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LETTERS TO THE EDITOR

Linearization of dissolution rate curves by the Weibull distribution

The quantitative interpretation of dissolution rate data is greatly facilitated by the application of a general mathematical expression which describes the entire curve in terms of meaningful parameters. In special case, the equation can be derived from a theoretical treatment of the process, e.g. the cube-root law or zero-order kinetics, see Wagner (1970). In the most general case of tablets, coated tablets, capsules, or sustained-release preparations, however, no such theoretical basis is available and a suitable function has to be found empirically. First-order kinetics were proposed by Gibaldi & Feldman (1967) and Wagner (1969) introduced the log-normal presentation for this purpose. Although these two models together describe most dissolution curves observed, they exclude each other and are, thus, of limited applicability: for example, see the discussion of Wagner (1970) relative to Figs. 20.2 and 20.3.

A more general function which may be applied successfully to all common types of dissolution curves, was described by Weibull (1951). All characteristics of this distribution function are discussed in detail by Kao (1959) and Ruzicka (1962). A concise survey is given by Grant (1964). When applied to dissolution rate data, the Weibull equation expresses the accumulated fraction, m, of the material in solution at time t, by

$$m = 1 - \exp\left[-(t - T_i)^{b/a}\right] \qquad (1)$$

In equation (1), the *scale parameter*, a, defines the time scale of the process. The *location parameter*, T_i, represents the time lag before the actual onset of the dissolution process which, in most cases, will be equal to zero. The *shape parameter*, b, characterizes the curve as either exponential ($b = 1$), S-shaped with upward curvature followed by a turning point ($b > 1$), or as one with steeper initial slope than consistent with the exponential ($b < 1$). These relationships are illustrated in Fig. 18–4 of Grant (1964).

The graphical presentation of data according to the Weibull distribution and the practical aspects of linearizing experimental data are discussed by Kao (1959) and Ruzicka (1962). Equation (1) may be rearranged into the form

$$\log\left[-\ln(1 - m)\right] = b \cdot \log(t - T_i) - \log a \qquad (2)$$

From equation (2), a linear relation is obtained for a log-log plot of $-\ln(1 - m)$ versus t, see Fig. 1. The shape parameter, b, is obtained from the slope of the line, and the scale parameter, a, is estimated from the ordinate value $(1/a)$, at $t = 1$. From my experience, it is convenient to replace the parameter a by means of the more informative *dissolution time*, T_d; this is defined by $a = (T_d)^b$ and is read from the graph as the time value corresponding to the ordinate $-\ln(1 - m) = 1$. Since $-\ln(1 - m) = 1$ is equivalent to $m = 0{\cdot}63212$, T_d represents the time interval necessary to dissolve 63·2% of the material and is, thus, comparable with the frequently quoted t_{50} value.

In order to facilitate the plotting of experimental data points, an auxiliary ordinate scale may be constructed for the original m values, as shown on the right-hand side of Fig. 1.

The location parameter, T_i is not obtained immediately from the Weibull plot, but has to be estimated indirectly by a least-squares calculation or a graphical

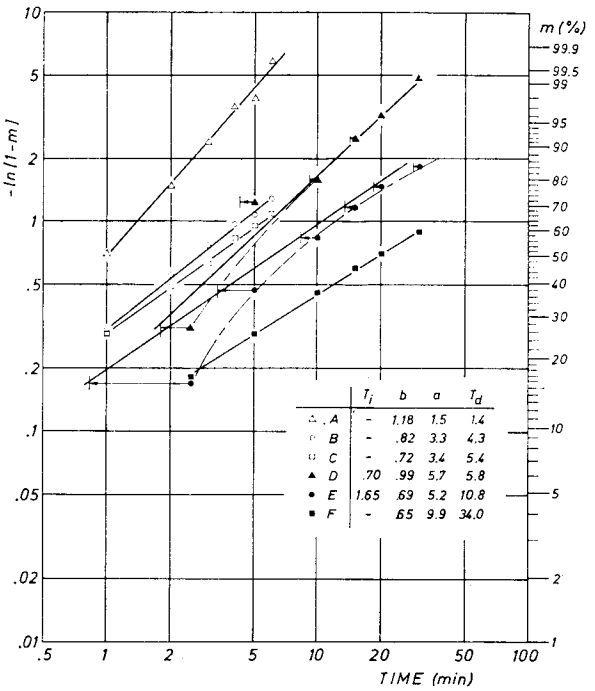

FIG. 1. *Weibull* plot for dissolution rate curves of Bufferin: data taken from Wood (1967); linearization by 1st order and log-normal transformation as discussed by Wagner (1970). For curves 'D' and 'E', the data points correspond to the original time values; the corrected values after adjusting the location parameter T_i are marked by arrow-heads. Estimates for *b* (shape parameter), *a* (scale parameter) and T_d (dissolution time) are given.

