1	5.7	11.6	14.0	16.5	16.9	16.9	17.1	17.4	17.1	14.2	0.8	2.1
35	1	2	1	4.3	10.0	11.2	12.1	12.6	13.2	14.0	16.8	17.4	39.6	0.4	10.1
36	1	2	1	5.0	11.0	14.0	15.6	16.3	16.4	16.8	17.0	16.6	14.7	0.9	2.5
41	1	1	2	4.8	9.4	12.5	13.7	14.4	14.8	15.7	16.4	15.8	18.5	0.7	4.5
42	1	1	2	3.8	10.6	13.0	15.4	16.6	17.6	19.1	20.7	20.5	34.1	0.6	6.7
43	1	1	2	5.3	9.2	12.5	15.2	15.8	16.5	18.0	21.4	24.5	78.8	0.5	5.7
44	1	1	2	5.0	9.4	11.3	13.1	14.4	15.3	17.0	20.1	31.2	305.3	0.4	5.2
45	1	1	2	4.8	9.0	11.7	14.5	15.8	16.4	17.7	19.2	19.5	36.9	0.6	2.6
46	1	1	2	4.6	10.7	13.0	14.4	15.6	16.4	18.0	20.2	20.9	41.7	0.5	7.4
51	2	2	1	2.4	4.6	6.1	7.0	8.1	9.2	10.9	12.6	30.2	1282.9	0.4	4.3
52	2	2	1	2.7	5.2	6.6	7.7	8.8	9.7	11.1	12.6	18.4	221.4	0.4	3.8
53	2	2	1	2.0	4.5	6.2	7.5	8.9	10.1	12.0	13.8	20.5	243.1	0.5	4.1
54	2	2	1	3.3	5.8	6.8	7.8	9.1	10.1	11.2	12.6	21.0	377.7	0.4	4.0
55	2	2	1	2.9	5.5	6.5	7.2	8.3	9.3	10.7	11.9	23.7	785.0	0.4	5.4
56	2	2	1	3.0	5.5	6.6	8.0	9.4	10.7	12.7	14.2	35.0	1426.4	0.4	4.3
61	1	2	2	3.8	4.9	5.6	6.1	6.3	6.5	6.7	7.0	9.1	41.8	0.2	6.6
62	1	2	2	3.7	5.3	6.0	6.7	7.3	7.5	8.0	9.3	17.7	1081.4	0.3	3.2
63	1	2	2	3.5	5.1	5.7	6.2	6.3	6.4	6.7	6.9	m[b]	m[b]	m[b]	6.1
64	1	2	2	3.4	5.5	5.9	6.2	6.3	6.5	6.5	6.9	7.8	13.1	0.3	7.0
65	1	2	2	3.8	5.7	6.6	7.5	8.1	8.4	8.2	8.5	8.5	13.0	0.5	1.9
66	1	2	2	3.4	4.7	5.5	6.0	6.3	6.8	7.0	7.3	7.8	20.2	0.4	2.2
71	2	1	2	1.8	7.0	13.2	23.5	32.9	42.5	58.4	89.4	521.7	2025.9	0.9	1.5
72	2	1	2	1.5	6.4	12.5	23.3	32.8	42.4	57.6	87.5	273.0	848.1	0.9	1.8
73	2	1	2	2.3	6.4	12.1	22.7	31.8	41.1	57.7	85.7	238.7	714.2	0.9	0.5
74	2	1	2	2.5	5.8	11.5	21.5	31.2	41.2	57.1	84.7	188.3	506.7	1.0	1.1
75	2	1	2	2.3	6.1	12.4	23.1	32.9	42.3	59.3	87.4	201.3	539.3	1.0	0.5
76	2	1	2	2.2	7.0	13.2	23.9	33.7	43.5	60.8	89.3	233.1	656.2	0.9	0.7
81	2	2	2	1.8	5.2	8.2	12.8	15.7	17.7	20.1	21.7	22.4	72.3	0.9	1.1
82	2	2	2	1.9	4.1	6.2	9.8	13.0	15.4	18.1	20.2	22.2	103.1	0.9	3.2
83	2	2	2	1.9	4.1	6.7	10.9	14.4	17.2	20.6	22.7	24.5	100.4	0.9	2.9
84	2	2	2	1.7	3.8	6.6	10.8	14.3	17.1	20.3	22.4	23.9	97.2	1.0	2.4
85	2	2	2	1.8	4.6	7.3	13.1	18.5	22.2	27.0	29.5	31.0	98.3	1.1	3.5
86	2	2	2	2.4	5.2	7.9	13.9	19.4	23.3	28.0	30.1	31.7	93.8	1.0	4.6
NEWV11	1	1	1	3.8	8.5	12.3	13.9	15.0	15.8	16.3	17.2				
NEWV12	1	1	1	4.2	10.0	14.6	17.2	17.5	17.6	17.9	18.3				
NEWV13	1	1	1	4.9	10.6	13.4	15.7	16.6	17.1	19.0	21.0				
NEWV21	2	1	1	4.8	9.5	14.9	27.5	38.7	48.2	66.8	86.3				
NEWV22	2	1	1	2.7	6.1	12.1	23.5	35.7	46.6	63.7	87.1				
NEWV23	2	1	1	3.4	7.5	12.5	21.1	31.0	39.9	51.2	81.7				
NEWV24	2	1	1	3.6	7.7	13.9	24.9	35.7	46.6	56.1	81.1				

