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STATISTICAL COMPARISON OF THE DISSOLUTION CURVES OF CONTROLLED-RELEASE SOLID ORAL DOSAGE FORMS

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ABSTRACT

This paper shows how the Box method, based on the statistical technique known as "split-plot" in general use for replicate measurements, may be used to quantify and compare in vitro dissolution curves of controlled release solid oral dosage forms. In this case, it is applied to the interpretation of the findings of a stability test on controlled-released lithium tablets formulated with a wax matrix and containing 10.8 mEq lithium per tablet. The findings showed that the total amount of lithium dissolved after the tablets had been stored for a period of six months was slightly greater than before storage; the dissolution mean rate went from 1.06 mEq/h to 1.17 mEq/h and the dissolution rate curve profile apparently registered less variation.

The method described here for the comparison of dissolution curves is particularly useful when the curves do not follow a set kinetic process and has proved sensitive to slight changes in the dissolution profile.

INTRODUCTION

Controlled-release solid oral dosage forms often have complex dissolution profiles which make them hard to interpret using kinetic models so that it is as well to have independent model methods to hand by which to quantify and compare in vitro dissolution curves.

The three types of apparatus suggested by USP [1] are closed, (there is no way for the dissolved drug to get out of the system), so that the curve of the dissolved drug is cumulative; statistical interpretation of this type of curve must take into account the possible correlation of the errors and the, at times, high number of points determining the curve, and well-known statistical methods such as the analysis of growth curves [2] must be applied. This paper shows how the Box method [3] may be used for this purpose; in this case, it is applied to the interpretation of the findings of a stability test of controlled-release lithium tablets.

STATISTICAL MODEL

The Box method is based on the statistical technique known as "split-plot" in general use for replicate measurements. In this case, from the cumulative dissolution curve defined by the points X_1, X_2....X_m (see Fig.

