

The use of the Durbin-Watson statistic for testing the validity of kinetic models for dissolution

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Introduction

Over the years many articles have been published discussing the dissolution kinetics of drugs. It appears that there is no general model, based on theory, which applies in all circumstances, but that dissolution behaviour varies with many factors, including the form and dimensions of the drug form under study, its porosity and the apparatus used.

As this stands, the need for the testing the validity of a hypothesized model in a particular situation is obvious. Nevertheless, some investigators rely only on a visual inspection to see if some model fits their data (Parrot et al., 1955; Goldberg et al., 1965; Langenbucher, 1969). Often linear regression is performed and the goodness of fit is then evaluated by looking at the correlation coefficient (Carstensen et al., 1978) or, what is equivalent, the standard error of the estimate (De Blaey and Van der Graaff, 1977). However, these measures are difficult to interpret: for instance, what is the conclusion when a correlation coefficient 0.998 is found?

In this article a method is described, which can be used to test statistically if an equation, which is expected to describe the dissolution kinetics, may be considered to be valid or not.

Methods

A kinetic model can usually be seen as a transformation of the data, after which the regression on time should be linear. Therefore testing if a model holds can best be done by testing the linearity of the regression line. But here we meet a problem: for a normal statistical test of linearity it is necessary to have more measurements made at each time to estimate the residual variance free of departure-from-linearity

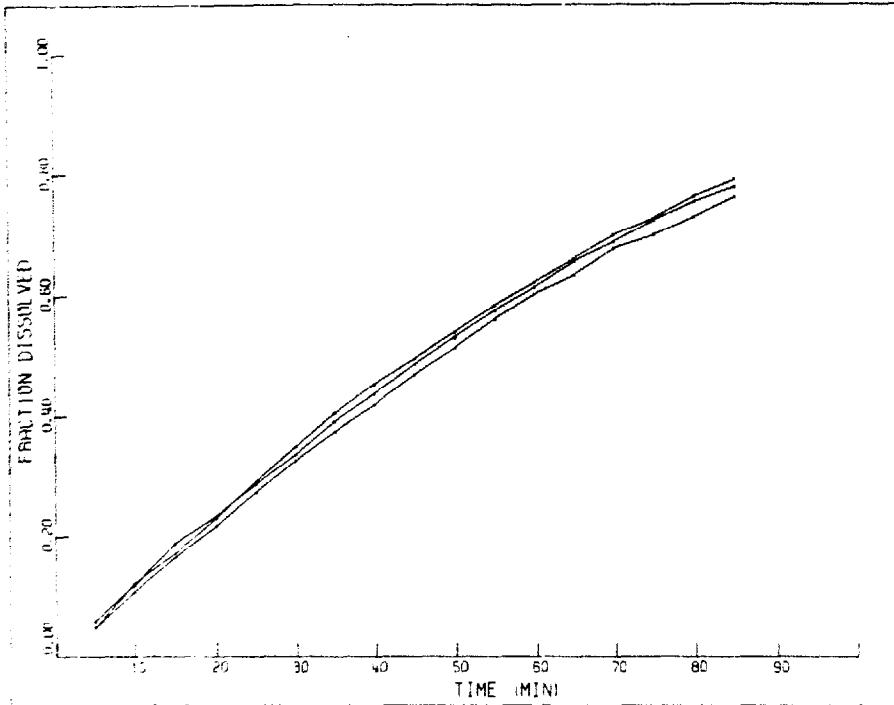


Fig. 1. Dissolution curves of 3 identical theophylline tablets in a sandwich apparatus.

effects. When two or more drug-forms are dissolved and measured to meet this difficulty, it appears that the variation between the measurements at the same time will be quite large. This is because the measurements made on one dissolving drug-form constitute a time series and are not independent from one another. Although the drug-forms will dissolve according to the same model, the dissolution rate may vary somewhat during the process, leading to small differences in the amount dissolved, and these differences will persist in all subsequent measurements (see Fig. 1).

Our approach to this problem is to test the linearity by looking at the residuals of the regression line as a time series. If a wrong model is used, a non-linear relationship will be obtained. This means that positive residuals will generally follow each other and negative residuals too (see Fig. 4b). On the other hand, if the residuals lie scattered randomly around zero, the conclusion is justified that the transformation has yielded a straight line, to which linear regression can be validly applied.