[a] RSD = relative standard deviation for the adaptation of the Weibull model (SD × 100/mean).

[b] m = Missing value due to lack of convergence.

by proc nlin of the SAS package (SAS Institute Inc., Cary, NC).

Predicted dissolution profiles were calculated from developed MLR models, one for each of the eight time points. Since the *X*-data were orthogonal, MLR could be used instead of PLS (9,10). The models included main and two-factor interaction terms:

$$Y_n = \beta_{0n} + \beta_{1n}X_1 + \cdots + \beta_{6n}X_2X_3$$

where Y_n = amount of substance dissolved at time point *n*, $X_{1,2,3}$ = value of variable *A*, *B*, or *C*, β_{0n} = constant at time point *n*, and β_{mn} = regression coefficient number at time point *n*. The performance of the eight models was evaluated by the calculated statistical parameters given in Table 2. The prediction error and the correlation between measured and predicted values are described by $\mathrm{SD_{TOTAL}}$ and the correlation coefficient *r*. An estimate of the modeling error, $\mathrm{SD_{MOD}}$, was calculated by the following standard formula applied to each time point:

$$(\mathrm{SD_{MOD}})^2 = (\mathrm{SD_{TOTAL}})^2 - (\mathrm{SD_{POOLED}})^2$$

where $(\mathrm{SD_{POOLED}})^2 = [(\mathrm{SD_{F1}})^2 + \cdots + (\mathrm{SD_{F8}})^2]/8$, with $\mathrm{SD_{F1}}$ the standard deviation for the six replicates from the first formulation. Multiple linear regression models for the measured responses and for the fitted Weibull parameters were compared. Principal component analysis and soft independent modeling class analogy were applied for evaluation of effects and classification. The Unscrambler (CAMO A/S, Trondheim, Norway), was used to perform MLR, PCA, and SIMCA.

All models were also validated by full cross-validation, leaving out groups of replicates. Validation by a totally independent test set would have been preferable, but this limitation is not considered detrimental to the conclusions drawn.

RESULTS AND DISCUSSION

Kinetic Models

The use of calculated Weibull parameters is a typical approach for improving solid formulations (11). Statistical regions of the combined parameters μ and β have been presented for similarity evaluation of parameters from new profiles (12). The main advantages of employing fitted parameters are the possibility of attributing the effects of different factors to specific physicochemical-related parameters (e.g., an increase in the factor *C* changes the release mechanism signified by an increase in β). However, the results in Table 1 expose a large variation among the fitted Weibull parameters in this case, indicating that some dissolution profiles are less suited for Weibull adaptation, and thereby limiting the applicability of this method. Relating the Weibull parameters to the formulation parameters by MLR revealed problems with model linearity and hence precision, resulting in correlation coefficients between predicted and measured (*r*) of 0.86 (μ), 0.59 (T_d) and 0.83 (β). In addition, the extra step of modeling Weibull parameters instead of raw data will accumulate extra noise, thereby obscuring the multivariate relations. A possible benefit from physicochemical interpretations of the effects may therefore be lost in the generated noise.

