

On methods of expressing dissolution rate data

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The value of the Weibull, logarithmic-logistic, and logarithmic-normal plots in expressing dissolution rate data is considered for the combinations of zero and first-order release with sink and non-sink conditions, and for actual dissolution rate data of diazepam from tablets in a medium of pH 2.

Dissolution rate studies normally have one of two purposes. Gibaldi & Feldman (1967) use them to arrive at a kinetic scheme for the overall dissolution process. Other workers have treated the results of such studies with one of several distribution functions to enable the data to be expressed in terms of the parameters of the chosen function. Recently, Langenbucher (1972) used the Weibull function, and Wagner (1969, 1970a,b) the logarithmic-logistic and logarithmic-normal functions, in this way, and Khan (1975) introduced the concept of dissolution efficiency. We now discuss how information may be obtained from these ways of treating kinetic data.

Table 1 lists the distribution functions and the parameters which are related to reaction rates.

DISCUSSION

1. Simulated dissolution rate data

Gibaldi & Feldman (1967) have shown that four limiting cases of dissolution kinetics exist. If the release process is zero order, the overall order is 0 or

1 under sink and non-sink conditions respectively; under the same conditions with a first order release process the overall order is 1 or 2, the kinetics being pseudo-first order for sink conditions. We therefore considered it useful to see what information the distribution functions give for data conforming to these limiting conditions. Table 2 sets out this information for zero, first and second-order data corresponding to $k = 0.05 \text{ mol litre}^{-1} \text{ min}^{-1}$, 0.05 min^{-1} , and $0.05 \text{ litre mol}^{-1} \text{ min}^{-1}$ respectively. In all except the two limiting cases referred to in Table 1 the effect of expressing the kinetic data in terms of a distribution function is to distort the original data; the values of k and $t_{\frac{1}{2}}$ calculated back from the plots are incorrect. We conclude that there is no advantage in expressing data which conform to these limiting cases in the form of a distribution function.

2. Actual dissolution rate data

We have studied one set of results, at different stirring speeds (22, 50, 60, 76 and 100 rev min^{-1}),

Table 1. *Distribution functions and the significance of their parameters.*

Function	Original form	Linear transform	Limiting cases	Significance of parameters
Weibull (a)	$F(t) = 1 - \frac{e^{-(t-\gamma)^\beta}}{\alpha}$	$\ln \ln [1 - F(t)]^{-1} = -1n\alpha + \beta \ln t(b)$	$1n\left(\frac{A_0}{A_t}\right) = -1n\alpha + \beta \ln t$ for 1st order kinetics	$t_{\frac{1}{2}} = 1n t$ when the ordinate is $1n \ln 2$ (-0.3666).
Logarithmic-logistic	$y = k[1 - e^{-(a+bt)}]^{-1}$	$1n\left(\frac{y}{1-y}\right) = \alpha + \beta t(c)$	$1n\left(\frac{A_0}{A_t} - 1\right) = \alpha + \beta t$ for 2nd order kinetics	$t_{\frac{1}{2}} = 1n t$ when the ordinate is zero
Logarithmic-normal (d-g)	$y = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{t-m}{\sigma}\right)^2}$	—	—	Standard deviation (σ) correlates with time-scale of reaction. Mean (m) gives an estimate of $t_{\frac{1}{2}}$

References: (a) Weibull (1951); (b) Kao (1959); (c) Berkson (1963); (d-f) Wagner (1969, 1970a,b); (g) Croxton & Cowden (1956).

Note: A_0 and A_t are concentrations at $t = 0$, $t = t$ respectively.

† Correspondence.

Table 2. Information obtained from distribution function and standard rate plots for single zero-, first- and second-order processes.