trial-and-error technique: data containing a significant time lag will exhibit a downward curvature in the initial part of the plot, as is seen for curve 'E' of Fig. 1. Whenever this occurs, it is possible to straighten the curve by shifting all data points horizontally by the same time interval. The time shift required to give the best linearization represents the location parameter, T_i (see curves 'D' and 'E').

Linearity of the Weibull plot requires that the data points asymptotically approach the final plateau $m_\infty = 1$. If this is not the case, a considerable curvature may be found in the upper tail of the plot. This lack of fit is overcome by estimating the correct 'plateau' value and adjusting all percentages accordingly. In general, it must be borne in mind that the Weibull distribution as well as other similar transformations greatly distorts the original scale of the observations: in particular, deviations occurring in the lower and the upper tail are extremely over-emphasized, when compared with those in the middle of the plot. Hence, the original m(t) plot rather than the Weibull presentation should be used to estimate the exactness of fit, in the graphical procedure as well as in the least-squares calculation.

With its three parameters, the Weibull distribution satisfactorily describes all common types of 'regular' dissolution curves, in particular the exponential and the sigmoid form. It combines the advantages of the first-order and the log-normal presentation. As illustration, Fig. 1 shows the Weibull plot of six dissolution curves originally reported by Wood (1967), in his Fig. 17. Wagner (1970) showed that neither the exponential nor the log-normal presentation is sufficient to describe all six curves, by the same model. Fig. 1 shows that all six curves can be perfectly linearized by the Weibull distribution.

From my experience, it is anticipated that the Weibull function will be useful in future work involving the quantitative interpretation of dissolution rate data.

Pharmaceutical Development,
CIBA-GEIGY Ltd.,
Basel, Switzerland.
F. LANGENBUCHER

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Urea increases serum albumin binding of drugs

Urea at concentrations higher than 2 M induces alterations in the molecular structure of bovine serum albumin (see for example Scheraga & Mandelkern, 1953; Gutter, Peterson & Sober, 1957; Williams & Foster, 1959; Santamaria, Fuerle & others, 1961).

We have investigated the effects of urea at physiological concentrations on the interactions of various drugs with serum proteins.

The drugs used doxycycline, metoclopramide, progesterone and sulfaethylthiazole, differ in chemical structure and physico-chemical features. For instance if the pH is increased from 5·2 to 9, the interaction of serum albumin with tetracyclines increases (Bononi, Pagnini & others, 1966) whereas the interaction with metoclopramide decreases (Pagnini & Di Carlo, 1972). Furthermore if the pH is increased from 5·5 to 11, the distribution coefficient chloroform/water decreases for tetracyclines (Von Wittenau & Yeary, 1963) whereas it increases for metoclopramide (Pagnini & Di Carlo, 1972).

Bovine serum albumin (Sigma Chem. Co. Frac. V) was purified from fatty acids (by extraction with acetic acid, 5% in isooctane, according to Goodman, 1957) and from ions (by dialysis in buffer tris HCl 0·05M, pH 7·4 after addition of EDTA).

The binding capability of the four drugs ($1{\cdot}13 \times 10^{-4}$M in buffer tris HCl 0·05M pH 7·4) with bovine serum albumin, with and without urea $1{\cdot}6 \times 10^{-3}$M, was assayed by the dialysis equilibrium technique (Klotz, Walker & Pivan, 1946). For this purpose 2 ml of bovine serum albumin solution ($5{\cdot}7 \times 10^{-4}$M) with or without urea was placed inside the dialysis tube (A. H. Thomas) and dialysed for 36 h at 5° against 6 ml of a solution of each drug. Then doxycycline (at 361 nm) and progesterone (at 240 nm) were assayed spectrophotometrically and metoclopramide and sulfaethylthiazole were assayed according to Bratton & Marshall (1939).

The binding capacity was expressed in terms of number of drug moles bound/mol of serum albumin (r).

The binding capability with serum albumin is greatest with sulfaethylthiazole >doxycycline >metoclopramide >progesterone (Fig. 1).

Addition of urea induces an increase of the binding capability of approximately 40% for all the drugs.