Inherent Independent Response Modeling

As can be seen from Table 2, the prediction error originated from uncertainty in both the replicates

Table 2

Statistical Parameters Describing Formulation, Analytical, and Model Error

Time (min)	Mean *Y*	$\mathrm{SD_{TOTAL}}$	$\mathrm{SD_{POOLED}}$	$\mathrm{SD_{MOD}}$	Corr. Coeff. *r*
5	3.5	0.6	0.5	0.2	0.90
15	7.7	0.9	0.8	0.6	0.95
30	11.1	1.3	1.1	0.8	0.95
60	15.7	2.1	1.5	1.5	0.96
90	19.1	2.4	1.6	1.8	0.97
120	22	2.6	2.0	1.7	0.98
180	26	2.7	2.6	0.9	0.99
300	32.4	3.6	3.6	0.4	0.99

(SD_{POOLED}) and the model (SD_{MOD}). The correlation between measured and model predicted values was found acceptable (0.90–0.99).

By programming the MLR models into a worksheet, the changes in dissolution profiles as a function of various formulations can easily be visualized, see Fig. 1. This approach makes it easy to investigate the absolute effect of formulation and process changes on every part of the dissolution profile. Any local accelerated or delayed release is highlighted by the procedure, improving detailed knowledge about the system. Including confidence limits ($\pm 2SD_{TOTAL}$) indicates whether changes in the formulation significantly affect the dissolution mechanisms. This information may also be used for the development of product quality specifications, describing the acceptable quantitative range of ingredients and production parameters, partially based on the expected variation in the original formulation.

Inherent Dependent Response Modeling

Using entire functions is essential, as mentioned above. Comparing the profile of a new formulation with a suitable confidence interval, such as in Fig. 1, will reveal significant deviating dissolution mechanisms or analytical artefacts. In order to reveal the reasons behind the changes in dissolution, the spreadsheet may be employed for prediction of the deviating profile. However, modeling the relationship between factors and responses frequently displays non-linearities, possibly obscuring effects of the examined factors. This signals the need for other multivariate methods in order to explain the observed changes. One such method is principal component analysis (13). In this case, PCA distributes the profiles as scores describing the multivariate weight of each sample to the corresponding principal component where the score position is dependent on the weight of the time points at the actual PCs (loadings).

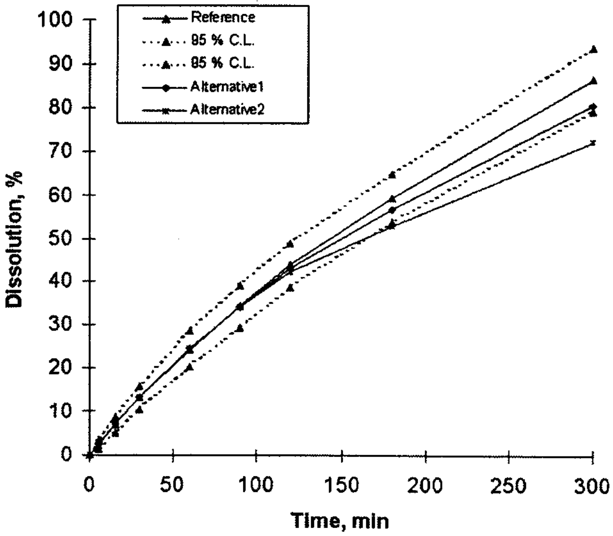

Figure 1. The predicted dissolution profiles with 95% confidence intervals. The dissolution rate is decreased as a function of decreased *C*. The following *A*:*B*:*C* combinations are shown: 2:1:2 (reference), 2:1:1.7, and 2:1:1.3. The latter is significantly different from the reference.

Performing a PCA on the dissolution profiles resulted in a dimensional simplification from eight time points to two latent variables (principal components) explaining 95% of the total variation in data. The score plot classified the profiles in three separated groups, as illustrated in Fig. 2. The location of the formulations in the score plot was directly dependent on the dissolution at the various time points. See Fig. 3 for loadings at the respective principal components. This plot may be employed for identification of important variables. To determine the significance of the formulation factors, MLR may be performed on the two-dimensional score. This approach is called principal component regression (PCR). By PCR the noise in single time measurements is reduced compared to inherent independent MLR modeling (see section on inherent independent response modeling). Further, the scores representing the profile are not required to depend on any kinetic model (see section on kinetic models).

