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ON THE ANALYSIS OF DISSOLUTION DATA

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ABSTRACT

Dissolution profiles for solid dose forms represent several observations over time on an experimental unit such as a tablet or capsule. The pharmaceutical scientist is interested in a (statistical) comparison of these profiles under a variety of conditions relating to formulation characteristics, and lot-to-lot and brand-to-brand variation.

This paper discusses the analysis of dissolution profiles using an analysis of variance approach. In particular, the profiles are tested for differences in level and shape. The latter characteristic is potentially important with respect to learning about differences in the dissolution mechanism.

An approximate F test is discussed with the possibility of an arbitrary covariance matrix in mind, and alternative conservative analysis methods are presented.

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Results from the analysis of variance of typical dissolution data show several important features. First, the analysis does not rely on curve fitting procedures and the data are used in their native form or as a simple transform. Second, the data can be analyzed using the fraction dissolved and/or the time for a particular fraction to dissolve, e.g., $t_{50\%}$, as the variable of interest. Finally, the analysis is capable of showing differences between profiles where a realistic variation from profile-to-profile exists.

INTRODUCTION

Dissolution profiles for solid dose forms are developed in connection with observations taken on a given experimental unit, such as a tablet or capsule, over time. The pharmaceutical scientist is interested in a comparison of these profiles under different conditions related to formulation factors, and lot-to-lot and brand-to-brand variation. Modeling is usually not the problem of primary interest in the analysis.

Comparison of profiles representing a cumulative event over time is not unique to the pharmaceutical sciences. Wishart's[1] early work was involved with the comparison of growth curves, where each individual growth curve classified by experimental condition was fitted via least squares with a polynomial over time. The coefficients of the polynomial represent the salient features of n observations on each curve (profile), and can be directly analyzed to compare the profiles.

Wishart's work points to a main question related to the specific problem of comparing dissolution profiles. How can the profiles be efficiently and adequately represented in order to provide a basis for a comparison which appreciates the significant differences between profiles for each experimental condition? A method due to Langenbucher[2] uses the Weibull function to fit the dissolution curves. This treatment leads to a set of parameters related to scale, location, and shape. Alternatively, some official dissolution tests rely on a single point on the dissolution profile, designated as the amount dissolved in a certain period.

Langenbucher's method provides an approach which yields parameters which adequately represent the profile, and provide a basis for analyzing the differences between curves using the parameters themselves. A possible disadvantage is the curve fitting process which this method requires. The approach relying on the amount dissolved in a certain time period, e.g., $t_{50\%}$, is expedient but may not adequately represent the curve. Therefore, an analysis which uses this parameter to determine differences between profiles is weakened.

The purpose of this paper is to demonstrate how a particular method of analyzing dissolution data in terms of curve shape and level can be applied to dissolution profiles. Quantitative profile analysis involving curve shape and level uses the data in its native form or as a simple transformation.

All, or a majority, of the data are included in the analysis scheme and a curve fitting process is not necessary.

THE PROBLEM

Snee[3] has observed that "It is not uncommon for a scientist to make several observations on a given experimental unit. If these observations can be associated with some continuous variable, such as time or temperature, they collectively form a curve." Such is the case for the dissolution profiles of solid dosage forms where amount or weight fraction dissolved is followed as a function of time.

Using the notation of Greenhouse and Geisser[4] this situation can be represented by letting p experimental observations be made on each of n_K individual testing units, i.e., tablet, capsule, etc., (K = 1,2,....,g) in each of the g established groups, i.e., manufacturers, lots, etc. Assume that the p observations are made with respect to a fixed variable, that the g groups are fixed, and that the n_K individuals are random. Then, the appropriate model for testing certain characteristics of the dissolution profiles is a mixed one. The matrix of observations is shown in Table 1, where rows are random and the columns are considered to be fixed. For dissolution curves each row represents a sample of observations which collectively form an individual dissolution profile, or an appropriate transform thereof, for each randomly chosen dosage (testing) units, i.e., tablet or capsule. The rows collectively