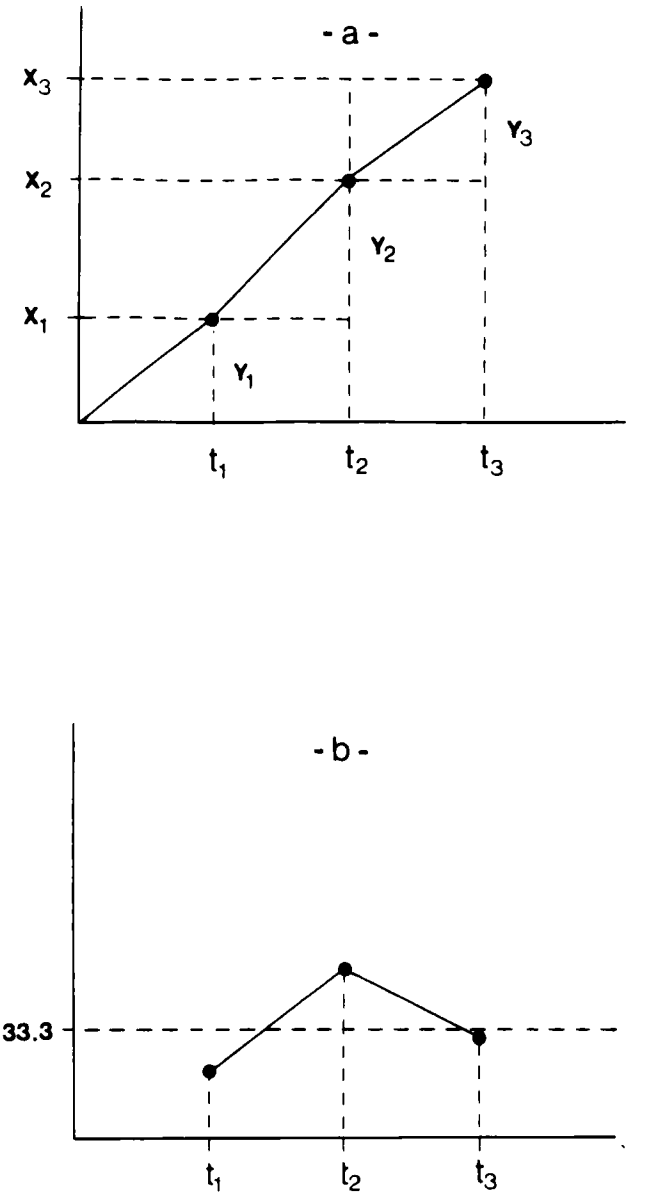

FIGURE 1

Cumulative dissolution curve (a) and derivation of dissolution rate curve (b).

1-a), a dissolution rate curve was constructed, defined by points Y_1, Y_2....Y_m (see Fig. 1-b) where $Y_i=(Y_i-Y_{i-1})/(t_i-t_{i-1})$. The mean dissolution rate, $\bar{Y}$, is calculated by the expression Y_i/m and equals the total of dissolved drug divided by the duration of the test and is thus independent of the dissolution curve profile. When two formulations are compared one of the following cases will occur (see Fig. 2): 1) both formulations show similar mean rates and dissolution profiles (Fig. 2-a); 2) the formulations differ only in the mean dissolution rates, with similar profiles (Fig. 2-b), ie, the dissolution rate is reduced in the same proportion in the various periods; 3) the mean dissolution rate is similar but the dissolution profiles differ (Fig. 2-c); 4) the formulations are different both in mean dissolution rate and dissolution rate curve profiles. The ANOVA statistical model for repeated measurements is the basis of the Box method, and is as follows:

$$X_{ijk}=\mu+\alpha_i+\pi_{k(i)}+\beta_j+\alpha\beta_{ij}+\beta\pi_{jk(i)}+\varepsilon_{m(ijk)} \qquad \text{Eq. (1)}$$

where α_i and β_j represent the effects of the formulation and the period taken, respectively; $\pi_{k(i)}$ is the effect of the Kth unit of the i formulation under study; the terms $\alpha\beta_{ij}$ y $\beta\pi_{jk(i)}$ correspond to the interactions "formulation by period" and "unit within formulation by period". If the formulation and period factors are assumed to be fixed and that of the unit tested aleatory, the mean squares expected for the source of each variation take the forms set out in Table I. There are two error