From the diverse statistics available for testing this so-called serial correlation, we have used the wellknown Durbin-Watson statistic d , which is defined by

$$d = \frac{\sum_{i=1}^{n-1} (e_{i+1} - e_i)^2}{\sum_{i=1}^n e_i^2} \quad (1)$$

where e_i = difference between the transformed value of measurement i and the value predicted from the regression line; and n = number of measurements. Note: measurements have to be equally spaced in time.

For $n = 1$ no regression line exists and for $n = 2$ all residuals will be zero. For $n = 3$ the absolute value of the second residual will always be twice that of the first and the third residual, which leads to a meaningless $d = 3$ invariably. But when $n > 3$ the Durbin-Watson statistic becomes a measure of serial correlation with values between 0 and 4. Durbin and Watson (1951) have given formulae for the mean and variance of d in the null case, i.e. when no serial correlation is present:

$$E(d) = \frac{2\left(n - 1 - \frac{6}{n(n+1)}\right)}{n-2} \quad (2)$$

$$\text{var}(d) = \frac{4\left(3n - 4 + \frac{72}{n^2(n+1)^2} - \frac{24}{n(n^2-1)} - \frac{n-2}{2}(E(d))^2\right)}{n(n-2)} \quad (3)$$

It can be noticed, that when n is not too small, $E(d)$ is approximately 2. When subsequent residuals tend to have the same sign, we have positive serial correlation. A high positive serial correlation leads to small values of d . A high value of d is obtained when a positive residual is most likely followed by a negative residual and vice versa. This uncommon situation is referred to as negative serial correlation and needs not bother us here any further. Non-linearity will normally result in a positive serial correlation, so our test will be one-sided and we will reject the kinetic model when d is lower than a certain threshold value. Unfortunately, the shape of the distribution of d is not exactly known, so exact critical values cannot be obtained. However, it is possible to calculate upper and lower bounds to these critical values. These are denoted by d_L and d_U and were tabulated by Durbin and Watson (1951) for $n \geq 15$ and several significance levels. Hannan (1957) has shown, that in simple linear regression and under certain conditions also in multiple regression, the upper limit d_U is an extremely good approximation to the correct acceptance limit, differences being of the order of $1/n^2$. So in testing kinetic models we will reject the model when $d < d_U$.

Another problem arises when we have less than 15 measurements, because no values of d_U (and d_L) are available. We can, however, approximate d_U by assuming that d has a normal distribution and then use Eqns. 2 and 3 for calculating a one-sided lower bound. For a significance level $\alpha = 0.05$ this approximate bound becomes:

$$d'_L = E(d) - 1.64 \sqrt{\text{var}(d)} \quad (4)$$

For $n > 15$ d'_L approximates d_U very closely. We therefore recommend for the sake of simplicity to discard of the use of d_U and to use the normal approximation d'_L in

all cases. It must be stressed, however, that we do not know at this moment how good the approximation is for small values of n .

For ready reference some values of $E(d)$ and d'_{U} , calculated with the above equations, are given in Table 1 and graphically shown in Fig. 2.

A practical example

One can use this test for a given dataset by computing just one regression line on all available measurements and then computing one value of d . But experience has shown, that the dissolution kinetics are often not constant during the process. The conclusion that a certain model does not match all measurements may be less important than the conclusion that the model does hold up to a certain point of the dissolution process. For this reason we use the following procedure: d is computed from the regression line through the first 4 points. Then one by one the other points are added in the regression and d is calculated each time. The graph of d against the

TABLE 1

VALUES OF THE EXPECTATION AND APPROXIMATE CRITICAL VALUES OF d DEPENDING ON THE NUMBER OF DATA POINTS n

n	$E(d)$	d'_{U} ($\alpha = 0.05$)
3	3.000	3.000
4	2.700	1.888
5	2.533	1.585
6	2.429	1.451
7	2.357	1.387
8	2.306	1.356
9	2.267	1.343
10	2.236	1.340
11	2.212	1.342
12	2.192	1.348
13	2.176	1.355
14	2.162	1.364
15	2.150	1.373
16	2.140	1.382
17	2.131	1.392
18	2.123	1.401
19	2.116	1.410
20	2.110	1.419
25	2.086	1.460
30	2.071	1.494
35	2.060	1.523
40	2.052	1.548
∞	2.000	2.000