Table 1 - Data Matrix

Group	Individual Units	X_1	X_j	X_{1p1}	
1	1	X_{111}	X_{1j1}	X_{1p1}	$\bar{X}_{1.1}$
	.				
	.				
	n_1	$X_{n_1\,11}$	$X_{n_1\,j1}$	$X_{n_1\,p1}$	$\bar{X}_{n_1\,.1}$
Means:	Group 1	$\bar{X}_{.11}$	$\bar{X}_{.j1}$	$\bar{X}_{.p1}$	$\bar{X}_{..1}$
	.				
	.				
g	1	X_{11g}	X_{1jg}	X_{1pg}	$\bar{X}_{1.g}$
	.				
	.				
	n_g	$X_{n_g 1g}$	$X_{n_g jg}$	$X_{n_g pg}$	$\bar{X}_{n_g .g}$
Means:	Group g	$\bar{X}_{.1g}$	$\bar{X}_{.jg}$	$\bar{X}_{.pg}$	$\bar{X}_{..g}$
Means:	All Groups	$\bar{X}_{.1.}$	$\bar{X}_{.j.}$	$\bar{X}_{.p.}$	$\bar{X}_{...}$

Note - $N = \sum_{k=1}^{g} n_k$

form groups and each group might be the manufacturer or lot. The columns are fixed with respect to the variable of interest. Commonly the variable is time and the unit observed or measured (the x's in Table 1) is concentration or percent dissolved (herein referred to as Case 1).

Another popular method of presenting dissolution data is in terms of the time, T, it takes for a particular percentage to dissolve, e.g., $t_{50\%}$. In this instance (herein referred to as Case 2) the column variables become $t_{20\%}$, $t_{40\%}$, etc. and the unit measured or observed (the x's in Table 1) is the amount of time, T, it takes for a specific percent of the dosage unit to dissolve.

For either Case 1 or Case 2, two questions concerning the dissolution profiles of the samples may be asked:

1) Are the population mean profiles similar in the sense of being parallel?, i.e., are the shapes of the profiles similar?
2) Are the dissolution profiles at the same level?

The first question seeks to answer whether or not the group profiles have the same shape. In other words, is distance, d, between $\bar{X}_{\cdot 11}, \bar{X}_{\cdot 12}$; $\bar{X}_{\cdot 21}, \bar{X}_{\cdot 22}$; and $\bar{X}_{\cdot p1}, \bar{X}_{\cdot p2}$ constant? The second question seeks answers as to the equality between the group means. Specifically, does $E(\bar{x}..1)=E(\bar{x}..2)=...=E(\bar{x}..g)$.

Dissolution Profiles (Case 1) - Concentration Versus Time

Box[5] has considered a data transformation which is useful in connection with the questions of parallelism and level for the curves in figure 1. Each dissolution profile for an individual tablet or capsule in a replicate series can be considered in terms of first difference, C, of the amount dissolved, c, at time t where

$C_1 = c_1 - c_0$ (time = 0 to time = 1),

$C_2 = c_2 - c_1$ (time = 1 to time = 2), etc.,

where time intervals are considered equal. The average amount dissolved per time interval, p, is given by

$$\bar{C} = \left(\sum_{j=1}^{p} C_j\right)/p \qquad (1)$$

and the total amount dissolved in p time intervals is $p \cdot \bar{C}$. Now, Table 1 takes form in terms of C's where $C_{111} = X_{111}$, $C_{1j1} = X_{1j1}, \ldots, C_{1p1} = X_{1p1}$. Each row represents the dissolution profile, in terms of first differences, for a single tablet or capsule. Each row mean, e.g. $\bar{C}_{1.1}$, is calculated from equation 1 and represents the average amount dissolved per time interval for a single tablet or capsule (individual testing unit) within a particular lot or manufacturer (group). Each column mean, e.g. $\bar{C}_{.11}$, is the mean of the replicate first differences of the amount dissolved in that particular individual interval, and $\bar{C}_{..1}$ is the group mean.