Type of plot	Order	k	Scale parameter $\ln \alpha$ at $\ln t = 0$	σ	$t_{\frac{1}{2}}$ (min)	Shape of plot
W	0	(0.0513)	-2.970	—	9.51	Concave upwards
LL	0	(0.0526)	-2.945	—	9.65	Concave upwards
LN	0	—	—	0.2778	9.21	Negatively skewed
S	0	0.05	—	—	10.00	Linear
W	1	0.05	-2.996	—	13.92	Linear
LL	1	(0.0513)	-2.970	—	13.92	Concave upwards
LN	1	—	—	0.4476	14.47	Negatively skewed
S	1	0.05	—	—	13.86	Linear
W	2	(0.0488)	-3.021	—	20.39	Concave downwards
LL	2	0.05	-2.996	—	19.90	Linear
LN	2	—	—	0.5062	17.63	Negatively skewed
S	2	0.05	—	—	20.00	Linear

Key to type of plot: W = Weibull. LL = Logarithmic-logistic. LN = Logarithmic-normal. S = Standard.

which are representative of many dissolution rate profiles of diazepam (Atensine, Berk) tablets, in a medium of pH 2. The method of obtaining the dissolution rate data has been described (Randall & Goldsmith, 1975).

(a) The Weibull and logarithmic-logistic plots. Table 3 shows that both plots can be used to reduce such data to linear form, the correlation coefficients being close to unity and the standard error of estimate being low. The shape parameter, β , of the Weibull plot is near 2 in all cases, corresponding to the sigmoid shape observed for the actual plots of cumulative fraction dissolved against time (Kao, 1959). $t_{\frac{1}{2}}$ is estimated both from the actual Weibull and logarithmic-logistic plots; in all cases the best straight line gives the higher estimate of $t_{\frac{1}{2}}$, corresponding to the negative deviation from linearity of both plots when dissolution nears completion.

The actual logarithmic-logistic plot gave the most accurate estimate of $t_{\frac{1}{2}}$.

(b) The logarithmic-normal plot. Table 4 shows that this plot gives a fairly satisfactory representation of the data. The standard deviations decrease with increasing stirring rate, corresponding to the shorter time-scale. The dissolution rate plots calculated from the logarithmic-normal distribution agree quite closely with the observed plots near the middle of the reaction, but tend to under-estimate the cumulative fraction dissolved near both the beginning and the end of the reaction.

(c) The concept of dissolution efficiency (DE). This has been suggested (Khan, 1975) as a means of conveying information about dissolution rate profiles; the DE is defined as the ratio of the area under the dissolution rate curve, between $t = 0$, $t = t$, to the area of the rectangle bounded by these time ordinates and by $x = 0$, $x = 100\%$ where x is the cumulative fraction dissolved. We evaluated the dissolution efficiency after 25 min (DE25) for five sets of dissolution rate data on the diazepam tablets, with stirring speeds of 50, 60, 76 and 100 rev min⁻¹; at 22 rev min⁻¹ the fraction dissolved after 25 min was about 70%, whereas Khan recommends that, for this approach to be adopted, a time should be taken at which x is greater than 90%. For stirring speeds of 50, 60, 76 and 100 rev min⁻¹, DE25 is 67.8 ± 0.2, 75.1 ± 0.1, 76.6 ± 0.1, and 79.4 ± 0.3%, respectively. This, therefore increases with stirring rate as expected. This is the least informative way, of those studied here, of expressing dissolution rate data, since it gives no information about the shape of the curve; Khan, indeed, anticipates this criticism, since he suggests using DE in conjunction with t_{20} , t_{50} , and $t_{90}\%$; but the shape of the curve is then reasonably well specified and one sees little advantage in adding the DE to this information, particularly if it is to be obtained by the time-consuming process of cutting-out and weighing.

Table 3. Parameters of the Weibull and logarithmic-logistic plots for dissolution of diazepam from tablets.