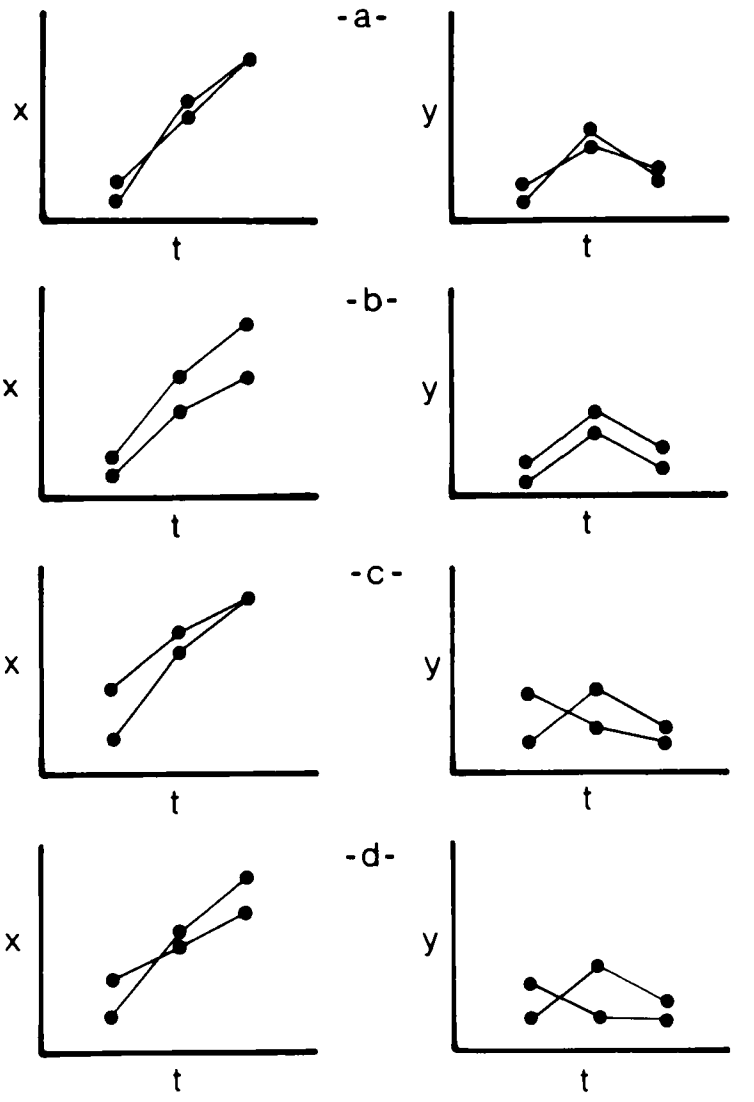

FIGURE 2

Possible cases when two formulations are compared

TABLE I

Expected Values of Mean Squares for "Split-plot" Design

Source of variation	Expected value of mean square
Formulation	$\sigma^2_\varepsilon + q\sigma^2_\pi + nq\sigma^2_\alpha$
Units within formulation	$\sigma^2_\varepsilon + q\sigma^2_\pi$
Period	$\sigma^2_\varepsilon + \sigma^2_{\beta\pi} + np\sigma^2_\beta$
Formulation by period	$\sigma^2_\varepsilon + \sigma^2_{\beta\pi} + n\sigma^2_{\alpha\beta}$
Units within formulation by period	$\sigma^2_\varepsilon + \sigma^2_{\beta\pi}$

p=number of tested formulations; n=number of units tested for each formulation; q=number of periods.

terms ("split-plot"): 1) "units within formulation" which monitors the effect of the formulations and 2) "interaction units within formulation by period" comparing the effect of the term "period" with "interaction formulation by period".

The Box method, as he enuciated it, also requires: homogeneity of the variance-covariance matrix for the different treatments and that all the elements of the diagonal on one side and the elements outside it on the other, of the combined variance-covariance matrix should be equal among themselves. This requirement may be checked by the Sheffé test for variance homogeneity [4] as reported by Greenhouse and Geisser [5]; if it is not met, these authors suggest the reduction of the degrees

of freedom of the terms "period", "formulation by period" and "period by units within formulation", multiplied by the factor:

$$\epsilon = \frac{q^2(\bar{v}_{ij} - \bar{\bar{v}})^2}{(q-1)(\sum\sum v_{jk}^2 - 2q\sum \bar{v}_j^2 + q^2\bar{\bar{v}}^2)} \qquad \text{Eq.(2)}$$

where $\bar{\bar{v}}$ is the mean value of all the elements of the combined variance-covariance matrix, V, $\bar{v}_{ij}$ the mean value of the diagonal and $\bar{v}_j$ the mean value of the row j.

Winer [6] details how the calculations should be made. We used the programme written by Davidson and Toporek [7] for uni-and multivariant analysis of the variance. In this programme ANOVA can be obtained from replicate measurements in the terms described and also from a multivariant approximation.

To interpret the ANOVA results the following must be taken into account: 1) if the null hypothesis for the effect "formulation" is valid, the mean dissolution rate must be the same for all the formulations tested; 2) if the null hypothesis for the term "period" is accepted. the dissolution rate must be constant throughout the test, ie, following zero-order kinetics; 3) if the null hypothesis for the term "interaction period by formulation" holds good, the dissolution rate curve profiles must be similar.