Classification and Significance

Multiple linear regression alone and in combination with PCA introduces noise in the correlation step. To avoid this, a classification method that only takes the dissolution profiles into account will prevent noise generated during regression on *X*. Significant effects of a factor are demonstrated by different levels of a factor being classified into different groups. This classification may be applied to designed variables as well as new unmodeled factors. In order to test the models for variations due to unknown factors, the new heat-exposed formulations were included in the PCA. The time points were standardized before the statistical analysis to

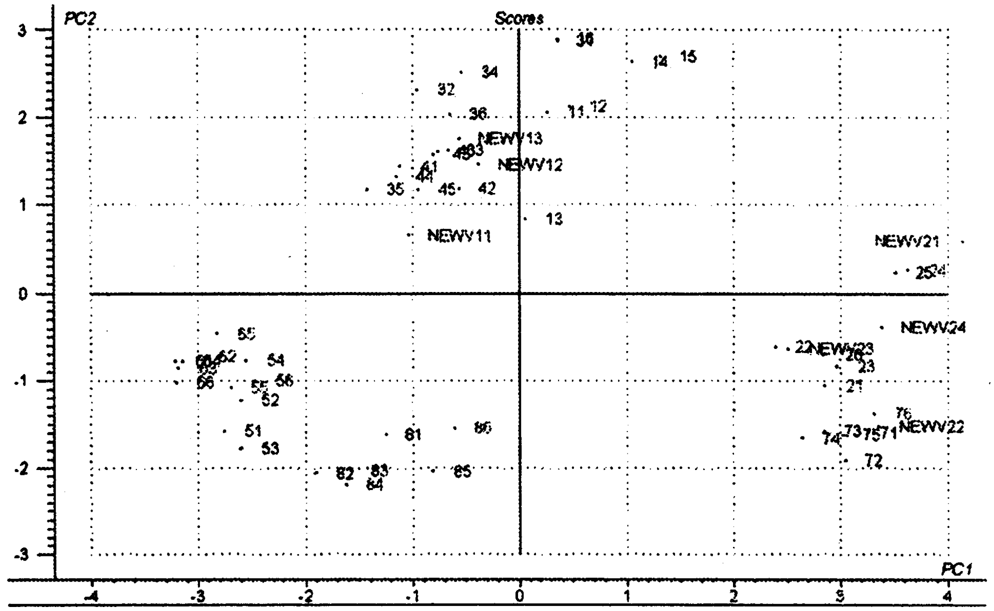

Figure 2. The PCA grouping of scores, each score representing a specific dissolution profile. The two displayed PCs explain 55% and 31%, respectively.