Stirrer speed rev min ⁻¹	Dissolution rate data		Weibull best straight line				Actual plot	Logarithmic-logistic best straight line				Actual plot	
	$t_{\frac{1}{2}}$ min	Scale factor (ordinate at $\ln t = 0$)	Slope (shape parameter)	Sx, y	Γ	$t_{\frac{1}{2}}$ min	$t_{\frac{1}{2}}$ min	Scale factor (ordinate at $\ln t = 0$)	Slope (shape parameter)	Sx, y	Γ	$t_{\frac{1}{2}}$ min	$t_{\frac{1}{2}}$ min
22	11.2	-5.0314	1.8595	0.1555	0.98	12.28	11.52	-5.1613	2.0738	0.0574	0.99	12.05	10.74
50	7.0	-4.4475	1.9566	0.1421	0.96	8.05	7.21	-4.7505	2.3934	0.0090	1.00	7.28	6.96
60	5.4	-4.2196	2.0532	0.1145	0.98	6.53	5.10	-4.4618	2.5614	0.1406	0.99	5.71	5.28
76	4.9	-3.6024	1.8023	0.1034	0.98	6.02	4.76	-4.0778	2.4416	0.0770	0.99	5.31	4.92
100	4.2	-3.1663	1.6637	0.1074	0.98	5.38	4.36	-3.4925	2.2511	0.1273	0.98	4.72	4.14

* Sx, y is the standard error of estimate; it gives a measure of the range above and below the calculated best straight line within which 68.27% of the items may be expected to fall if the scatter is normal.
 Γ is the coefficient of correction.

Table 4. Parameters of the logarithmic-normal distributions for dissolution of diazepam from tablets, and calculated and observed dissolution times for specified fractions of the reaction.

SS	Mean	σ	Pearson skewness	Calc. %			Observed %		
				20	50	80	20	50	80
22	0.8807	0.2603	-1.82	5.66	10.68	—	5.4	11.20	—
50	0.7944	0.2438	-1.04	4.22	6.95	12.98	4.0	7.00	12.93
60	0.6966	0.2123	+0.04	3.42	5.45	9.68	3.4	5.40	8.43
76	0.6577	0.2123	-0.54	3.25	5.15	8.72	3.14	4.90	8.0
100	0.6159	0.2015	-0.57	2.98	4.32	8.14	3.14	4.20	7.2

SS = stirring speed (rev min⁻¹).

Pearson skewness, Sk (log), as applied to a log-normal curve, is defined as

$$Sk(\log) = \frac{\log Q_1 + \log Q_3 - 2 \log Q_2}{\log Q_3 - \log Q_1}$$

where Q_1 , Q_2 , Q_3 are the ordinates corresponding to the lower and upper quartiles and the mean, respectively. The curve may be considered as log-normal if $Sk(\log) < 0.15$.

CONCLUSION

Plots of cumulative fraction of sample dissolved against time can be described by the Weibull or logarithmic-logistic plots, using their scale factors and slopes as parameters, or by a logarithmic-normal plot, using the mean and standard deviation as parameters. This applies both to the dissolution rate data observed for diazepam from tablets in a medium of pH 2, and to the data which we have constructed for overall zero-, first- and second-order kinetics.

All three methods give estimates of $t_{\frac{1}{2}}$; a smooth curve drawn through the points in the Weibull or logarithmic-logistic plot leads to a better estimate of $t_{\frac{1}{2}}$ than does the best straight line through the points.

This is due to the marked negative deviation from linearity found in both plots as the reaction nears completion.

With two exceptions, these plots give no information about the kinetics of the process; these exceptions are the Weibull plot for overall first-order kinetics and the logarithmic-logistic plot for second-order kinetics.

In both cases the slope of the line is unity and the rate constant is the antilogarithm of the intercept at \log (or $1n$) $t = 0$. These situations arise because in each case the appropriate plot is simply a log-log plot of the standard expression for first or second order kinetics.

Although all three methods provide representations of dissolution rate curves in terms of parameters related to the time-scale of the process, it seems to us unnecessary to treat dissolution rate data in such ways. Firstly, the additional work involved in such calculations does not lead to any fresh information and, in fact, as Tables 2, 3 and 4 show, slightly distorts the experimental results. It may be argued that the parameters of these plots provide a useful short description of the dissolution rate curves, but, in our opinion, such a description could equally well be provided in terms of the times at which specified fractions of the material are found to be dissolved.

Acknowledgements

The authors wish to express their appreciation of the facilities made available by Dr J. S. Burton, the Scientific Director of Berk Pharmaceuticals Ltd.

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