We now turn to the question of equality of levels for the curves shown in Figure 1. The test for level depends on a comparison between group means, e.g. $\bar{C}_{..1}$ and $\bar{C}_{..2}$ ($\bar{X}_{..1}$ and $\bar{X}_{..2}$ from Table 1). The group means are calculated from the row means via

$$\bar{C}_{..1} = (\bar{C}_{1.1} + \bar{C}_{2.1} + \ldots + \bar{C}_{n1.1})/nj \qquad (2)$$

Therefore, the test for level compares the grand means for the row means in each group.

We may visualize typical dissolution curves shown here in figure 1.

The test for parallelism for the curves in figure 1 is made by comparing the distance, d, between the column means $\bar{C}_{.11}$, $\bar{C}_{.12}$; $\bar{C}_{.21}$, $\bar{C}_{.22}$; and $\bar{C}_{.p1}$, $\bar{C}_{.p2}$. It is evident that the parallelism test compares the means for the replicate first differences of the concentration dissolved in that particular time interval. In other words, if the dissolution curves in terms of the first difference transform are parallel then the distance between the column means should be equal.

Dissolution Profiles (Case 2) - Time for ln T Versus $t_{\%}$

For the Case 2 profiles we are interested in the dissolution curves in terms of the times, T, that it takes for a particular concentration to dissolve, i.e., $t_{20\%}$, $t_{40\%}$, etc. In order to understand shape features of dissolution curves in terms of times we turn to the concept of time scaling due to Pedersen and Brown[6]. According to this concept, two dissolution