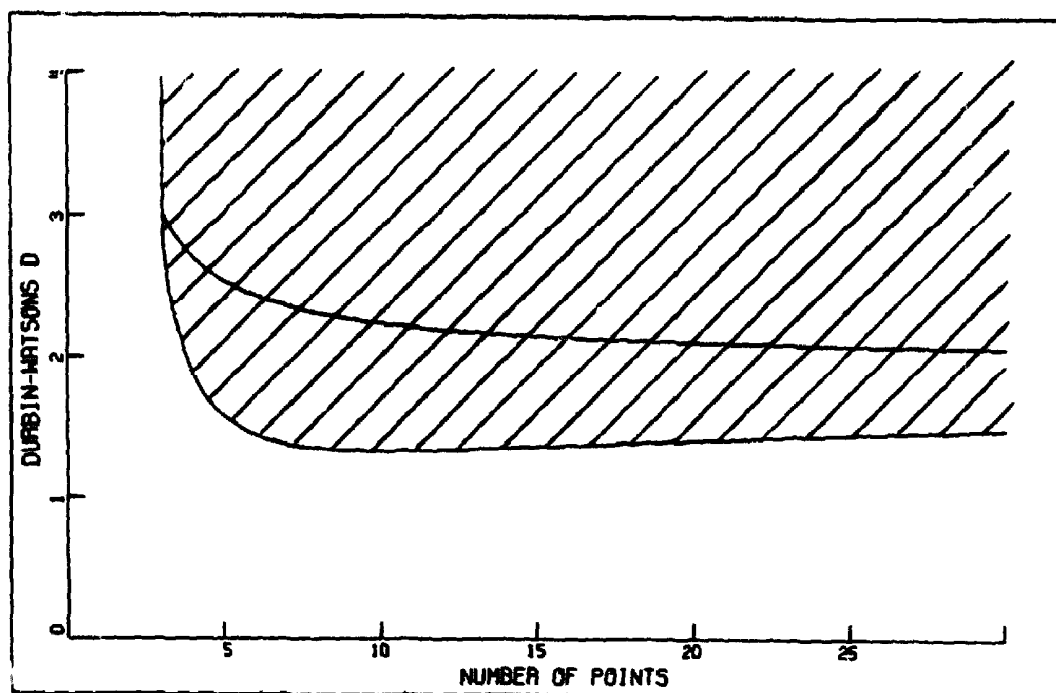


Fig. 2. Expectation and critical values of d as a function of the number of data points in the regression n . A value of d falling outside the shaded area means that we cannot use the dissolution model to obtain a straight line.

TABLE 2

CORRELATION COEFFICIENTS AND DURBIN-WATSON STATISTICS ACCORDING TO 2 DIFFERENT MODELS

n	Time (min)	Frac-tion dis-solved	Square-root law $p = 1/2$		Cube-root law $p = 1/3$	
			Corr. coef.	Durbin-Watson stat.	Corr. coef.	Durbin-Watson st.
4	20	0.228	0.99944	2.04	0.99959	2.06
5	25	0.284	0.99972	2.19	0.99979	2.58
6	30	0.338	0.99983	2.16	0.99982	2.07
7	35	0.390	0.99987	1.88	0.99978	1.34
8	40	0.436	0.99991	2.15	0.99984	1.19
9	45	0.485	0.99994	2.23	0.99982	1.04
10	50	0.528	0.99995	2.27	0.99983	0.81
11	55	0.574	0.99995	2.23	0.99974	0.71
12	60	0.614	0.99996	2.15	0.99970	0.50
13	65	0.650	0.99997	2.20	0.99971	0.40
14	70	0.688	0.99997	2.27	0.99966	0.38
15	75	0.716	0.99993	1.56	0.99971	0.41
16	80	0.748	0.99991	1.00	0.99973	0.41
17	85	0.777	0.99989	0.72	0.99973	0.37

number of measurements involved (or equivalently, against time) now shows up to what point the measurements do not contradict the model.