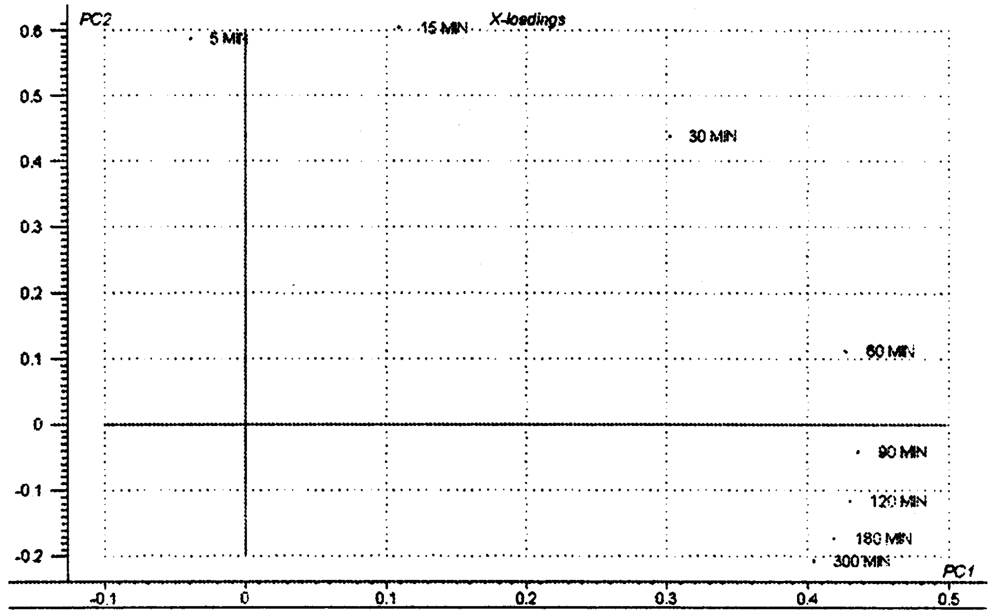

Figure 3. The loadings showed the variables explaining the two PCs. Consequently, a high score on PC1 in Fig. 2 represents a formulation that is highly dissolved at the late time points. The two displayed PCs explain 65% and 31%, respectively.

let each time point have equal influence on the evolving PCA model. The scores for NEWV1*n* were comparable to formulation samples 1*n*, 3*n*, and 4*n*, and NEWV2*n* comparable to 2*n* and 7*n*, as illustrated in Fig. 2. The indicated complex mechanistic relations have been dealt with elsewhere (8). For our purpose, the following question arises: "Are the new formulations equal to the groups they appar-

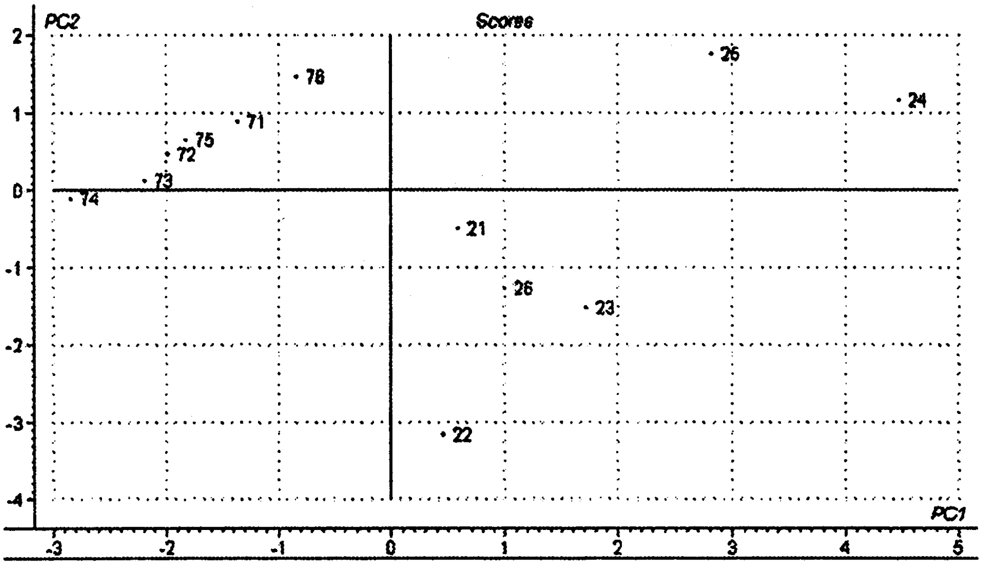

Figure 4. The PCA model constructed for the 2*n* and 7*n* formulations, to be used for SIMCA classification. The two displayed PCs explain 64% and 24%, respectively.