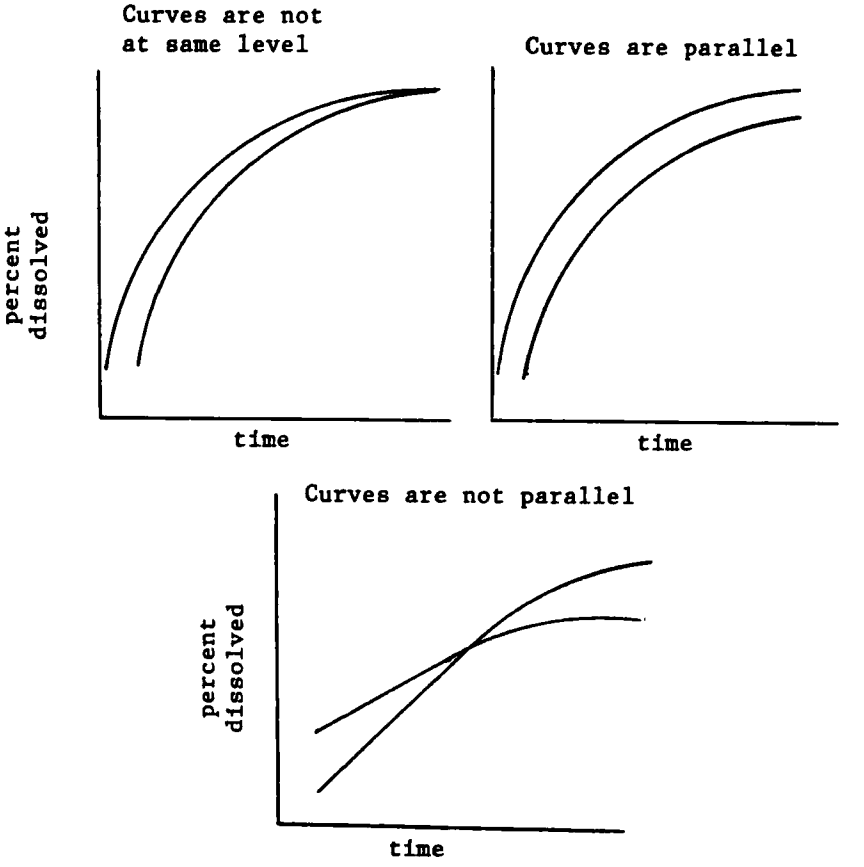

FIGURE 1

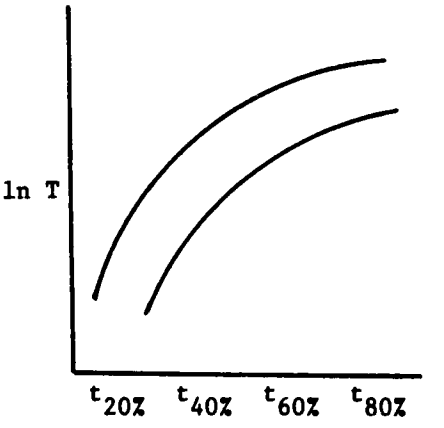

FIGURE 2

curves having the same intrinsic dissolution profile can be brought onto each other by a time scaling factor. This scaling factor is a constant over time and represents a ratio of times for a corresponding amount to dissolve for each profile. That is, the scaling factor is simply the ratio of the times for $t_{20\%}$, 40%, etc. for each curve. The logarithm of a constant ratio is in fact a difference which is constant itself. Therefore, a logarithmic transformation of the time, T, for $t_{20\%}$, $t_{40\%}$, etc. is a simple transformation which allows us to test for parallel curves in the sense of the time scaling factor.

For data analysis in the Case 2 sense Table 1 takes form in terms of ln T's where $\ln T_{111} = X_{111}$, $\ln T_{1j1} = X_{1j1}$,....., $\ln T_{1p1} = X_{1p1}$. Each row represents the dissolution profile, in terms of the logarithmic transform of T, for a single tablet or capsule. Each row mean, e.g. $\overline{\ln T_{1.1}}$, is calculated from

$$\overline{\ln T} = \left(\sum_{j=1}^{p} \ln T_j\right)/p \qquad (3)$$

and the group mean, e.g. $\overline{\ln T_{..1}}$ is calculated from

$$\overline{\ln T}_{..1} = (\overline{\ln T}_{1.1} + \overline{\ln T}_{2.1} + \ldots + \overline{\ln T}_{n1.1})/n_1 \qquad (4).$$

The logarithmic time average in equation 3 has less intuitive meaning than the average amount dissolved per interval which is calculated from equation 1. If we were to "sample" the curves in figure 1 we would do so by locating, say, the 20% amount

dissolved on the y axis and find the corresponding time for the 20% value on the x axis. This process would be repeated for each percent dissolved of interest. Following the logarithmic transformation of each T we would calculate an average ln T according to equation 3. Roughly speaking ln T is a "random" variable and $\overline{\ln T}$ is the average for this population. This average is more meaningful than the commonly used $t_{50\%}$ since it embodies a collective appreciation of the profile (Note the sum sign in equation 3), whereas $t_{50\%}$ represents the profile with but a single point.

The tests for level and parallelism in the Case 2 sense are similar to those in the Case 1 sense. The test for level depends on a comparison between groups means, e.g. $\overline{\ln T}_{..1}$ and $\overline{\ln T}_{..2}$ ($\bar{X}_{..1}$ and $\bar{X}_{..2}$ from Table 1), and the test for parallelism depends on a comparison of the distance, d, between the column means, say $\overline{\ln T}_{.11}$, $\overline{\ln T}_{.12}$; $\overline{\ln T}_{.21}$, $\overline{\ln T}_{.22}$; and $\overline{\ln T}_{.p1}$, $\overline{\ln T}_{.p2}$.