In our example the dissolution process of theophylline tablets with a porosity of about 1.5% was studied by sampling the dissolution medium (0.1 N HCl) at equal time intervals. The release studies were performed at $37 \pm 0.5^\circ\text{C}$ in a sandwich apparatus (De Haan and Lerk, 1982). Two models are tested: the well-known cube-root law, based on theory, and an empirical square-root law (De Blaey and Van der Graaff, 1978). The transformations applied were

$$y = 1 - (1 - f_t)^p$$

where f_t = fraction dissolved at time t , $p = 1/3$ for the cube-root law, and $p = 1/2$ for the square root law. Values of y for 3 tablets were averaged and regression on t then yielded values of d according to the procedure mentioned above. These results are given together with the correlation coefficients (for comparison) in Table 2, and they are shown graphically in Fig. 3. For a better understanding we show the plots of residuals e against time in Fig. 4:

Departure from the cube root-law is observed rapidly ($t = 35$ min, about 40% dissolved), whereas the square-root law seems to fit the data well up to $t = 70-75$ min, when about 70% is dissolved. It has to be stressed, that deviations from linearity would have been detected earlier, when the time interval between measurements would have been shorter. When a large number of points is considered, serial

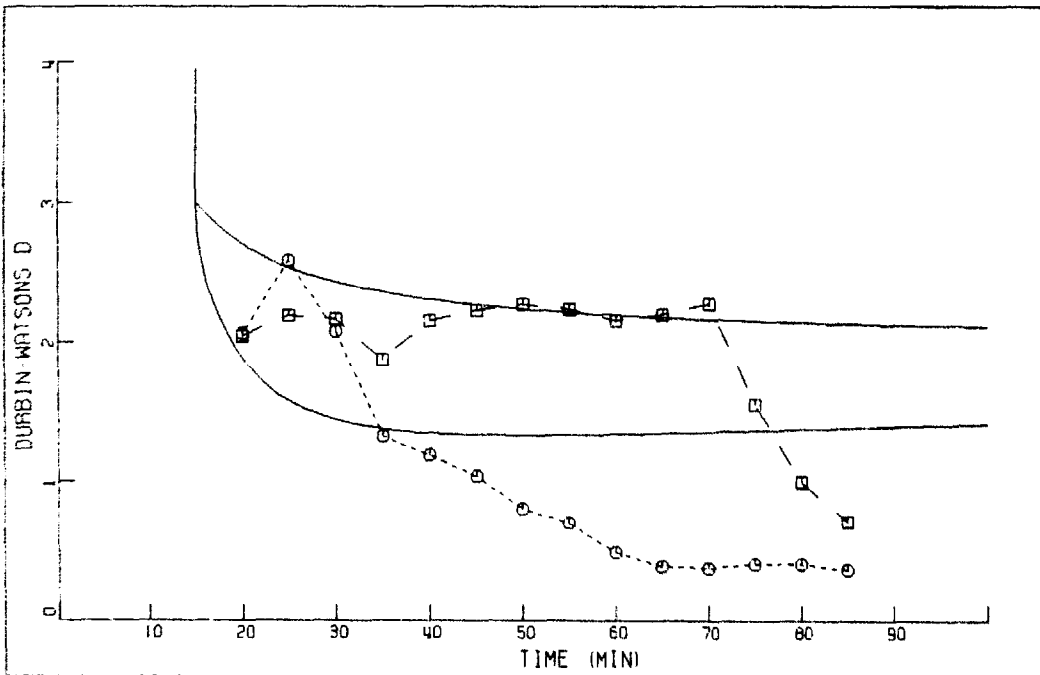


Fig. 3. Values of d in a practical example (see text). □, square-root law; ○, cube-root law.

correlation will always be found, whatever the kinetic model is. In other words, we use the Durbin-Watson test to detect departures from linearity, and at the same time have a tool to check, if the dependency between subsequent measurements, which in theory of course always exists, will be troublesome for the application of linear regression analysis.