MATERIAL AND METHODS

The samples tested were lithium carbonate (Merck) tablets formulated with a wax matrix and contained 10.8

mEq lithium per tablet. For the dissolution tests the USP Apparatus I (Disolutest Turu Grau, Mod. D-6) was used for six simultaneus tests at 100 r.p.m. with hydrochloric acid (Merck AR) 0.1N with 0.1% polyoxyethylene sorbitan monooleate (Merck SR) as dissolution medium. The sampling times were after 0.5, 1.5, 3.5, 4, 7 and 8 hrs. Atomic absorption spectrophotometry (Perkin Elmer 603) was taken after dilution with deionized water at 335.8 nm using an air/ acetylene flame.

RESULTS AND DISCUSSION

Figure 3 shows the cumulative dissolution curves of the tablets before and after being stored for six months. The total amount of lithium dissolved in 8 hrs. was slightly greater; the mean rate went from 1.06 mEq/h to 1.17 mEq/h. The dissolution rate curve profile (Fig. 4) apparently registered less variation.

Table II sets out the summarized ANOVA findings: it can be seen that the difference in the mean dissolution rate is not significant, although almost 0.05; this is not true of the terms "period" and "interaction period by formulation". This latter, intended as a check on the statistical equality of both profiles, illustrates the change in the release profile during the storage of the tablets.

The lithium release process does not follow zero order kinetics since the null hypothesis for "period" does not good. Moreover, the curve profile can not be interpreted by any simple kinetic process.

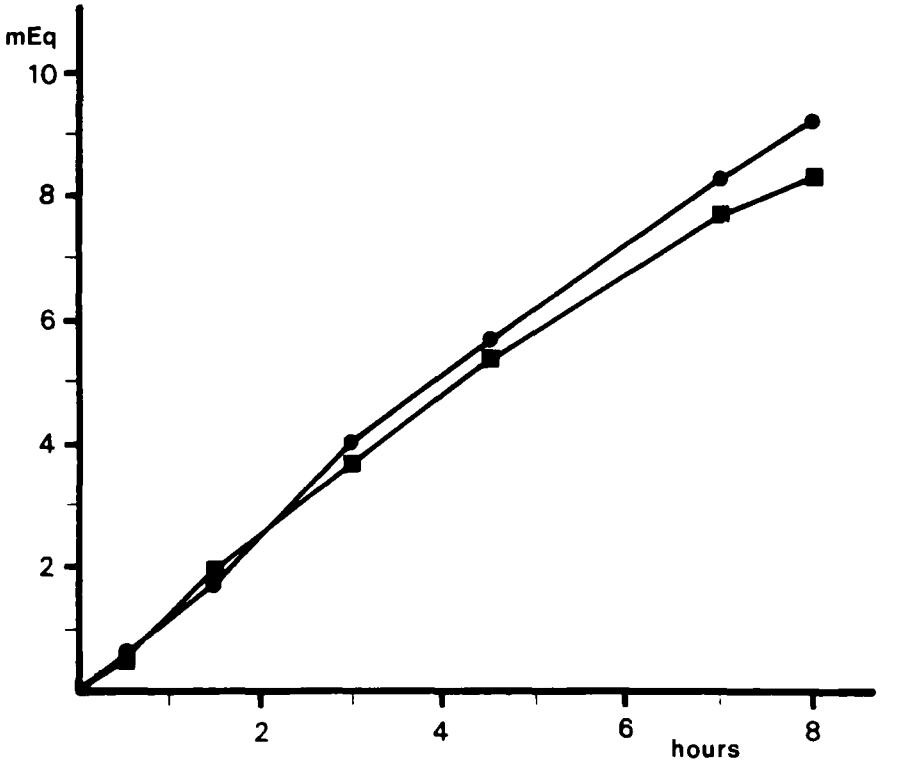

FIGURE 3

Cumulative dissolution curves of the tablets before (■) and after (●) being stored for six months.