THE STATISTICAL ANALYSIS

In order to realistically test for curve shapes and level in either the Case 1 or the Case 2 sense, we must be able to analyze the data with an appropriate test statistic; in this case the F statistic. Greenhouse and Geisser[4] have already discussed classical analysis of variance tests for mixed models which apply to dissolution profiles. The analysis of variance

is shown in Table 2 with the sum of squares, degrees of freedom and F's. The tests refer to time intervals in Case 1 and to $t_{20\%}$, $t_{40\%}$, etc. in Case 2 and groups refer to manufacturer or lot, etc. The statistics F_2 and F_3 are used to test hypotheses of group means (levels) and the non-existance of group-test interaction (parallelism or curve shape), respectively. One further statistic, F_1, may be used to test a hypothesis of homogeneity of test means. Test statistics F_2 and F_3 are probably of greatest interest to the present application. Note that the data transforms for Case 1 and Case 2 analysis of dissolution profiles are exactly in keeping with the data matrix in Table 1 and the analysis of variance in Table 2. It should also be noted that, except for the transforms, the data set is much more completely used in its native form when compared with an analysis which relies on some univariate characteristic of the profile (e.g. $t_{50\%}$). Finally, two univariate characteristics or indices, the average amount dissolved per unit time and the average logarithm of times, are available as a natural by-product of the calculation procedure in Table 2.

ASSUMPTIONS ABOUT THE ANALYSIS OF VARIANCE

Box[5] and Greenhouse and Geisser[4] have discussed restrictions related to ANOVA when it is used to analyze data which are, of the multivariate type; the case at hand. Greenhouse and Geisser observed that the classical ANOVA

Table 2

Analysis of Variance

Source	D.F.	Sum of Squares	F
Tests	p-1	$Q_1 = N\sum_{j=1}^{p} (\bar{x}_{.j.} - \bar{x}_{...})^2$	$F_1 = (N-g)\frac{Q_1}{Q_5}$
Groups	g-1	$Q_2 = p\sum_{k=1}^{g} n_k(\bar{x}_{..k} - \bar{x}_{...})^2$	$F_2 = \frac{(N-g)\ Q_2}{(g-1)\ Q_3}$
Individuals (within Groups)	N-g	$Q_3 = p\sum_{k=1}^{g}\sum_{i=1}^{n_k} (\bar{x}_{i.k} - \bar{x}_{..k})^2$	
Group x Tests	(p-1)(g-1)	$Q_4 = \sum_{k=1}^{g}\sum_{j=1}^{p} n_k(\bar{x}_{.jk} - \bar{x}_{.j.} - \bar{x}_{..k} + \bar{x}_{...})^2$	$F_3 = \frac{(N-g)\ Q_4}{(g-1)\ Q_5}$
Indiv. x Tests (within Groups)	(p-1)(N-g)	$Q_5 = \sum_{k=1}^{g}\sum_{i=1}^{n_k}\sum_{j=1}^{p} (x_{ijk} - \bar{x}_{.jk} - \bar{x}_{i.k} - \bar{x}_{..k})^2$	
Total	Np-1	$Q_6 = \sum\sum\sum_{kij} (x_{ijk} - \bar{x}_{...})^2$	

approach is only valid when the variance-covariance matrix is of the special form

$$\underset{\rho x \rho}{\Sigma^*} = \sigma^2 \begin{bmatrix} 1 & \rho & . & . & . & \rho \\ \rho & 1 & . & . & . & \rho \\ . & . & . & . & . & \rho \\ \rho & \rho & . & . & . & 1 \end{bmatrix}$$

where ρ is the correlation between any two elements in the same vector. Box showed that a first difference transformation of data correlated over time was paritally successful in forming the above matrix. For cumulative dissolution data the form of the variance-covariance matrix is rarely subjected to tests of the hypothesis $\Sigma = \Sigma^*$, or is consideration given to the consequences of analyzing data where Σ is arbitrary. In the event that the matrix is of the proper form then F_1, F_2, and F_3 from Table 2 are free of restrictions and the ANOVA follows the normal approach. When Σ is arbitrary, however, the F_1 and F_3 are not distributed like the tabulated F distribution. Cole and Grizzle[6] have mentioned that F_2 does not change when Σ is not uniform.