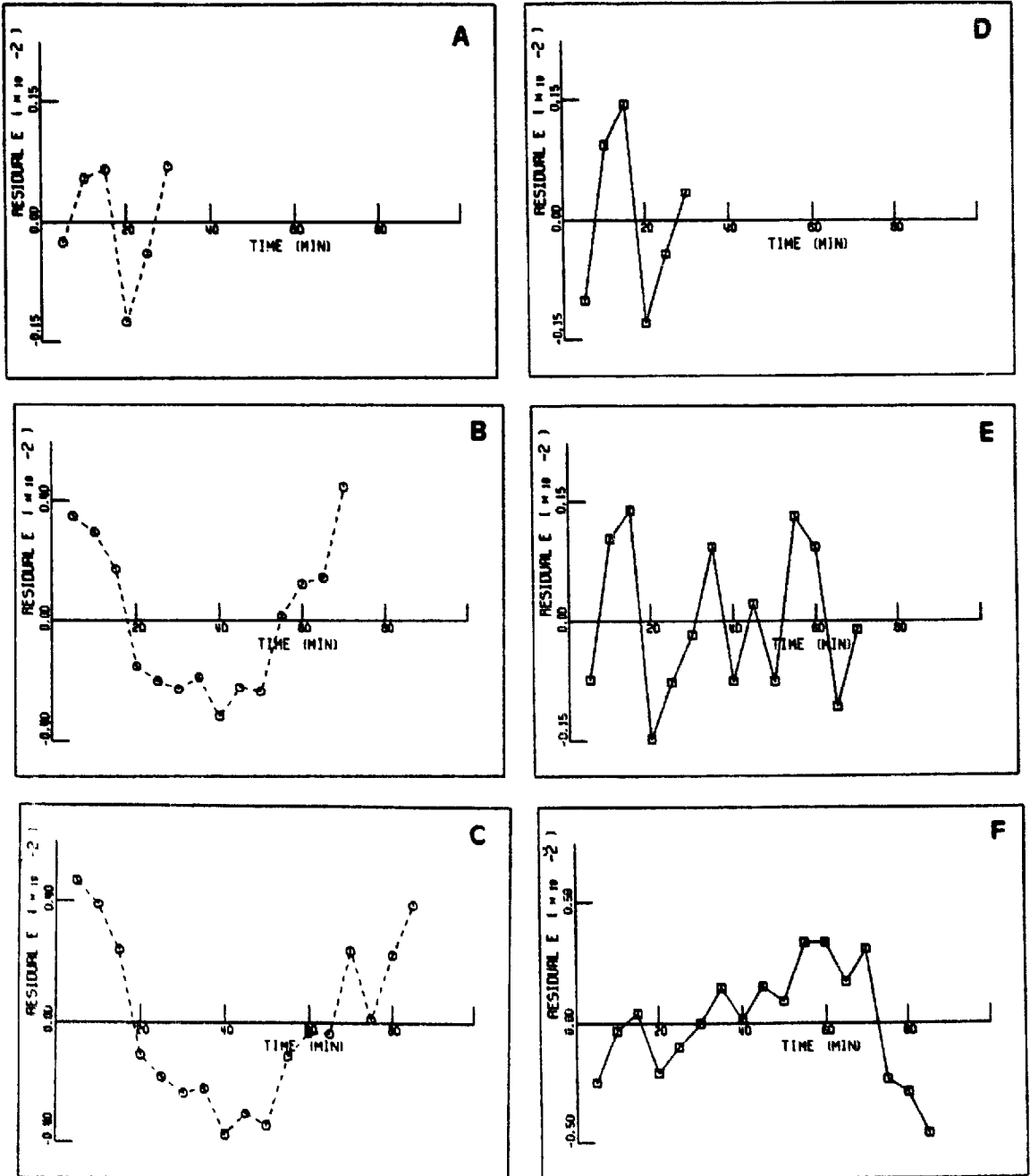


Fig. 4. Plots of residuals against time for regression lines based on 2 different models for up to $t = 30$ min (cube-root law = A, and square-root law = D), $t = 70$ min (resp., B and E) and $t = 85$ min (resp. C and F).

Conclusions

The Durbin-Watson statistic for serial correlation can be used to test the validity of kinetic models for dissolution, especially to examine if it is allowed to apply linear regression analysis to the transformed measurements. When the test statistic d is lower than the critical value d'_U , we can state with an inconfidence level of approximately 5% that the data points cannot be fitted properly by the hypothesized model.

By adding the measurements one by one to the regression analysis, a point can be established up to which the model can be used.

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