It should be noted that the degrees of freedom were reduced when testing "period" and "formulation by period" (from 5 and 50 to 2.8 and 27.8, respectivily) due to the form of the combined variance-covariance matrix; as a general rule the faster the dissolution rate the greater the variability; variability was also greater at the outset of the dissolution test, so the Greenhouse and Geisser aproximation should be systematically applied.

Of the various methods proposed for the analysis of the growth curves, that of Box was chosen for the

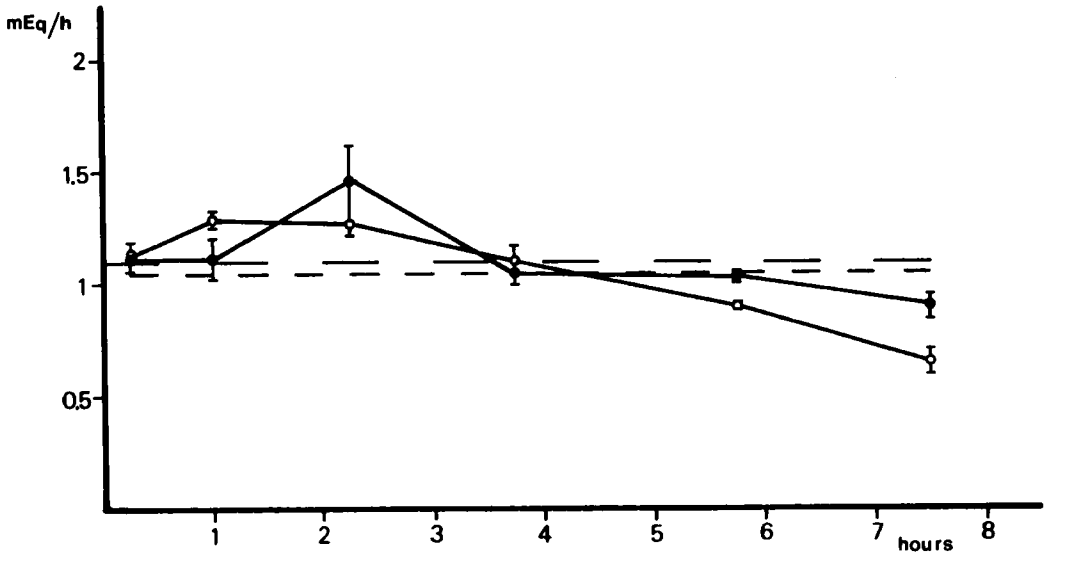

FIGURE 4

Dissolution rate curve profiles of the tablets before (o) and after (●) being stored for six months.

following reasons: 1) it does not require any kinetic or empirical model to interpret the dissolution curve; 2) the ANOVA findings are easily assessed, as explained above; 3) the calculations involved are relatively simple and 4) it permits comparison between pairs of formulations or the inclusion of differing experimental designs with a view to the development of pharmaceutical forms. The "split-plot" method has also been advocated by Westlake [8] for the comparison of serum level-time curves or urinary excretion in bioavailability testing, with the logarithmic conversion of the data to obtain a suitable form of combined variance-covariance matrix.

In conclusion, the method described here for the comparison of dissolution curves is particularly useful

TABLE 2

Summarized ANOVA findings.

Source of variation	MS	F	DF	P
Formulation	0.231	4.4	1-10	0.0616
Error	0.0521			
Period	0.478	25.8	5-50	<0.0005
			2.8-27.8*	<0.0005
Formulation by period	0.0635	5.8	5-50	0.0002
			2.8-27.8*	0.0037
Error	0.0108			

*=degrees of freedom adjusted according to Greenhouse and Geisser method.

MS=mean square; F=Snedecor's F; DF=degrees of freedom P=probability of null hypothesis testing.

when the curves do not follow a set kinetic process and has proved sensitive to changes in the dissolution profile caused by excipient in the tablets.

ACKNOWLEDGEMENTS

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