Greenhouse and Geisser have found an approximate sampling distributions for F_1 and F_3 which depend on the elements of the population variance-covariance matrix. Since this is rarely known, one must use the sample variance-covariance matrix, with unknown consequences.

Alternatively, Greenhouse and Geisser show that the lower bound for correcting F_1 and F_3 is independent of the elements of the variance-covariance matrix. The alternative procedure is a conservative one which gives the maximum reduction in degrees of freedom for F_1 and F_3. With this plan the significance of F_1 and F_3 is judged by entering the standard F tables with 1 and (N-g) d.f. and (g-1) and (N-g) d.f., respectively. The next section will show how this conservative test can be applied to dissolution data, and compared with the standard ANOVA.

The preceding discussion applies to the pooled matrix obtained by averaging corresponding entries in the individual matrices. Rejection of the hypothesis that the multivariate normal populations have equal covariance matrices rules against pooling since the pooled matrix is no longer an unbiased estimate of Σ. The test statistic to detect changes in the variance-covariance pattern from group to group is discussed by Box.

RESULTS AND DISCUSSION

An immediate purpose of this study was to conduct an analysis of dissolution data with known characteristics in order to demonstrate the use and limitations of the analysis outlined in Table 2. Two dissolution profiles, A and B, were generated using the following models:

$$A_d = 1 - ((10 - 2 * t)^3/10^3)$$

and

$$B_d = 1 - ((10 - 1 * t)^3/10^3).$$

Random samples were taken from both deterministic models at particular times, t, and these data are shown below in Table 3. The random values were generated according to

$$A = A_d\,(1 + (R - 0.5)\,\frac{2E}{100})$$

or

$$B = B_d\,(1 + (R - 0.5)\,\frac{2E}{100}).$$

where A_d or B_d are the deterministic values, R is a random number drawn from a rectangular distribution, E is the maximum percent error, and A or B are the randomized values. The value chosen for E was 10.

The first difference transform for these data yield the data shown in Table 4.

The first difference data (Case 1) were analyzed and a summary of the analysis of variance is given in Table 5.

The analysis shows that the observed test statistic for level, F_2, leads to rejection of the hypothesis of homogeneity of group means. The observed value for F_3 leads to a similar conclusion, and one concludes that the mean profiles differ in shape from group to group.

A closer examination of the data will show the meaningful characteristics of this analysis. Curve set 1 of figure 1 is an approximate outline of the population (deterministic) profiles for models A and B, and it can be seen that curve A reaches a plateau much earlier than curve B. Therefore, the average

TABLE 3

Dissolution Data for Models A and B

Group	Individual	t = 1	t = 2	t = 3	t = 4
A	1	.509	.822	.942	1.05
	2	.456	.826	.928	.973
	3	.444	.757	.867	.921
B	4	.272	.536	.736	.751
	5	.293	.486	.674	.774
	6	.247	.457	.726	.770

TABLE 4

First Difference Transform of Dissolution Data

Group	Individual	$\Delta t1^*$	$\Delta t2$	$\Delta t3$	$\Delta t4$
A	1	.509	.313	.120	.108
	2	.456	.370	.102	.045
	3	.444	.313	.110	.054
B	4	.272	.264	.200	.015
	5	.293	.193	.188	.100
	6	.247	.210	.269	.044

*each Δt represents a time interval of 1

TABLE 5

ANOVA Table for First Difference Data

Analysis of Variance				
Source	d.f.	SS	F	PR > F
Time Intervals	3	.32479		
Groups	1	.017550	$F_2 = 32.18$	0.0048
Individuals within Groups	4	.00218167		
Groups x Time Intervals	3	.077880	$F_3 = 19.20$	0.0001
Individuals x Time Intervals within Groups	12	.016227		

amount dissolved per time interval, i.e., the level, is greater for curve A when compared with curve B. This conclusion is in keeping with the observed test statistic for level from the analysis of variance.