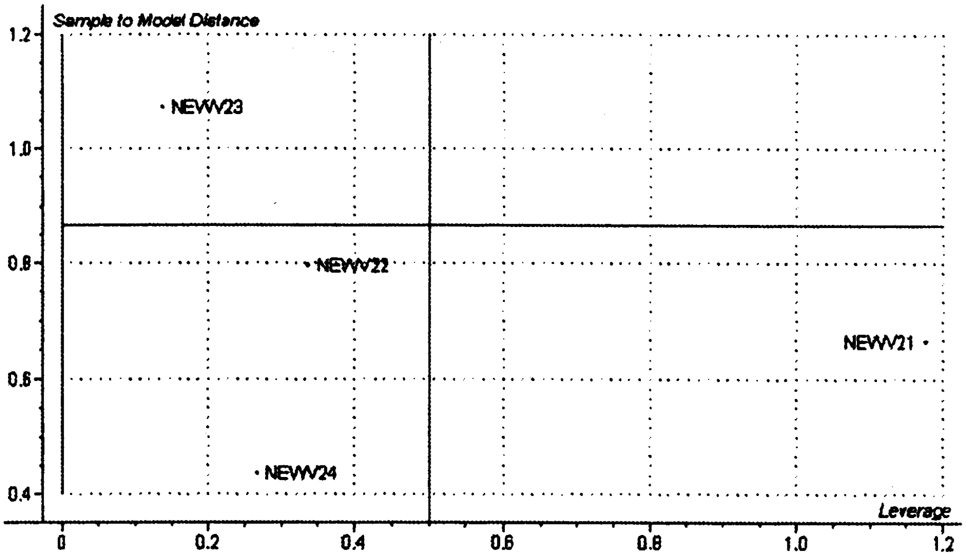

Figure 5. Comparing the NEW formulations with the 2*n* and 7*n* ones by a 99% significance level SIMCA classification. The sample NEWV21 possesses a large distance from the model center (leverage), while NEWV23 was only moderately described by the model due to some deviating time points (residuals).

ently belong to with respect to the entire dissolution profile, or not?" This question corresponds to problems frequently encountered in pharmaceutical production, where changes in excipients or process parameters may or may not lead to unacceptable alterations in, e.g., the dissolution profile. To answer such questions, SIMCA is suggested as a suitable tool. The philosophy behind SIMCA is to make a model describing the systematic variation in the group chosen to be compared with new samples, measure the distance from the model center to the new samples (leverage), and simultaneously take the sample residual into account. In general, there are several advantages in the use of SIMCA. It can be used in cases consisting of few samples compared with the number of variables (as here), a sample can be compared with many classes (a sample can fall within more than one class), it can be used together with many principal component-related methods, and simple software is available.

To test the membership of NEWV1*n* and NEWV2*n*, PCA was performed on 1*n*, 3*n*, 4*n*, and on 2*n*, 7*n*, respectively, resulting in a 3-PC model and a 2-PC model, see Fig. 4. In our context, deviations within these two groups were regarded as acceptable, however, SIMCA might also have been performed on replicates of a single formulation, comparing the new samples with 1*n* and 2*n*, respectively. The optimal number of PCs can be determined by cross-validation or by visual PC inspection and consideration (13,14). The latter was used in this case.

By employing SIMCA on the new formulations, all NEWV1*n* samples were found comparable to the 1*n*, 3*n*, and 4*n* group, while only NEWV22 and NEWV24 were members of their corresponding group. NEWV21 and NEWV23 were found to have too long a distance to the model center and too large a residual, respectively; see Fig. 5 for SIMCA classification. Consequently, the profile of NEWV21 was on average higher compared to the group, while NEWV23 only deviated for some time points (>60 min). This is illustrated by performing PCA on 2*n*, 7*n*, and NEWV2*n*.

The SIMCA test was based on a 99% significance level in this case. The significance level should be chosen individually based on product knowledge and the acceptable product variation.

CONCLUSION

Determination of the significance from investigated *X*-variables on multivariate kinetic profiles is often unclear due to their various influences on various parts of the profile. The understanding is further blurred by noise added from instrumental single measurements and modeling non-linear relationships. Hence, it is reasonable to evaluate the effect of a formulation variable on the entire profile. Direct multivariate regression of dissolution data was shown to be a useful method for modeling and illustrating the changes in the whole dissolution profiles as a function of formulation variables. Fitting of the Weibull equation to the dissolution data was somewhat tedious, it did not provide any additional information, and resulted in poorer models for the current dataset. The selection of kinetic model is crucial in finding the significant formulation variables.

The use of PCA/PCR reduces the influence of noise from single measurements in a kinetic profile and develops statistical parameters representing the profile without being dependent on a physicochemical modeled profile. The combination of PCA and SIMCA was found to be well suited for classification based on the entire profile, and hence able to determine significant formulation variables, reducing the influence of noise from poor modeling.

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