The shape of the curves shown in curve set 1 of figure 1 suggests that they are not parallel. First difference transformation of the data does not alter this characteristic. The analysis of variance confirms the difference in shape between curves A and B via the probability associated with F_3.

The analysis of the data for models A and B were next analyzed in terms of the time, T, for a particular amount of drug to dissolve. A randomization method identical to that used for the first difference data was employed, and the random samples were transformed to ln T. Note that the matrix of observations given in Table 6 is given in terms of the natural logarithm of the time, T, it takes for a particular percentage to dissolve.

The ln T data (Case 2) were analyzed and a summary of the analysis of variance is given in Table 7.

In order to interpret the data from the analysis of variance table it is useful to refer to figure 2. This graphical presentation of data closely approximates the deterministic ln T profiles for models A and B. Notice that the ln T values for model A are consistently higher than those for model B. Therefore, it is not surprising that the test for

TABLE 6

ln T Transform of Dissolution Data

Group	Individual	$t_{20\%}$	$t_{40\%}$	$t_{60\%}$	$t_{80\%}$
A	1	-1.10	-.290	.207	.642
	2	-1.08	-.163	.300	.678
	3	-1.10	-.224	.278	.779
B	4	-.238	.525	.978	1.48
	5	-.361	.470	.900	1.47
	6	-.252	.392	.892	1.41

TABLE 7

ANOVA Table for ln T Data

Analysis of Variance				
Source	d.f.	SS	F	PR > F
Time Intervals	3	10.18		
Groups	1	3.182	$F_2 = 484.6$	0.0001
Individuals within Groups	4	.02627		
Groups x Time Intervals	3	.01999	$F_3 = 3.59$	0.0464
Individuals x Time Intervals within Groups	12	.02227		

level rejects the hypothesis concerning homogeneity of group means (level).

Profiles A and B in curve set 1 of figure 2 are parallel. The mathematical models representing A and B only differ by a constant factor of 2, and the concept of time scaling is evidenced in these profiles since each curve is displaced from the other by a constant distance. We now turn to the analysis of variance table in order to determine if the test statistic for shape, F_3, leads to a similar conclusion about the parallelism between profile A and B.

In fact, the observed value for F_3 is such that

$$.05 > P(F_3(3,12) > 3.59) > .025$$

with

$$P(F_3(3,12) > 3.59) = 0.0464.$$

Thus, the decision to reject or accept the hypothesis will depend upon the level of significance chosen and certain fundamental assumptions regarding the validity of the test statistic.

The question of parallelism in the Case 2 sense is of interest to pursue since the test statistic for shape will contradict the null hypothesis at the .05 level of significance when it is known that models A and B are in fact parallel. This apparent contradiction is related to the variability of the data. When E, the maximum error, in the error recipe is reduced

from 10 to 5, the resulting data matrix, when analyzed for shape, yields

$$P\ (F_3\ (3,12) > 1.43) = .283.$$

Now, we can easily accept the hypothesis of no interaction and conclude that the mean profiles do not differ in shape from group to group.

The form of the covariance-variance matrix is another consideration related to the acceptance or rejection of the null hypothesis concerning profile shape. For dissolution experiments, where a cumulative event is observed over time, we expect the observations that are adjacent to be more highly correlated than more distant measurements. With this in mind, it is of interest to analyze the observed F_3 statistic for the ln T data again. This time, however, we will use the conservative test suggested by Greenhouse and Geisser where

$$P\ (F_3\ (1,4) > 3.59) = .131$$

and the null hypothesis is easily accepted.

The particular example at hand points to potential problems in the data analysis scheme. However, a fundamental characteristic remains and is important to keep in mind. This characteristic relates to an interest in the shapes of the profiles and an interest in comparing the underlying (mathematical) models for the dissolution profiles. The worked example has shown that the ln T transform rather than the first difference data transform is of particular interest when

comparing profiles which are driven by the same model and only differ by a time scaling factor.

As mentioned at the outset, mathematical modeling is not the primary interest of the pharmaceutical scientist who wishes to determine significant characteristics of likeness or difference between dissolution profiles. However, proof of similar shape via the test for parallelism does in fact suggest that an undeterminded underlying model is operating over time. Equally important is the suggestion that manufacturing characteristics from lot-to-lot or brand-to-brand for a tablet or capsule lead to a similar dissolution process. This is a much more powerful interpretation than the more commonly used approach where decisions regarding similarity are reached by comparing the $t_{50\%}$ values.

SUMMARY

A particular analysis of variance approach has been applied to dissolution profiles. The level and shape are characteristics of the profiles which are tested. Profile shape is suggested as being a particularly important characteristic since it appreciates the process over time, and implies whether or not different formulations are dissolving according to similar dissolution mechanisms.

The calculation procedure for the analysis is simple enough to be carried out using a hand held calculator. However, certain assumptions regarding the variance-covariance matrix

make the procedure somewhat restrictive. This restriction can be relaxed (though not eliminated) by applying a conservative test.

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APPENDIX

The data from Table 4 are analyzed[1] to illustrate the computational procedure associated with Table 1.

Group g=2	Individual	p=4 Δt1	Δt2	Δt3	Δt4	Total	
	1	.509	.313	.120	.108	1.05	
A	2	.456	.370	.102	.045	.973	
	3	.444	.313	.110	.054	.921	
Total		1.409	.996	.332	.207	2.944	$N_A=3$
	4	.272	.264	.200	.015	.751	
B	5	.293	.193	.188	.100	.774	
	6	.247	.210	.269	.044	.770	
Total		.812	.667	.657	.159	2.295	$N_B=3$
Grand Total		2.221	1.663	.989	.366	5.239	N=6

$$Q1 = \underset{N}{1/6}\,[2.221^2 + 1.663^2 + .989^2 + .366^2] - [5.239^2/(6)(4)]$$
$$= .32479 \qquad N \quad p$$

$$Q2 = \underset{p}{1/4}\,[2.994^2/3 + 2.295^2/3] - [5.239^2/(6)(4)]$$
$$= .017550 \qquad N_A \qquad N_B$$

$$Q3 = \underset{p}{1/4}\,[1.05^2 + ... + .770^2] - \underset{p}{1/4}\,[(2.944^2/3) + (2.295^2/3)]$$
$$= .0021817 \qquad N_A \qquad N_B$$

[1]This computational procedure is consistent with Table 1 and is discussed by D. Morrison, "Multivariate Statistical Methods", 2nd. edition, McGraw-Hill, New York, 1976, p. 213.

$$Q4 = \underset{N_A}{[1.409^2 + ... + .207^2]/3} + \underset{N_B}{[.812^2 + ... + .159^2]/3} - [5.239^2/(6)(4)] - Q1 - Q2$$
$$= .077880$$

$$Q5 = Q6 - Q1 - Q2 - Q3 - Q4$$
$$= .016227$$

$$Q6 = [.509^2 + ... + .044^2] - [5.239^2/(6)(4)]$$
$$= .43863$$

The test statistic for level is

$$F2 = \frac{(N-g)\ Q2}{(g-1)\ Q3} = \frac{(6-2)\ (.017550)}{(2-1)\ (.0021817)} = 32.18$$

with (g-1) = 1 and (N-g) = 4 degrees of freedom.

The test statistic for parallelism is

$$F3 = \frac{(N-g)\ Q4}{(g-1)\ Q5} = \frac{(6-2)\ (.077880)}{(2-1)\ (.016227)} = 19.20$$

with (p-1)(g-1) = (4-1)(2-1) = 3 and (p-1)(N-g) = (4-1)(6-4) = 12 degrees of freedom. For a conservative test with maximum reduction of degrees of freedom use (g-1) = (2-1) = 1 and (N-g) = 4.